QUINOLINES

Part I

This is the thirty-second volume in the series

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

A SERIES OF MONOGRAPHS

ARNOLD WEISSBERGER and EDWARD C. TAYLOR

Editors

QUINOLINES

Part I

Edited by

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The Chemistry of Heterocyclic Compounds

The chemistry of heterocyclic compounds is one of the most complexes branches of organic chemistry. It is equally interesting for its theoretical implications, for the diversity of its synthetic procedures, and for the physiological and industrial significance of heterocyclic compounds.

A field of such importance and intrinsic difficulty should be made as readily accessible as possible, and the lack of a modern detailed and comprehensive presentation of heterocyclic chemistry is therefore keenly felt. It is the intention of the present series to fill this gap by expert presentations of the various branches of heterocyclic chemistry. The subdivisions have been designed to cover the field in its entirety by monographs which reflect the importance and the interrelations of the various compounds, and accommodate the specific interests of the authors.

In order to continue to make heterocyclic chemistry as readily accessible as possible new editions are planned for those areas where the respective volumes in the first edition have become obsolete by overwhelming progress. If, however, the changes are not too great so that the first editions can be brought up-to-date by supplementary volumes, supplements to the respective volumes will be published in the first edition.

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Preface

In the first Part of the volume dealing with the chemistry of quinolines we have tried to cover, in as comprehensive a manner as is possible, the properties of quinoline itself and of the haloquinolines, and to survey the ways in which the quinoline ring system can be formed. With a limited topic, such as is dealt with in Chapter 1 and Chapter 3, a very comprehensive coverage is possible. In the former, the only deliberate omissions are the metal complexes in which quinoline is a ligand, and the reactions in which quinoline functions purely as a base (and where any other high boiling base would have done as well). The same degree of comprehensive coverage has not been possible with Chapter 2—the ring syntheses. Here the object has been to condense as many ring syntheses as possible into a readable article. No attempt at complete tabulation has been made; illustrative tables for some major syntheses are given. In all three chapters the abstracts are covered to early 1976, and one or two later items will be found. Compounds mentioned in the text or tabulated in the text will be found in the subject index; compounds tabulated at the ends of chapters are not entered in the subject index.

I must thank Dr. Smalley for his efforts on a truly enormous task, and our respective wives for accepting our apparently endless writing. They had even the fortitude to prepare jointly the author index.

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CHAPTER 1

The Physical and Chemical Properties of Quinoline

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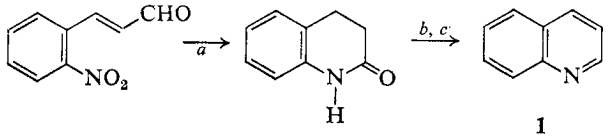
I. Introduction

Quinoline was discovered in coal tar distillate by Runge[1] in 1834 and named "Leukol" (from λευκσ- and oleum). The base was also obtained by Gerhardt[2] in 1842 by alkaline distillation of quinine, cinchonine, or strychnine, and was named by him "Chinolein" or "Chinolin". Not until 1882 was the identity of leukol and chinolin firmly established, when Hoogewerff and Van Dorp[3] showed that the samples from coal tar and from alkaloid distillation had the same boiling point, formed the same hydrate ($3H_2O$), platinichloride, bichromate, and argentonitrate. Both specimens were also converted by oxidation into quinolinic acid, which was decarboxylated to nicotinic acid. Körner was cited as the first to propose the structural formula for quinoline (in *Die Chemie von Pyridins und Seiner Derivate* by A. Calm) but Dewar[4] in 1871 suggested that quinoline bore the same relationship to pyridine that naphthalene bore to benzene. The structure (**1**) was confirmed by the syntheses in which allylaniline was passed over glowing lead oxide,[5] or from *o*-nitrocinnamaldehyde as shown in reaction (1).[6]



1 (1)

[a] Zn/HCl. [b] $POCl_3/PCl_5$. [c] HI, AcOH, 240 °C.

The molecular dimensions of quinoline have not been accurately determined, but an X-ray structure determination of a nickel complex containing quinoline[7] gives the dimensions shown in Fig. 1. Crystal structures of some other quinoline complexes have been reported;[8-10] in one of them[10] the bond lengths and angles reported for the quinolinium ion show appreciable differences from those shown in Fig. 1.

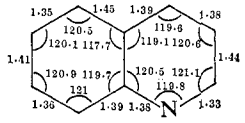


Fig. 1. Dimensions of quinoline in $Ni[S_2\text{-}PEt_2].C_9H_7N$ (bond lengths in Å, angles in degrees, central bond 1.43 Å)

II. Theoretical Chemistry

Quinoline has proved a popular subject for theoretical chemists since Coulson and Longuet-Higgins first attempted to produce π-electron densities for nitrogen heterocycles in 1947.[11] The major difficulties attending such calculations are exemplified in their treatment which followed an earlier calculation on pyrrole and pyridine by Wheland and Pauling.[12] The resonance integral $\beta_{r,s}$ was taken as equal to β, the resonance integral for the C—C bond in benzene, or to zero, according as atoms r and s were or were not joined by a bond; and α_r was taken as $\alpha+2\beta$, $\alpha+\frac{1}{2}\beta$,* or α, according as r was a nitrogen atom, a carbon atom bonded to nitrogen, or any other carbon atom respectively, and α was the Coulomb integral for a carbon atom in benzene. The implications (which have not subsequently been accepted) were that there is no interaction between non-bonded atoms, and that the values given for α_N can be used for any nitrogen heterocycle. The calculations showed very low π-electron densities at position 2 and position 4 in quinoline, in accord with the known preference for nucleophilic attack at these positions. The figures given for π-electron density can less confidently be used for discussion of electrophilic attack because the nitration quoted as proceeding at the 5-position and the 8-position was performed under protonating conditions.

Since 1947, many other calculations based on the simple HMO treatment have been published; a review of the literature to 1954 was given by Zahradnik and Parkanyi.[13] The electron-density figures for quinoline and for its protonated form are

(A) (B)

Fig. 2. Electron-density figures for (A) quinoline and (B) protonated quinoline

shown in Fig. 2 and are typical of those obtained by the HMO treatment (in the protonated quinoline $\alpha_N = \alpha_c+2\beta$; in the unprotonated quinoline $\alpha_N = \alpha_c+0.5\beta$).

* Wheland and Pauling used $\alpha+\frac{1}{5}\beta$ for this integral.

All simple Hückel calculations show π-electron deficiency at positions 2 and 4 which correlated with the experimental observation of nucleophilic substitution at these positions (p. 37): however, all Hückel calculations show the highest π-electron density at positions 1(N), 8, 3, and 6, and protonation leads to an increase in π-electron density at position 3. No simple Hückel treatment correctly correlates π-electron density with the actual pattern of electrophilic substitution in protonating media (at positions 5 and 8, see page 42 and following). A number of simple Hückel calculations on quinoline have been reported since 1964;[14–19] Adam, Grimison and Rodriguez[17] pointed out the difficulty of computing the effect of protonation which at first sight affects only the σ-electrons directly. Melhorn and Mayer have attempted to calculate the ground-state property of dipole moment.[18]

Since 1958 more attention has been given to the application of Self Consistent Field (SCF) calculations; a semiempirical approach to the calculation of electronic spectra in quinoline (among other heterocycles) was suggested by Mataga[20] and by McWeeny and Peacock.[21] Many of the authors have been concerned with the calculation of singlet and triplet energies, where opportunities are available for comparison with experimental values. Dewar and Gleicher have pointed out[22] that in such calculations configuration interaction is essential, as excited states can mix; they also suggested that parameters should be fixed for some ground-state property and based their resonance energy integrals on thermochemical data. Many groups have used the Mataga treatment, or a modification of it.[23–35] Typical figures for the first three singlet transitions are 4.085, 4.224, and 5.554 eV (*f* values 0.048, 0.107, and 0.080) compared with experimental values of 3.96, 4.591, and 5.509 eV.[36]

Use of the Pariser–Parr type of approximation for two-centre Coulomb repulsion integrals was said to give better triplet-state zero field splitting parameters.[37] The first four triplet-state energies have been estimated by Jaffé and Masmanides,[38] using two methods (CNDO/SCI using virtual orbital method, and direct SCF) and the values obtained were:

State	3A′	3A″	3A′	3A′
VO (eV)	2.81	4.25	3.84	4.02
SCF (eV)	2.51	3.83	[a]	[a]
Natural radiative lifetime (s)	18	0.004	11	1.7

[a] Not accessible to SCF calculation.

Bloor and Breen[39] have used simplified Roothahn calculations to provide a calculated dipole moment of 2.34D (the observed moment is 2.31D [40]) and to provide a plot of ^{13}C chemical shift against total electron density. Gondo, Masanori, and Kanda have studied the effect of two-centre Coulomb repulsion integrals on spin density and expectation values of S^2 in radical anion and cation by unrestricted Hartree–Fock calculation; the Pariser–Parr approximation was said to give better results for magnetic properties than the Nishimoto–Mataga approximation.[41] Transition energies for the radical cation have been calculated[42] by using published photo-electron and optical spectra. Discussion of the deficiencies of the Pople and of the extended Hückel theory in predicting ^{13}C chemical shifts has been given with the experimentally determined values by Pugmire, Grant, Robins, and Robins.[43] Calculation of hyperfine splittings for protons and ^{14}N in the radical anion showed that best results were achieved by using a restricted Hartree–Fock treatment with configuration interaction.[44] Electron-density calculations for the excited singlet and for the excited triplet state have suggested that quinoline should show increased

basicity in the excited singlet state, but decreased basicity in the excited triplet state, relative to the ground state.[45]

One alternative theoretical method used in calculations on quinoline is the Variable Electronegativity SCF approach favoured by R. D. Brown and his co-workers[46–48] which has produced good calculated values for dipole moments (2.33D against experimental values[48, 49] for the vapour state of 2.31 or 2.29D); another alternative is the "frontier electron" theory of Fukui. He and his co-workers suggested[50] that reaction should occur at the position having the highest density of electrons in the "frontier orbitals"; these are defined according to the type of reaction, namely the highest occupied orbital in electrophilic substitutions, the lowest vacant orbital in nucleophilic substitutions, and both these orbitals in radical substitutions. The calculated density of "frontier electrons" for electrophilic and for nucleophilic reactions on quinoline is indicated in Fig. 3.[51] The chemical reactivity of quinoline towards

(A) (B)

Fig. 3. Calculated density of "frontier electrons" calculated[51] for electrophilic (A) and nucleophilic (B) reactions on quinoline

nucleophilic substitution by OH^-, BF_4^-, and CN^-, and also towards sulphonation, nitration, and mercuration, has been calculated[52] by the method of Klopman and Hudson.[53]

A more interesting development is the return to the "dynamic" method of calculation in which both reagent and aromatic substrate are considered.[54, 55] In application of this approach to quinoline[55] the objectives have been to obtain satisfactory explanations of the differing ratios of 2-substituted and 4-substituted quinolines when strong or weak nucleophiles attack 1-alkylquinolinium salts, and also the change in electrophilic substitution pattern observed in weak acid (3-, 6-, and 8-substitution) as against strongly acid media (5- and 8-substitution). The attacking species has been represented by a single orbital with energy in the form of $\alpha_x = \alpha^0 + K\beta^0$; agreement with the Wheland intermediate model was reasonable, and a satisfactory gradation from 4-substitution to 2-substitution was obtained on passing from a weak nucleophile (CN^-) to a stronger nucleophile (OH^-). However, it was not possible to correlate the observed nitration in weak acid (3- > 6- and 8-substitution) with the delocalized transition-state molecule; it had previously been suggested[56] that an addition–elimination mechanism may operate (this suggestion is dealt with in more detail on p. 60).

III. Physical Properties

1. Electronic Spectra

The spectrum of quinoline in the ultraviolet region was recorded as long ago as 1910.[57, 58] Purvis[57] found absorption bands in the regions 317–310, 308–303, and 303–289 nm in an alcohol solution and also in the vapour phase; Dobbie and Lauder recorded more absorption bands in 1911.[59] Since then a considerable number of

measurements have been made; a detailed modern determination is given in Fig. 4.[60] The maxima have been assigned as ^1L_a (275 nm) (highest occupied to lowest vacant) with degeneracy giving ^1L_b (weak, 315 nm) and ^1B_b (intense, 232 nm),[61] and the ^1L_a transition calculated as polarized at 29° 13′ to the x-axis.[62] Singlet → singlet transitions have been studied in dilute solutions in melt-grown single crystal hosts at 4.2 K.[63]

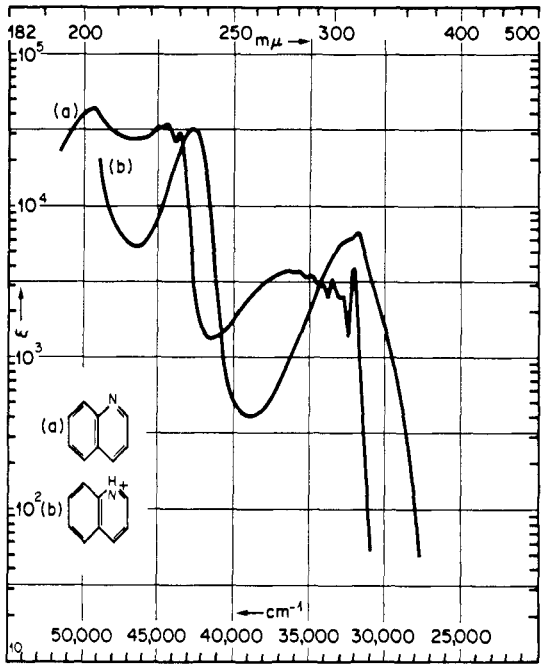


Fig. 4. Ultraviolet spectrum of quinoline. Reproduced, by permission of Messrs. Butterworths, London, and Verlag Chemie, Weinheim, from the DMS UV Atlas, London, 1966, Spectrum H1/1

Most reported spectra of the free base have been determined in polar media such as ethanol,[64-74] methanol,[75, 76] or water[68, 74, 77-81] Non-polar solvents used were hexane,[74, 82-84] cyclohexane,[76, 85] and chloroform.[86] Addition of alcohols to hexane solutions of quinoline gave increasing intensity to the 287 nm band and moved the 269 nm band to longer wavelengths.[84] Equilibrium constants for the quinoline–ROH (1 : 1) complexes were determined.[84] The slight changes in the spectrum observed when solutions of quinoline in aqueous and in cyclohexane solutions were compared was interpreted as a demonstration of an $n \rightarrow \pi^*$ transition in quinoline, although no marked inflection could be observed.[87] An alternative approach to the identification of an $n \rightarrow \pi^*$ transition in the quinoline spectrum through the electronic spectrum involved the addition of small amounts of acid to a hexane solution of quinoline (the acid being itself undissociated in this solvent); the $n \rightarrow \pi^*$ transition was said to be at 318 nm ($\varepsilon = 80$).[88] A line spectrum of quinoline vapour was reported to show $n \rightarrow \pi^*$ lines at 312.5, 313, and 313.3 nm;[89] Byrne and Ross[90] have

since suggested that the $n \rightarrow \pi^*$ transitions quoted by Mataga and his co-workers[89] were due to isoquinoline impurity and that the first transition is $\pi \rightarrow \pi^*$. A more recent determination of the electronic spectrum in the vapour phase has shown that the strongest band in the $n \rightarrow \pi^*$ region, undiminished at low pressure, is at 32,245 cm^{-1} (310.1 nm); assignment of other bands to excited state vibrations were also made.[91] The electronic spectrum of quinoline in a naphthalene host crystal at 4 K has been determined;[92] the polarized absorption spectrum was given an electronic origin at 29,754 cm^{-1} and one $n \rightarrow \pi^*$ singlet state was identified.

The spectrum of the quinolinium ion has been determined in hydrochloric[64, 70, 71, 73, 77, 79, 93, 94] and in sulphuric acid;[80, 95] the spectrum in aqueous hydrochloric acid is shown in Fig. 4. In the cation the ^1L_a band moved to longer wavelength while the ^1L_b band was little changed; hence the spectrum appeared to have two bands only, although a shoulder could be distinguished on the longer-wavelength band. The effect of hydrogen bonding on the spectrum has been discussed.[89, 96] Spectra taken at low temperatures (for example, in ethanol–ether at −83 °C) showed much improved fine structure;[97–99] a small foreband could be distinguished at 31,200 cm^{-1} (320.5 nm; $\log_{10} \varepsilon$ 1.8) in the spectrum of the free base.[98] The absorption spectrum of the quinoline radical anion showed a maximum at 720 nm ($\varepsilon = 2730$).[100] By γ-irradiation of quinoline in suitable glasses at 77 K the absorption spectra of either the radical anion or the radical cation could be observed.[101] The radical anion was formed in tetrahydromethylfuran, the radical cation in *sec*-butyl chloride, and the radical cation was formed by abstraction of an electron from the π-system.

The fluorescence and phosphorescence of quinoline and of the quinolinium cation have been thoroughly investigated. A complete emission spectrum of quinoline has been published,[102] recorded in glasses at 77 K. In ether–pentane–alcohol (EPA) there were fluorescence bands at 313.7, 322, 326.8, 335.5, 342, 351.2, and 357.8 nm; phosphorescence bands were at 456, 467, 487, 500, and 526 nm, and a charge-transfer maximum was observed at 382 nm. A list of energies for various states has been obtained from the threshold electron excitation spectrum.[103] These were 2.45 eV ($n \rightarrow \pi^*$, t), 3.00 eV ($^3B_{2u}$, t), 3.80 eV ($n \rightarrow \pi^*$, s), 4.15 eV ($\pi \rightarrow \pi^*$, s), 4.65 eV ($\pi \rightarrow \pi^*$, s), 5.25, 6.10, and 7.35 eV ($\pi \rightarrow \pi^*$, s). The fluorescence of quinoline is extremely weak unless hydrogen-bonding solvents are used; a variety of values has been recorded for the range of emission. For a cyclohexane solution a value of 330 nm has been recorded (giving a $\Delta\lambda$ of 13 nm);[104] a stronger emission was obtained in ethanol,[105] with a maximum around 400 nm. The latter value is in the range ascribed[89] to the quinolinium cation fluorescence (340–440 nm). Mataga and his co-workers reported the change in fluorescence intensity with change in solvent, from 10^{-3} in benzene, through 3×10^{-2} in ethanol or butanol, to 1.0 for aqueous solutions at pH 4.79. An examination of the fluorescence of quinoline in ethanol at 93 K showed much fine structure in the fluorescence band, which must, therefore, be derived from the ^1L_b band.[106] In contrast, the fluorescence spectrum of quinolinium perchlorate showed a strong and unstructured band, with a maximum around 390 nm and is derived from the ^1L_a band.[106] Zimmerman and Joop also reported the absorption-polarization and the fluorescence-polarization spectra.[106] Schulman and Capomacchia[107] have reported a dual fluorescence of the quinolinium cation. They observed a blue quinolinium fluorescence maximum at pH 4 which remained essentially constant until a Hammett acidity of zero in dilute sulphuric acid was reached; with further increase in sulphuric acid concentration a sharp rise in fluorescence intensity was observed, culminating at H_0 −4. A discussion of the relative acidities of the ^1L_a and ^1L_b states of the quinolinium cation and of the possibility that the two states are nearly degenerate led to the suggestion that

thermal equilibrium between the states only obtains when the medium is sufficiently acidic to protonate both. Excimer fluorescence in quinoline (160 K) has been reported at 400 nm,[108] and so has the formation of hetero-excimers between quinoline and electron donors.[109]

Fluorescence quenching has been noted when halide ions were added to quinolinium sulphate solutions; the quenching efficiency increases from chloride to iodide.[110] Other quenching studies showed that *o*-aminophenol was the most effective quencher in a series of phenols for the fluorescence of the quinolinium cation, and that the decay of intensity with quencher concentration followed the Stern–Volmer equation.[111] The bimolecular quenching constant for hydrocarbons with quinolinium sulphate has been determined; it was suggested that in the excited state of the hydrogen-bonded complex a hydrogen is transferred from salt to hydrocarbon, an electron donor–acceptor pair is formed, and that subsequent electron transfer occurs.[112] A number of other reports on the fluorescence of quinoline are also available.[113-119]

The phosphorescence spectra of quinoline[102, 120, 121] and of the quinolinium cation[102, 121] have been determined (in ethanol at 90 K and in EPA at 77 K), and the values used to calculate pK_T (5.8).[121] There is general agreement that the phosphorescence maximum is at 21,800 cm^{-1} (458.7 nm) and Dörr and Gropper have reported that the polarization of the phosphorescence spectrum is strongly negative, indicating a transition moment at right angles to the plane of the molecule.[120] This direction of polarization has been confirmed by measurement of the polarization of phosphorescence in a quinoline–tetrachlorophthalic anhydride charge-transfer complex.[122] The mean lifetime of phosphorescence at 77 K has been shown to be shorter in methylpentane (0.9 s) than in an EPA mixture (1.3 s);[102, 123] this has been taken as evidence for vibronic interaction between (n, π^*) and (π, π^*) triplet states.[123] A similar argument has been used to explain the quenching of fluorescence of quinoline in hydrocarbon solvents relative to that of quinoline in hydroxylic or polar solvents.[123] Several authors have compared the phosphorescence : fluorescence ratios of quinoline and of naphthalene; the former is higher, indicating a higher probability of inner conversion (singlet to triplet) in quinoline.[124, 125] While the ratio is independent of solvent for naphthalene there is an increase in the fluorescence of quinoline when small quantities of hydroxylic compounds are added; this has been ascribed to the formation of hydrogen bonds by the quinoline–nitrogen lone pair, with diminishing probability of inner conversion to the triplet state.[126] Sensitization of quinoline phosphorescence by carbazole (donor) in a glassy medium at 77 K was said to show efficient triplet–triplet energy transfer ascribed to a hydrogen-bonding interaction.[127] The phosphorescence spectra of quinoline in an *n*-pentane solution at 90, 120, and 140 K were found to differ from those in *n*-hexane or in *n*-heptane over a roughly similar temperature range.[128] Increasing pressure (0–40 Kbar) has been shown to have little effect on the intensity of phosphorescence of quinoline in plastic matrices; a steady drop in lifetime was observed.[129] Studies of phosphorescent quinoline in durene crystals at 1.2 and 4.2 K with pulsed microwave showed a Carr–Purcell multiple spin echo for the T_z–T_x transition at 3598 MHz;[130] under similar conditions an ENDOR spectrum in zero field gave a quadrupolar ^{14}N splitting in the phosphorescent state $\nu_- = 3.04$ and $\nu_+ = 4.57$ MHz.[131]

The lowest triplet level of quinoline is metastable, and it has been shown that a sufficiently high concentration of molecules in this state can be built up to obtain triplet–triplet excitation on further irradiation.[132] The excited triplet has a high energy (42,250 cm^{-1}, 236.4 nm), is yellow, and has a lifetime of 0.5 s. An attempt was made to determine the fate of these highly excited triplet molecules by searching for the fluorescence from the lowest excited singlet state with a lifetime identical with

that of the metastable excited triplet state.[133] It was established that excited triplet–singlet crossing could be only a minor pathway in the de-excitation of excited triplet molecules.

The quantum yield for radiationless intersystem crossing has been shown to be 0.5 ± 0.1 (in an alcohol glass at 77 K) and 0.43 ± 0.08 (in a hydrocarbon glass), almost twice that of naphthalene.[134] The decay rates from individual spin levels of quinoline (in durene at 1.5 K) have been studied; the effect of sudden saturation of a microwave transition between a pair of spin levels was observed.[135] Such sudden sweeping by microwave of a zero-field resonance during phosphorescent decay resulted in spectacular changes in the intensity of phosphorescent emission, thought to be due to a transfer from a populated non-radiative state to an empty radiative state.[136] Electron-spin echoes have been observed in a photo-excited triplet state in zero magnetic field.[137]

Much work has been done on the triplet–triplet spectrum of quinoline; the triplet–triplet components were reported to deviate by a maximum of 25° in polarization angle from the *x*-axis.[138] The extinction coefficient of the 400 nm triplet–triplet transition was found to be 7.1 $(\pm 0.7) \times 10^3$ l mol^{-1} cm^{-1};[139] in ethanol solution biphotonic reaction measurements gave an extinction coefficient at 425 nm of (6.5×10^3).[140] Differences between singlet–singlet and triplet–triplet absorption spectra for quinoline in a hydrocarbon glass at 77 K (15,000–45,000 cm^{-1}) have been reported, and new bands assigned to transitions from the lowest triplet state to a triplet state doubly excited with respect to the closed-shell ground state.[141] Dimethylmercury solutions of quinoline have been used when measuring the singlet–triplet absorption spectrum.[142]

TABLE 1. Charge-transfer Complexes of Quinoline

Acceptor	Temp. (K)	Solvent[a]	λ (nm)	ε	Ref.
Trinitrobenzene	77	E/IPA	505		143
p-Benzoquinone	77	E/THF/M	520		143
p-Benzoquinone	—	Ethanol	390, 500		148
Tetrachloro-1,4-benzoquinone	77		605		143
Iodine	298	$CHCl_3$	398 (402)	1520	149, 150
ICl_3					151
Tetrachlorophthalic anhydride			355		152

[a] E = Ether. IPA = Isopropyl alcohol. THF = Tetrahydrofuran. M = Methanol.

Quinoline forms a number of charge-transfer complexes, acting as donor. Spectral details of some of the better-characterized examples are given in Table 1. Some of the complexes were reported[143] to have very low stability, showing much reduced intensity of absorption at temperatures much above 77 K; and this has cast doubt on many earlier reports of complex formation.[144] Most of the complexes reported are of the n–π type, although it has been suggested that with the rather diffuse π-orbital of tetrachlorophthalic anhydride a π–π complex is involved.[122] A number of stable charge-transfer complexes with interhalogen compounds have been reported, but no spectral details were given.[145] Low-temperature luminescence spectra of quinoline on zeolites have been said to confirm the presence of acidic centres in the zeolite.[146, 147]

2. Infrared and Raman Spectra

A few very detailed studies of the infrared absorption of quinoline have been made; the spectrum is shown in Fig. 5.[153] The CH stretching bands have been reported[154] at 3058, 3039, 3012, 2950, 2932, and 2578 cm^{-1}, and the harmonic and combination bands at 1953 (m), 1931 (m), 1898 (w), 1842 (vw), 1815 (w), and 1745 cm^{-1}.[155-157]

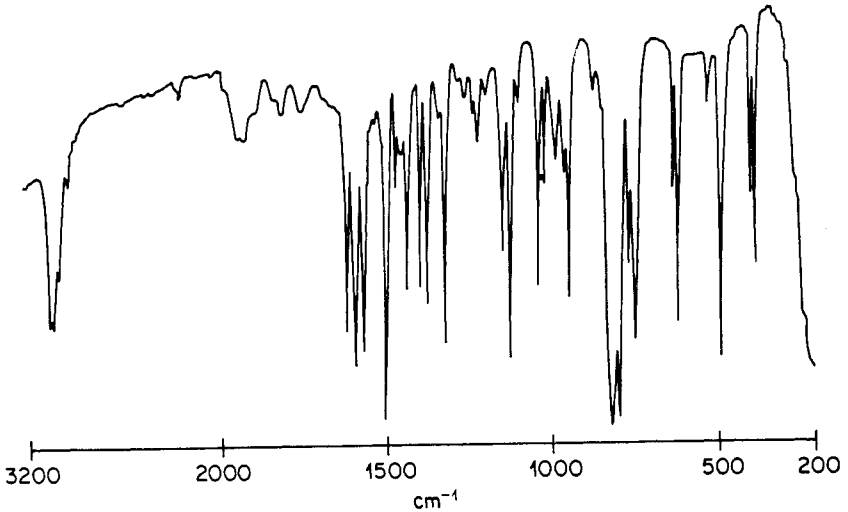


Fig. 5. Infrared spectrum of quinoline. Reproduced, by permission, from S. C. Wait, Jr., and J. C. McNerney, *J. Mol. Spectrosc.*, **34**, 56 (1970)

The region from 1650 to 650 cm^{-1} has been the subject of several detailed reports;[91, 153, 155, 158-162] one of these includes a study of a number of deuteriated quinolines.[160] Chiorboli and Bertoluzza made virtually complete assignments of all the bands, based on previous assignments for bands in naphthalene,[155] but one of their assignments was rejected by Katritzky and Jones,[158] and many more by Wait and McNerney.[153] Wait and McNerney have completely assigned the fundamentals, many of their changed assignments following from changes in naphthalene assignments. They reported out-of-plane force constants and planar force constants, using calculated geometry, and statistical thermodynamic functions. Additional interest in the CH out-of-plane deformation region has centred on attempts to determine substitution patterns (for example in the alkylquinolines[163]) but the results tend to be ambiguous. The spectrum of quinoline at very long wavelength (70–250 cm^{-1}) has been measured, both free (in cyclohexane)[164, 165] and adsorbed on a commercial aluminosilicate catalyst.[164] The infrared absorption of quinoline hemiperchlorate has been reported.[166] An $\overset{+}{N}H$ deformation in the quinaldinium ion was assigned[167] at 1298 cm^{-1} with the $\overset{+}{N}D$ band at 950 cm^{-1} and it seems very likely that the position of the bands would be very similar in the quinolinium ion. Intermolecular vibration spectra of solid and liquid quinoline from −120 to +60 °C have also been reported.[168]

The Raman spectrum of quinoline has been determined and the bands fully assigned first by Chiorboli and Bertoluzza[155] and again by Wait and McNerney;[153] there are, moreover, other reports.[91, 169-175] The Raman spectra of quinoline and phenol, and of quinoline and acetic acid, have also been reported.[155] Much has

been published since 1970 on light scattering of laser-produced light; most of the interest has been in physics rather than in chemistry.[176-185]

The infrared spectrum has found limited use in analysis; the bands used were in the 938 and 1093 cm^{-1} regions for mixtures of quinoline and tetrahydroquinoline,[186] and in the 802 and 823 cm^{-1} regions for mixtures of quinoline and isoquinoline.[187] Changes in the region round 1000 cm^{-1} have been used to show complexing between quinoline and halogens or interhalogens;[188] the infrared spectrum of the quinoline and iodine charge-transfer complex was said to resemble those of the hydrogen-bonded quinoline–phenol spectra.[189] The Raman and infrared spectra have been determined for molecular compounds between quinoline and boron trifluoride, and the infrared spectrum has been measured for quinoline and aluminium chloride.[190]

3. Nuclear Magnetic Resonance Spectra

The various nuclear magnetic resonance spectra of quinoline (^1H, ^{13}C, ^{14}N, and ^{15}N) have all been determined, and in most cases completely analysed. The ^1H-nmr. spectrum of quinoline at 100 MHz has been reported and completely analysed;[191] a 220 MHz spectrum has been published[192] and shifts and coupling constants from a

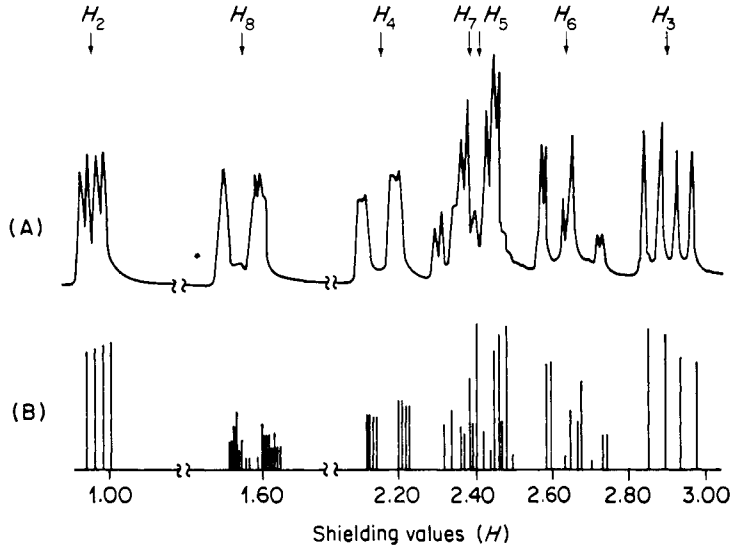


Fig. 6. The 100 Mhz nmr spectrum of quinoline. (*a*) Experimental; (*b*) calculated; as pure liquid. Reproduced, by permission, from P. J. Black and M. C. Heffernan, *Austral. J. Chem.*, **17**, 558 (1964), Fig. 6

220 MHz spectrum have been assigned.[193] The 100 MHz spectrum is shown, with a calculated spectrum, in Fig. 6. In Table 2 are shown the chemical shifts (δ) for each proton of quinoline, neat, in neutral (CCl_4) solution,[191] and in trifluoroacetic acid (0.5M).[194] Also shown are the coupling constants used in the calculated spectrum,[191] all of which were assumed to have the same sign, as had previously been shown to be the case for the 2-, 3-, and 4-protons.[195]

The coupling constants for neutral quinoline have been shown to have the same relative sign, which was said to be positive.[193] Particularly interesting in the coupling constants are the widely differing values of $J_{2,3}$ and $J_{3,4}$, and the cross-ring coupling, $J_{4,8}$, first demonstrated for some substituted quinolines by Anet.[196] There are also other recorded spectra.[197, 198]

TABLE 2. ^{1}H-Nmr Data for Quinoline

Chemical shifts								
Proton	1	2	3	4	5	6	7	8
δ (neat)[191]		9.52_2	7.10_2	7.82_7	7.58_1	7.34_9	7.59_8	8.43_1
δ (CCl_4)[191]		8.80_8	7.26_3	8.00	7.68_5	7.43_1	7.61_3	8.05_5
δ (TFA)[194]	14	9.12	8.07	9.00_7	8.3	8.05	8.23	8.34

Coupling constants[191] (in CCl_4)										
Protons	2, 3	2, 4	3, 4	5, 6	5, 7	5, 8	6, 7	6, 8	7, 8	4, 8
Value in Hz	4.1_9	1.7_5	8.2_8	8.2_2	1.4_6	0.5_5	6.9_2	1.0_9	8.6_2	0.9

The effect of varying solvents on the relative shifts of the different protons in quinoline has been studied by a number of workers. Schaefer has used *n*-hexane, acetone, and benzene;[199, 200] the shifts were plotted relative to their position for carbon tetrachloride as solvent[191] (including also pure liquid values). The effects (largely of shift to higher field in benzene, and to lower field in acetone) appear to reach a maximum for protons 3 and 4 (almost 1 ppm for the 3-proton in benzene). Ronayne and Williams[201] arrived at rather smaller shift differences for benzene solutions (a maximum of 0.6 ppm) and noted a slight downfield shift of the 8-proton; they interpreted the benzene shifts as due to the benzene solvation of the positive end of the quinoline dipole. Such oriented solvent molecules will have an anisotropic shielding effect on positions 3 and 4; position 8 is at the negative end of the quinoline dipole. It has been found that in hexamethylphosphoramide the 8-proton signal is displaced upfield and the 4-proton signal downfield, reversing their usual displacement;[100] in dimethyl sulphoxide there are small downfield shifts of the signals for proton 2 and proton 3.[202]

The assignment of signals for individual protons given in Table 2 has been confirmed by determination of the pmr spectra of all the monodeuterioquinolines;[203] comparison of the observed spectra with those calculated by using the parameters derived by Black and Heffernan[191] showed a slight downfield shift in the observed spectrum. Other workers have reported the ^{1}H-nmr spectrum of 5,6,8-trideuterioquinoline[204] and of 2,7,8-trideuterioquinoline.[205]

As expected, the absorptions for the heterocyclic ring protons shift to a lower field under acid conditions (Table 2). A study of the system quinoline–trifluoroacetic acid has shown that the 4-proton is most affected but that the shift is concentration-dependent, reaching a maximum for a 2 : 1 acid-to-base ratio;[206] a comparison with chemical shifts determined in acetic acid is available.[207] It has also been observed that *N*-protonation has a very specific effect on the coupling constant between H-2 and H-3, raising it by 1.5 ± 0.2 Hz whereas other coupling constants change by only 0 ± 0.3 Hz.[208] A similar effect is shown when a Lewis acid (such as BF_3) is present.[208]

The ^{13}C chemical shifts for all the carbon atoms in quinoline have been determined in neutral and in acidic media and are given in Table 3.[43, 209]

Curves for pH against ^{13}C shift for all quinoline carbon atoms have been published[210] and show some disagreement with the values quoted in Table 3, notably

in the reversed behaviour of carbon atoms 5 and 8. The titration curves could be used to estimate the pK_a of quinoline, giving values around 4.5. Variations of the shifts with concentration (in an acetone solution) were also reported.[209]

The ^{13}C–H coupling constants have been determined for position 2 (177.5 Hz) and for position 3 (163.5 Hz); from those observed for some monomethylquinolines it would be expected that the constant for position 4 would be in the range 157–160 Hz and that for position 8 about 160 Hz.[211]

TABLE 3. ^{13}C-Nmr Shifts of Quinoline Carbon Atoms[a]

Position		2	3	4	5	6	7	8	9	10
Shift	(CCl_4)	150.89	121.67	136.12	128.46	126.95	129.86	130.5	149.28	128.89
	(CH_3OH)	150.46	121.77	136.98	128.37	126·85	130.18	129.11	148.12	128.78
	(H_2SO_4)	144.94	122.75	149.39	130.19[b]	131.64	136.88	120.92[b]	137.74	129.76

[a] In ppm from TMS. [b] C-5 at ~120 and C-8 at ~129 in ref. 210.

The ^{14}N chemical shift for quinoline has been reported as $+72 \pm 0.2$ ppm relative to nitrate,[212] and as $+71 \pm 3$ ppm with a half-height signal width of 650 ± 15 Hz.[213–215] The decoupled ^{14}N signal for a solution of quinoline in acetone was reported at -292.8 ± 1 relative to the ammonium ion signal.[216] The quinolinium ion absorption shows a considerable shift difference appearing at $+185 \pm 2$ ppm, and appears as a doublet with a $J_{N,H}$ of 68 ± 1 Hz. The ^{15}N completely decoupled signal (for a carbon tetrachloride solution) appears as a singlet at 288.5 ppm downfield from $^{15}NH_4Cl$.[209] In methanol there was a slight upfield shift to 273.7 ppm, which, when compared with that of the fully protonated quinolinium nitrogen (sulphuric acid) at 159.4 ppm, indicated approximately 19% of protonation by methanol.

The ^{15}NH coupling constants have been reported for quinoline and for its ethiodide and *N*-oxide.[217] In aprotic solvents the $J_{^{15}N-H2}$ is -11.1 Hz and the $J_{^{15}N-H3}$ is -1.4 Hz; thus the ^{15}N fully coupled signal appears as a doublet (1 : 1) of triplets (1 : 2 : 1) due to coupling with H-2 (large) and then with H-3 and H-8 (approximately equal).[209] Protonation or quaternization causes a spectacular drop in the value of $J_{^{15}N-H3}$ to -4.5 Hz. All the ^{15}N–^{13}C coupling constants have been determined, and are given in Table 4 for solutions in carbon tetrachloride, methanol,

TABLE 4. ^{13}C–^{15}N Coupling Constants of Quinoline (in Hz)

^{13}C Position	2	3	4	5	6	7	8	9	10
CCl_4	1.4	2.7	3.5	~0	0.9	3.9	9.3	0.6	2.1
CH_3OH	2.4	2.6	3.7	~0	~0	3.9	8.4	8.4	2.0
H_2SO_4	15.9	~1.0	4.6	~0	~0	2.7	~1.0	13.8	<1.0

and sulphuric acid. The most notable changes with differing solvents are those in C-2 and C-9 (much increased on protonation) and in C-8 (much decreased on protonation), the last being ascribed to a lone-pair effect.[209]

A number of efforts have been made to correlate nmr shifts with electron density[17, 39, 43, 194, 218, 219] or with reactivity indices.[220]

Several detailed studies of the effect on the nmr spectra of quinoline caused by paramagnetic shift reagents have been published.[192, 221–232] An examination of the contact shifts induced in ^1H and ^{13}C chemical shifts by nickel acetylacetonate[192]

TABLE 5. Lanthanide Shifts for ^{1}H and ^{13}C Signals in Quinoline

Nucleus	$Pr(fod)_3$[a]	$Pr(dpm)_3$[a, b]	$Nd(dpm)_3$[a]	$Eu(fod)_3$[a]	$Eu(dpm)_3$[a,b]	$Gd(dpm)_3$[a]	$Dy(dpm)_3$[a]	$Ho(dpm)_3$[a]	$Er(dpm)_3$[a]	$Yb(dpm)_3$[a, c]
C-2	+139.8	+99.5	+55.0	−119.5	−90.0	−76	+558	+152	−196	−139
C-3	+ 37.1	+27.5	+ 9.0	0	− 6.0	+27	+251	+ 86.5	− 56.5	− 50.0
C-4	+ 33.5	+25.0	+12.5	− 29.0	−22.0	−14	+169	+ 48.5	− 65.0	− 44.5
C-5	+ 21.5	+15.5	+ 7.0	− 10.8	− 7.5	0	+123	+ 42.0	− 37.5	− 28.5
C-6	+ 15.5	+11.0	+ 5.5	− 12.0	− 7.0	0	+101	+ 32.0	− 32.5	− 23.0
C-7	+ 26.3	+18.5	+12.0	− 24.6	−14.0	− 9	+126	+ 38.0	− 48.0	− 28.0
C-8	+ 80.1	+54.0	+30.0	− 69.3	−46.0	−29	+374	+109	−137	− 83.0
C-9	+ 87.3	+71.5	+33.5	− 55.0	−44.0	+11	+601	+208	−178	−144
C-10	+ 26.3	+20.0	+ 2.5	+ 9.6	+ 2.5	+49	+277	+ 98	− 59.5	− 57.5
H-2	+ 74.1	+53.5 (59.4)	+22.0	− 27.3	−24.5 (25.1)		+465	+123	−112	− 74.0 (85.2)
H-3	+ 20.7	+16.0 (17.0)	+ 7.0	− 10.1	− 8.0 (7.95)		+135	+ 39.5	− 37.0	− 27.5 (31.5)
H-4	+ 17.0	+13.5 (13.6)	+ 5.5	− 10.9	− 7.5 (7.63)		+112	+ 33.0	− 34.5	− 25.0 (27.6)
H-5	+ 13.3	+ 9.0 (10.2)	+ 4.5	− 7.9	− 5.5 (5.18)		+ 84.0	+ 29.5	− 27.0	− 20.0 (22.0)
H-6	+ 10.4	+ 7.5 (7.46)	+ 4.0	− 7.4	− 4.5 (4.27)		+ 60.5	+ 21.0	− 27.0	− 13.5 (14.2)
H-7	+ 11.9	+ 7.0 (8.34)	+ 4.0	− 7.1	− 4.0 (3.18)		+ 77.0	+ 23.5	− 22.5	− 13.5 (13.3)
H-8	+ 61.5	+44.5 (49.0)	+22.0	− 39.6	−22.0 (20.6)		+423	+136	−147	− 74.0 (78.6)

[a] Ref. 221. [b] Ref. 223 (parentheses). [c] Ref. 228 (parentheses).

showed that ^1H contact shifts were all downfield except for H-6; for the ^{13}C absorptions C-2 and C-4 showed upfield shifts; a detailed discussion of contact shifts and spin densities was given. The most comprehensive study of lanthanide shifts has been made by Chalmers and Pachler,[221] who also calculated contact and pseudocontact for the $Eu(dpm)_3$ reagent and gave ratios for the other lanthanides. The lanthanide shifts of ^1H- and ^{13}C-nmr signals are assembled in Table 5 (p. 14), extrapolated in all cases to a quinoline–lanthanide ratio of 1.0; downfield shifts are negative. It should be noted that in one case, that of $Eu(pta)_3$, the shifts continue to change for H-2 and H-8 (in the latter, passing through a maximum) with further addition of shift reagent above the 1 : 1 ratio usually quoted.[230]

Other discussions of the contribution of contact and pseudocontact contributions are available;[222, 223, 233] in general there is agreement that the nitrogen–lanthanide axis is displaced slightly from the N–C-4 line, away from the carbocyclic ring. The nitrogen–lanthanide distance has been estimated as 3.87 Å.[221] In general it appears that contact terms are very small in ^1H-spectra; in ^{13}C-spectra the contact effects are much larger for europium than for praseodymium shift reagents. Reuben and Leigh[223] also discussed the line broadening and the change in longitudinal relaxation rate for the ^1H-spectrum. They gave the dissociation constant of the $Eu(dpm)_3$–quinoline adduct in carbon tetrachloride as 0.07 M and its mean lifetime 2×10^{-7} s; the mean lanthanide–nitrogen distance in the adducts was estimated as 4.0 Å.

A number of studies of relaxation phenomena in quinoline, alone[224–226] and mixed with amines[226] have been reported. The spin–lattice relaxation of ^{15}N in quinoline was said to be due to dipole–dipole interaction;[224, 225] others have correlated spin–spin relaxation times T_2 for ^{14}N with viscosity, alone or mixed with aniline in solutions in carbon tetrachloride and in carbon disulphide.[226, 227]

4. Electron Spin Resonance

The esr spectrum of the quinoline radical anion has been reported by a number of workers.[100, 234–236] The hyperfine splitting constants for solutions of quinoline radical anion in hexamethylphosphoramide (HMPA)[100] and in tetrahydrofuran (THF)[236] are given in Table 6; the assignments are in both cases uncertain to some degree.

TABLE 6. Hyperfine Splitting Constants for the Quinoline Radical Anion

Atom	1 (N)	2	3	4	5	6	7	8
G (HMPA)[100]	3.95	3.29	1.26	7.80	3.90	1.14	2.02	3.46
G (THF)[236]	3.83	4.40	0.86	8.44	4.06	0.73	2.40	2.73

In one case[100] a simulated spectrum was given, obtained by using the experimental splitting constants. Paramagnetic resonance measurements have also been reported for the phosphorescent (triplet) state of quinoline,[237, 238] confirming the polarization as perpendicular to the plane of the molecule and the $\pi \rightarrow \pi^*$ derivation of the phosphorescent state.

By irradiation of halogenoquinolines with sodium atoms in argon matrices first with "red light" ($\lambda > 580$ nm) (producing haloquinoline anions) and then with "yellow light" ($\lambda > 500$ nm), esr signals due to the 2-quinolyl, 3-quinolyl, and 4-quinolyl radicals were obtained.[953] All were found to be σ-radicals, but unlike the pyridyl radicals they were stable to ultraviolet irradiation.

5. Mass Spectrum

The mass-spectral fragmentation pattern of quinoline shows little of interest. The base peak is due to the molecular ion (129) and the only important fragmentation appears to be loss of HCN (27) from the molecular ion.[239, 240] This process has been studied by using partially deuteriated quinolines (2-$^2H_1$-quinoline, 3-$^2H_1$-quinoline, and 5,6,8-$^2H_3$-quinoline) and two different experimental approaches lead to the conclusion that there is complete randomization of hydrogen over the quinoline ring before HCN elimination.[241] Multiply charged ions have been reported; they were suggested as a general experimental empirical indication of aromatic character.[242] Photoionization of quinoline, in which proton transfer took place, was followed by mass-spectral appearance potentials of primary and secondary ions at 7–13 eV.[243]

6. Photoelectron Spectroscopy and Electron Spectroscopy (ESCA)

The photoelectron spectrum of quinoline has been determined[244–247] and orbital correlations performed. The bands at 8.62, 9.20, and 10.58 eV have been assigned respectively to a_u, b_{1u}, and 6_{2g}, with the lone-pair band 9.2–9.3 eV.[245] These values were confirmed by Spanget–Larsen,[246] who used an interactive Hückel level method to calculate the thirteen highest molecular orbital energies; the remaining two π-levels occurred close to 11.5 and 13 eV.

The bonding energy determined by electron spectroscopy of quinolinium bromide has been compared with those of *N*-ethylquinolinium bromide, *N*-(*n*-butyl)quinolinium bromide, and *N*-(*n*-butyl)quinolinium iodide; the hydrobromide had an electron binding energy of 398.5 eV compared with figures of 399.2–399.6 eV for the quaternary compounds.[248]

7. X-ray Diffraction

As mentioned on p. 3, there is no X-ray structure determination available on a simple quinoline derivative; the bond lengths given there are for quinoline contained in a nickel complex.[7] There is an early report of the X-ray diffraction of quinoline liquid.[249]

8. Separation, Identification and Purification

The problem of separating quinoline from mixtures (usually with other bases of similar structure) has been examined by almost every chromatographic method. Paper chromatography, mainly on buffered paper (for example, sodium hydrogen phosphate and citric acid), has been performed with a variety of polar[250, 251] and non-polar[252–261] solvent systems. The use of paper impregnated with cupric chloride gave dark grey to grey-blue spots which were extracted and shown by polarography to be $(C_9H_7N)_2.CuCl_2.2H_2O$.[255] In other cases detection of the quinoline spots on the paper has been by Dragendorff's reagent (potassium bismuth iodide)[252, 260] and by iodine.[251] Another approach has been to treat the mixture containing quinoline with a reagent and to chromatograph the products; thus, a mixture of pyridine and quinoline was oxidized by hydrogen peroxide in acetic acid and, after reaction, chromatographed on paper, sprayed with acridine, and viewed under ultraviolet light.[262] There is one report of the paper chromatography of quinoline hydrochloride.[263] Quinoline bases were also separated by ionophoresis on Whatman 3MM saturated with DMF solutions of benzoic acid and sodium carbonate.[264]

More recently greater attention has been given to thin-layer chromatography (tlc), using silica gel[265–272] or alumina[258, 271, 273, 274] as adsorbents. The quinoline has been detected by treatment of the adsorbent with iodine vapour,[268] Dragendorff's reagent,[266, 270, 274] cupric chloride (adsorbent pre-treated),[258, 273] tetracyanoethylene,[271] potassium permanganate,[266] or *p*-(dimethylamino)benzaldehyde.[267] The borane complex of quinoline has been separated from other borane complexes by t.l.c. on alumina or silica gel.[275] A quantitative estimation of quinoline on paper impregnated with cation-exchange resin has been reported.[276] Alumina,[277–281] silica gel,[282] and calcium carbonate[278] have been used for column chromatography of quinoline. A separation of quinoline from isoquinoline has been reported by column chromatography of a nitrated mixture on alumina,[283] and a patent reports the separation of isoquinoline and quinoline on zeolite metallo-aluminosilicates of 10 Å pore diameter.[284] Quinoline was separated from isoquinoline by complexing components with metal salts (such as $CoCl_2$) on an adsorbent such as alumina.[285] Quinoline is among compounds subjected to gel permeation chromatography;[286] quinoline was separated from other aromatics on polystyrene gel in tetrahydrofuran, by utilizing a molecular-sieving effect.[287] The adsorption of quinoline and other aromatic compounds from methanol or propan-2-ol on to Sephadex LH-20 dextran has been related to resonance energies; bases such as quinoline were more strongly adsorbed than predicted, possibly because of hydrogen bonding.[288, 289]

Gas chromatography has proved very effective for the analytical separation of quinoline from mixtures; a variety of columns, polar and non-polar, have been used. Polar columns reported are polyethylene glycol, alone[290] or mixed with bases,[291] polypropylene glycol adipate,[292] hexakis(cyanoethyl)melamine,[293] "diglycerol",[294] polyethyleneglycol adipate[295–297] and succinate,[298] and trinitrofluorene.[298] Non-polar columns used have been mainly silicone oils and greases[292, 293, 299–303] with some reports of Carbowax,[304] Apiezon,[292, 305] and activated carbon.[306] A comparison of relative retentions of quinoline on four different columns over a range of temperatures has been made.[307] A mixture of silicone and Bentone 34 (on aluminosilicate) gave increased retention over silicone alone, owing to hydrogen bonding.[308] Most reports emphasize the necessity for a basic wash of the support (for example with potassium hydroxide[304] or sodium carbonate[296]) to avoid tailing, but there are reports of acid-washed supports.[298] Capillary columns[291, 309, 310] and inorganic salt eutectic packings[311] have also been used. Quinoline hydrochloride has been hydrogenated, acylated with propionic anhydride, and then subjected to gas chromatography.[312]

Large-scale separations of quinoline (as in the purification procedures used to isolate quinoline from coal tar oil) use distillation (see p. 18), distribution between solvents and acids, or precipitation and recrystallization of suitable salts. Distribution between benzene and 2N-hydrochloric acid (countercurrent) is reported to give quinoline of 99.5% purity from a mixture of quinoline and isoquinoline;[313] pure quinoline was obtained from technical-grade material by solution in 20% sulphuric acid, steam-distillation, and final distillation at 100 mm through a column of 40 theoretical plates.[314] Distribution of quinoline between a number of organic solvents and 3M-sodium perchlorate solution,[315] between aqueous methanol and iso-octane,[316] and between octan-1-ol and 50mM-sodium phosphate (pH 7.4),[317] has been studied, the last being said to be a measure of lipophilicity. Quinoline has been separated from quinaldine by countercurrent extraction, using dinitriles such as $(NCCH_2CH_2)_2O$ and saturated hydrocarbons,[318] and from isoquinoline by using a cyclohexane–benzene–aqueous buffer mixture.[319] Borate esters have been used to separate quinoline from isoquinoline and quinaldine.[320] The extraction of quinoline from non-aqueous solutions by cationic ion-exchangers in the H-form has been reported; stirring increased the rate of extraction by a factor of eight or more.[321]

The most commonly used preparative separation procedures make use of the differing solubilities of salts (principally phosphates and sulphates) of quinoline, isoquinoline, and quinaldine. The solubility of quinoline phosphate in water (155 g per l. at 20 °C [322]) is much less than that of isoquinoline phosphate, so that recrystallization provides a method of purification.[323] The solubility of quinoline dihydrogen phosphate in aqueous methanol and aqueous ethanol mixtures has been reported with a view to their use in purification.[324] The acid sulphate of quinoline is 2–3 times as soluble as isoquinoline sulphate in ethanol, and crystallization has been used to separate them.[325, 326] There are also reports of the use of the hydrochloride,[327] the zinc chloride/quinoline hydrochloride double salt,[328] and the hydrate[329] for purification; other notably insoluble salts of quinoline are the dichromate (7.0 g per l.),[322] the phthalate,[330] and the reineckate (stable to 215 °C and suitable for gravimetric analysis).[331] The phosphomolybdate is sufficiently insoluble for use to estimate phosphorus in geochemical samples.[332] Crystallizing quinoline from a melt followed by fractional melting was reported to give a one-cycle product of greater than 99% purity.[333] Quinoline has been separated from dodecane by thermal diffusion in an annulus having a temperature gradient of 25°.[334] Since quinoline is hygroscopic, final purification must involve drying (usually with barium oxide, although phosphorus pentoxide or ethylmagnesium bromide has been used), followed by fractional distillation with an efficient fractionating column.[335]

For detection and for estimation of quinoline a variety of visual and electrical methods have been used; a review has been published.[336] Colour test reagents used are Ehrlich's reagent (yellow or orange colour),[337, 338] ferric chloride with pyrogallol (violet),[339] reduction with zinc and hydrochloric acid with subsequent colour tests for the reduced quinoline,[340] conversion into a quaternary salt which gives sulphur dioxide when heated with sodium thiosulphate,[341] various cupric salt combinations,[338] a malonic acid–acetic anhydride mixture,[342] barbituric or thiobarbituric acids and malonates,[343] and oxidation with peroxydisulphate in acetic acid.[344] An olfactory method makes use of a mixture of an *N*-monosubstituted formamide and an arenesulphonyl chloride to obtain an isocyanide.[345] Spectrophotometric methods have made use of absorbance at 289 and 312.7 nm,[346] or at 802 and 823 cm^{-1}.[187] External heavy-atom effects have been used to increase the sensitivity of spectrophosphorimetry to 8×10^{-8} g ml^{-1}.[347, 348] A titrimetric estimation of quinoline has been reported, involving mercury thiocyanate;[349] an antimony microelectrode has been reported to detect the presence of quinoline in non-conducting solvents by potentiometric changes.[278] In addition to the reineckate, already mentioned, quinolinium salts have been estimated as periodides.[350]

9. Freezing Point, Boiling Point, and Azeotropic Data

The freezing point of pure quinoline has been reported as −15.6 °C [351, 352] and more recently by Witschonke as −14.94 °C.[353] The latter author gives a cryoscopic constant of −1.95 mole per cent per degree Centigrade. The calculated freezing point is −14.85 °C.[353] The boiling point of quinoline at 760 mm has been determined as 237.1 °C [351] and 237.63 °C.[354] The vapour pressure over a range of temperatures from 237.94 to 164.67 °C is given in Table 7, and the boiling point at pressures greater than 1 atmosphere in Table 8. The critical temperature of quinoline has been reported as 509 °C [356] and 515 °C.[355]

Some azeotropes of quinoline are given in Table 9;[357] boiling point data for mixtures of quinoline and isoquinoline have been determined.[358]

Deviations from Raoult's Law were reported for azeotropes of quinoline and *m*-cresol at 760 and 200 mm,[359] also in the binary system quinoline–*pseudo*-cumene,

and for *pseudo*-cumene, *m*-cresol, and quinoline at 760 mm (zero class of ternary mixtures),[360] as well as for *m*-cresol, naphthalene, and quinoline (second class, type one).[361].

TABLE 7. Vapour Pressure of Quinoline[354]

Pressure (mm Hg)	Temp. (°C)	Pressure (mm Hg)	Temp. (°C)
765.23	237.94	615.44	227.98
762.18	237.75	568.48	224.46
753.81	237.25	510.00	219.75
748.13	236.90	427.7	216.53
728.56	235.65	430.6	212.64
722.23	235.27	388.4	208.42
714.98	234.80	348.1	204.02
707.01	234.28	307.9	199.18
692.05	233.29	307.9	199.21
686.54	232.92	261.3	192.95
676.32	232.23	225.4	187.51
666.58	231.59	173.1	178.15
647.57	230.26	117.9	165.37
635.44	229.43	115.5	164.67

TABLE 8. Boiling Point of Quinoline from 1 to 30 atm.[355]

Pressure (atm.)	1	2	3	4	5	6	7	8	9
B.p. (°C)	237.7	270	292	308	322	335	344	354	362
Pressure (atm.)	10	12	14	16	18	20	25	30	
B.p. (°C)	369	383	396	405	417	424	444	462	

TABLE 9. Azeotropes of Quinoline[357]

Substance	B.p. of azeotrope (°C)	Substance	B.p. of azeotrope (°C)
Ethylene glycol	196.35	2-Methylnaphthalene	237.25
Dibutyl glycol	Below 229.5	*p*-Nitrotoluene	237.2
Methyl triglycol	235.55	Anethole	234.7
Diglycol	233.6	Safrole	235.15

10. Density, Surface Tension, Viscosity, and Related Properties

The published density of quinoline varies from 1.10957 at 0 °C[351] to 0.9319 at 220 °C.[358] Complete figures are given in Table 10. The variation per degree from 0 to 30 °C is 0.00079[351] and there is little variation from this figure over the larger range. The variation of density with temperature has also been reported for some quinoline–water mixtures.[362] The viscosity of quinoline has been determined from 1 to 209 °C and is given in Table 11; from the first two figures $d\gamma/dt$ was calculated to be 0.09.

The surface tension of quinoline at 20 °C is 45.62 dyne/cm,[230] at 30 °C is 44.82 dyne/cm,[351] and at 209 °C is 24.7(4) dyne/cm,[363] other values are given in ref. 351; $d\gamma/dt$ was calculated as 0.080.

TABLE 10. Density (d) of Quinoline from 0 to 220 °C

Temp. (°C)	d	Ref.	Temp. (°C)	d	Ref.
0	1.10957	351	31	1.08500	351
1	1.108	364	31.1	1.08407	362
5	1.10562	351	32.1	1.08413	351
8.2	1.10309	351	40	1.0785	358
9.8	1.10183	351	53	1.06725	362
10	1.10167	351	60	1.062	364
10.5	1.10127	351	73.5	1.0509	362
15	1.09771	351	80	1.0478	358
16.2	1.09676	351	120	1.0150	358
20	1.09376	351	160	0.9826	358
24.9	1.08989	351	200	0.9489	358
25	1.08981	351	209	0.937	363
30	1.08579	351	220	0.9319	358

TABLE 11. Viscosity (γ) of Quinoline from 1 to 209 °C

Temp. (°C)	γ (c.g.s.) $\times 10^4$	Ref.	Temp. (°C)	γ (c.g.s.) $\times 10^4$	Ref.
1	606.5	364	40	237.8	364
15	435.4	351	60	167.6	364
20	361.8	364	209	39	363
30	299.7	351			

Other determinations of the density and viscosity of quinoline[365] and of quinoline–octane mixtures have been published.[366] The solubility of quinoline in water at 20 °C has been determined spectrophotometrically (ultraviolet) to be 1 part in 153 (0.65% weight to volume)[367] and by infrared measurement to be 6110 mg per l.[368] Solubilities from 10 to 73 °C are given in Table 12,[369] where the value near 20 °C is considerably higher than that obtained by the other workers. The acoustic relaxation in quinoline has been determined by measuring the velocity of propagation of ultrasonic waves.[370, 371]

TABLE 12. Solubility of Quinoline in Water from 10 to 73 °C [369]

Temp. (°C)	10.0	15.5	19.1	23.5	29.7	36.0	43.5	52.0	60.0	66.0	73.0
Solubility (g/l.)	8.4	8.6	9.1	9.4	9.7	10.0	10.4	10.7	11.1	11.5	12.0

The critical dissolution temperature of quinoline in various n-alkanes (C_5–C_{11}) has been determined by a polythermal method. The t_c-dependence on n for quinoline had a parabolic form with a minumum at $n = 6$; in C_8H_{18} t_c for quinoline was $+1.6$.[372, 373]

The parachor of a mixture of quinoline and chloroform has been reported.[369]

11. Optical and Magnetic Properties: Dipole Moment

The refractive index of quinoline at different wavelengths (at 15 °C) is summarized in Table 13.[351] The molar refraction at the D-line is 41.7 (calculated value 40.97). The molar Kerr constant of quinoline at infinite dilution in carbon tetrachloride has been found to be 149×10^{-12} at 25 °C.[374, 375]

TABLE 13. Refractive Indices of Quinoline at 15 °C [351]

Hα	D	He yellow	He green	Hβ	He violet	Hγ
1.6212[a]	1.62928	1.62954	1.64743	1.6522[b]	1.66683	—

[a] Extrapolated. [b] Interpolated.

A study of Kerr constants for solution of quinoline in dioxan has been reported[376] for temperatures from 25 to 65 °C at 546 nm. The optical properties of liquid quinoline have been examined for photon energies from 2 to 10.6 eV, giving the real and imaginary parts of the complete index of refraction, and the absorption cross-section as a function of incident photon energy.[377]

The mean polarizability of quinoline is less than that of naphthalene. The difference is greatest normal to the molecular plane; quinoline is more polarizable than naphthalene along axis b_2 (Fig. 7). The molar Cotton–Mouton constant,

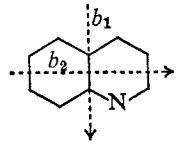


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Fig. 7. Polarizability of quinoline.

defined as the difference between molecular refractions parallel and perpendicular to a magnetic field of unit strength, determined[378] for quinoline at infinite dilution in carbon tetrachloride (20 °C, at the D line) was $7.2_3 \times 10^{-15}$; the ${}_mC_{liq}$ was 6.54×10^{-15}. The molecular magnetic rotatory power relative to water (1 Ω 1) at 15 °C has been given as 20.875.[379] The Verdet constant of quinoline at 546 nm was found invariant under magnetic fields <220 koe.[380] The molecular optical anisotropy of quinoline has been determined by depolarized Rayleigh diffusion; γ^2 Å^6 = 182.[381] Further determinations have been made with a ruby laser source.[181] The electrical birefringence of quinoline is 466;[382] the molecular magnetic susceptibility $-\chi \times 10^6$ is 86.55.[383]

The dipole moment of quinoline has been determined in the vapour phase (2.29D)[49] in light petroleum (2.17D),[49] in carbon tetrachloride (2.27D),[49] in benzene (2.24D,[49] 2.15D [384]) and in dioxan 2.24).[385] A number of earlier determinations are listed under ref. 386. The moment has been said to be almost parallel with the short axis (b_1 in Fig. 7) in the plane of the ring.[364, 387] The slight difference between the moment in carbon tetrachloride and that in benzene solutions has been suggested as evidence for CCl_4–lone-pair interaction,[388] and the difference between dioxan and benzene to a weak $n\pi^*$ charge transfer with dioxan as donor.[385] The dipole moment of quinoline picrate is 7.92D.[389]

12. Dissociation Constant, Titrations, and Electrical Properties

The dissociation constant of quinoline in water at 25 °C is 8.9×10^{-10}, determined spectrometrically.[390] An earlier value[391] at 20 °C was 5.96×10^{-10}. Conversely, pK_A values obtained were 4.94 [392] (potentiometric at 20 °C), 4.96 [79] (from the ultraviolet absorption, at 20 °C), and 5.0 [393] (from partition coefficients). Addition of non-aqueous solvents leads to the expected decrease in basic dissociation constant; in a solvent mixture of 10% ethanol in water the dissociation constant[390] was 4.9×10^{-10}. The effect of varying percentages of ethanol, methoxyethanol, and 1,2-dimethoxyethane on the value of pK_A is shown in Table 14.[394]

TABLE 14. Effect of Mixed Solvents on the pK_A of Quinoline at 25 °C [394]

% of non-aqueous solvent	20	30	40	50
pK_A with added ethanol	4.53	4.28	3.96	3.67
pK_A with added $HOCH_2CH_2OMe$	4.48	4.25	4.00	3.75
pK_A with added $MeOCH_2CH_2OMe$	4.33	4.03	3.70	3.37

A few values for the dissociation constant of quinoline in non-aqueous solvents are available; in ethylene glycol at 30 °C, pK_{BH+} was found to be 5.39, in propylene glycol 5.27 (pK_b is given as 10.21 and 11.49 respectively).[395] In anhydrous acetic acid at 25 °C pK_A was found to be 4.45,[396] and figures for the half-neutralization potential in nitromethane[397] and in acetic acid–chloroform–carbon tetrachloride mixtures[398] have been determined. A figure of 0.44 for $-\log_{10} K_b$ of quinoline in anisole has been reported;[399] the variation of the dissociation constant with the dielectric constant of the solvent has been calculated.[400]

Non-aqueous titrations involving quinoline and a wide variety of acids (protonic and Lewis acids) are listed in Table 15.

TABLE 15. Non-aqueous Titrations Involving Quinoline

Solvent	Acid	Method of detection	Ref.
Acetic acid	Perchloric	Potentiometric	401, 402
	Perchloric	Spectrometric	403
	Fluorosulphonic	Potentiometric, visual	404
	o-Sulphobenzoic	Potentiometric	405
Acetic acid–butanone	Chlorsulphonic	Potentiometric	406
Propionic acid	Toluene-*p*-sulphonic	Visual indicators	407
Propionic anhydride	Toluene-*p*-sulphonic	Visual indicators	407
Acetic anhydride	Toluene-*p*-sulphonic	Visual indicators	408
	Fluorosulphonic	Conductometric	409
		Potentiometric	
	Sulphuric	Visual indicators	
		Biampeometric	410
Ethyl acetate	Perchloric	Visual indicators	411
	Perchloric	Potentiometric	412
	Fluorosulphonic	Visual indicators	411
	Toluene-*p*-sulphonic	Visual indicators	411

TABLE 15 (*cont.*)

Solvent	Acid	Method of detection	Ref.
Nitromethane	Perchloric (in dioxan)	Potentiometric	412, 413
Benzene–methanol	Perchloric (in dioxan)	Potentiometric	414
Methanol–ethylene glycol	Fluorosulphonic	Visual indicators	415
Acetonitrile	Perchloric (in dioxan)	Potentiometric	412
Nitrobenzene	Perchloric (in dioxan)	Potentiometric	412
Acetamide (at 100 °C)	Titanium tetrachloride	Conductometric	416
	Stannic chloride	Conductometric	416
Dimethylformamide	Antimony pentachloride	Thermometric	417
	Titanium tetrachloride	Thermometric	417
	Stannic chloride	Thermometric	417
	Sulphur trioxide	Thermometric	417
	Arsenic trichloride	Thermometric	417
	Fluorosulphonic	Thermometric	418
	Sulphuric	Thermometric	418
	Disulphuric ($H_2S_2O_7$)	Thermometric	418
	Hydrogen chloride	Thermometric	418
Sulpholane	Various	Glass electrode	419

Quinoline has been titrated against perchloric acid in aqueous mixtures of ethanol, acetone, or dioxan (conductimetrically).[420] A simple high-frequency titration apparatus has been described to estimate quinoline in coal tar.[421]

Dielectric constants and dielectric losses for pure liquid quinoline at temperatures from −30 to 60 °C are given in Table 16 (p. 24). The calculated molecular relaxation time was 3.3×10^{-11} (s).[422] The dielectric constant for pure quinoline has been reported as 2.9.[425] Supplementary figures for dielectric properties are given in refs. 426–429. There is a report on the chronopotentiometry of quinoline in basic solution.[430]

Relaxation times and dielectric constants for solutions of quinoline in a number of solvents have also been reported. For solutions in naphthalene[424] the results suggest that considerable orientation takes place out of the plane of the ring. Other solvents used were Nujol,[431] carbon tetrachloride,[432] benzene,[432] *p*-xylene,[433] *n*-heptane,[432] and cyclohexane.[433] In most cases the results were compared with those for isoquinoline, and agreement with theoretical results derived from various equations was investigated.[432–434] Measurement of dielectric constants has also been used to obtain information on association between quinoline and phenol[435] (1 : 1 complex), and between quinoline and acetic acid (2 : 1 acetic acid–quinoline).[436] The change in dielectric constant ($\Delta\varepsilon'$) when solutions of organic bases (including quinoline) in benzene or toluene are mixed with aqueous acid has been compared with the relative dissociation constants of the bases; quinoline has a decreased $\Delta\varepsilon'$ and it was suggested that this could be accounted for by the formation of quadrupoles with mutually compensated dipoles.[437]

The specific conductance of quinoline in methanesulphonic acid has also been determined.[438]

TABLE 16. Dielectric Constants and Dielectric Losses in Pure Liquid Quinoline from −30 to +60 °C (collected from refs 364, 423, and 424)

λ (cm)	0.847		1.24		3.279		10.66		33.3				
Temp. (°C)	ε'	ε''	ε'	ε''	ε'	ε''	ε'	ε''	ε'	ε''	ε_∞	ε_0	$\tau_m \times 10^{11}$ (s)
−30	3.33	0.38			3.40	0.55					3.34	11.2[a]	
−20	3.31	0.50			3.52	0.82					3.36	10.8[a]	
−10	3.29	0.60			3.64	1.10					3.35	10.4	
0	3.26	0.72			3.75	1.39					3.31	9.94	
1			3.227	0.75	3.532[b]	1.42[b]			9.325	2.19	—	9.70	7.7
10	3.23	0.82			3.87	1.68					3.25	9.54	
20	3.20	0.94	3.226	1.04	4.01	2.03	6.84	2.53	8.896	1.27	3.13	9.15	4.4
30	3.19	1.05			4.17	2.33					2.99	8.72	
40	3.18	1.16	3.276	1.29	4.35	2.53	7.16	2.06	8.473	0.86	2.84	8.37	2.97
50	3.18	1.27			4.59	2.77					2.57	7.92	
60			3.441	1.63	4.898[b]	2.32[b]	7.27	1.62	8.082	0.64		7.81	1.97

[a] Supercooled liquid. [b] At 3.22 cm.

13. Thermochemical Data and Heats of Neutralization

There are no recent figures for the heat of combustion of quinoline, and none for the heat of hydrogenation. A determination by Parks, Todd, and Moore[439] in 1936 gave ΔH_{298}^0 as 35,650 cal mol^{-1} (149.15 kJ mol^{-1}), ΔF_{298}^0 as 63,200 cal mol^{-1} (264.43 kJ mol^{-1}), and ΔS_{298}^0 as -92.5 e.u. A calculated mesomeric energy is 48,400 cal mol^{-1} (202.5 kJ mol^{-1});[440] a calculated resonance energy is 34.1 kcal mole^{-1} (142.67 kJ mol^{-1}).[441] Earlier figures are available for heat of combustion,[442, 443] heat capacity,[444] specific heat,[445] and coefficient of entropy.[444, 445]

A number of values have been obtained for the heat of neutralization of quinoline in various solvents and against a number of different acids. In aqueous solution against hydrochloric acid for the reaction

$$\text{Quinoline (aq.)} + H^+ \text{ (aq.)} \rightleftharpoons \text{Quinoline } H^+ \text{ (aq.)} \quad \text{at } 25\ ^\circ\text{C}$$

the values recorded[446] were $-\Delta F = 6550$ cal mol^{-1} (26.66 kJ mol^{-1}), $-\Delta H = 5365 \pm 15$ cal mol^{-1} (21.84 kJ mol^{-1}), and $-\Delta S = 3.95$ e.u. By comparison with pyridines, the heat of neutralization was lower than expected on the basis of the quinoline pK_A value (taken as 4.8); this was thought to be due to the low ΔS, indicating that fewer water molecules were associated with the nitrogen atom of quinoline than of the pyridines studied. Earlier figures are available [447] for neutralization of quinoline against hydrochloric and sulphuric acid, and against water-free formic, acetic, and propionic acid. Thermometric titration values for the heats of neutralization of quinoline against Lewis acids[417] in dimethylformamide, and against protonic acids in dimethylformamide[418] and formamide[448] have been obtained; subsequent determinations have been made in methanol[449] and butanol.[450]

The heat of mixing of quinoline with acetic acid[451, 452] and with carbon tetrachloride[453, 454] have been interpreted in terms of complex formation; the enthalpies of mixing of quinoline with water and with isoquinoline have been reported.[455]

IV. Chemical Properties

The chemical properties of quinoline are discussed under the general headings of addition, substitution, oxidation, lone-pair reactions, and miscellaneous destructive reactions such as pyrolysis. It will be obvious that some reactions do not fall clearly into one class, but any such will be mentioned in both appropriate sections.

1. Addition Reactions

The most obvious addition reactions of quinoline involve reduction, but because of the stability of many 1,2-dihydroquinolines there is a substantial number of reactions involving 1,2-addition to the C=N bond.

Reduction

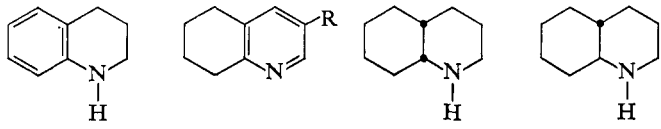
The polarographic reduction of quinoline has been examined in aqueous media at varying pH,[456-461] in tetrahydrofuran,[462] and in dimethylformamide[463-466] (in the last two cases with added tetraethylammonium salts). Kaye and Stonehill,[467] working with an acid medium, found a total two-electron wave made up of two overlapping one-electron waves and indicating the intermediate formation of a semiquinone. Yurkina,[461] working over a wider pH range, found one to three waves and noted that quinoline could be estimated by polarography at pH 12.8 where wave height is linearly related to concentration.

Reduction at a vibrating dropping mercury electrode showed two reduction waves, corresponding to a one-electron, one-proton input, the proton at nitrogen;[468] a subsequent paper described two successive catalytic waves at more negative potentials.[469] These and the other results appear to be at variance with those of Wiberg and Lewis,[465] who performed both polarography (in dimethylformamide) and cyclic voltammetry, finding a single-electron transfer $E_{\frac{1}{2}} = -1.59$ (-1.602) volts; the lifetime of the reduced species was estimated at 3 s, and no dimeric product was observed. Reduction of 1-methylquinolinium iodide was reported[470] to be two-stage (one electron, one electron plus one proton) with the energy difference between the two steps extraordinarily large compared with that of the free base. Polarographic data have been correlated with ease of oxidation in a solid oxidizing agent.[471].

Electrolytic reduction should in theory be convenient for the production of dihydroquinolines or of 1,2,3,4-tetrahydroquinoline (**2**); in practice it has not been possible to isolate more than traces of the reactive dihydroquinolines which give mainly dimers or trimers.[472] Electrolytic reduction provides a practical route (70–75% yield) to 1,2,3,4-tetrahydroquinoline (**2**) with the additional advantage that the anolyte can provide reasonable quantities of quinolinic or nicotinic acids (see p. 63). In recent procedures a lead cathode is used with a fairly high concentration of sulphuric acid as catholyte,[473] although it has been pointed out[474] that the yield of dihydroquinoline products increases with increasing concentration of sulphuric acid. A study of the variation in the yield of tetrahydroquinoline with different cathodes showed that the best current yields were obtained by using lead or thallium; indium, cadmium, and mercury were inferior.[475, 476] Khomutov and Tsodikov have made thorough investigations of electroreduction with stationary and rotating electrodes, using nineteen different electrodes;[477–479] additionally they have examined the kinetics of electroreduction, using the polarization curves over a wide range of temperatures.[480] They concluded that electroreduction is favoured by a flat orientation of the quinoline molecules which is possible at zero or small surface charge.[481] Khomutov and Tsodikov have also studied the partial current density (c.d.) of quinoline reduction where $a_q = i_1 + i_2$ (i_1 and i_2 were the limiting currents of the first and the second wave of the partial polarization curve)[482] for a lead cathode and a sulphuric acid electrolyte. The highest current yield of dihydroquinoline products has been obtained when using a graphite cathode.[319] Variation of the acid medium (using sulphuric, perchloric, hydrochloric, and phosphoric acids) confirmed that a maximum yield was obtained when sulphuric acid (8–10 mol l^{-1}) was used;[483] it has been reported that polymer formation increases with increasing pH, probably owing to formation of 1,2-dihydroquinoline.[484] On the other hand, improved yields of dihydroquinoline products resulted from the use of an alkaline medium; the results were better with methylquinolines, where the dihydroquinolines themselves could be isolated, than with quinoline itself.[472, 485] Quinoline is used as a brightener during electrodeposition of zinc[486, 487] or iron,[488] and studies have been made of the reduction of the quinoline to hydrogenated quinolines and polymers thereof; at pH 2 more dihydroquinoline products were formed, but this may be a result of chemical reduction.[486]

Catalytic hydrogenation has been used to produce either 1,2,3,4-tetrahydroquinoline (**2**) or 5,6,7,8-tetrahydroquinoline (**3**; R = H), as well as *cis*- (**4**) and *trans*-decahydroquinolines (**5**); under drastic conditions the ring system breaks, giving ammonia, amines, and hydrocarbons. The earliest reports of catalytic hydrogenation of quinoline, giving decahydroquinoline, were by Ipatiev[489] (using nickel oxide) and by Sabatier and Murat[490] (using nickel); 1,2,3,4-tetrahydroquinoline (**2**) was obtained by Darzens[491] (using nickel). Skita and Mayer first used colloidal platinum in acetic acid to obtain decahydroquinoline and reported that interruption of

the hydrogenation enabled the 5,6,7,8-tetrahydroquinoline (**3**; R = H) to be isolated.[492] The easiest hydrogenation product to obtain is 1,2,3,4-tetrahydroquinoline (**2**); there are reports of quantitative yields with nickel[493-495] (200 °C., 30 atm); lower but still



2 **3** **4** **5**

good yields have been reported when using W-nickel sulphide 8376[496] (83%), nickel (70 °C, 70 atm., 71%),[497] platinum oxide in ethanol,[498] nickel–chromium oxide,[499] copper,[500] ruthenium oxide (80 °C, 82 atm., 60%),[501] tungsten trioxide–nickel oxide–alumina (25 : 5 : 70) (250 °C, 100 kg/cm^2),[502] and tungsten disulphide–alumina.[502] Other reports of the preparation of 1,2,3,4-tetrahydroquinoline concern use of calcium metal and hydrogen,[503] aluminium–nickel catalyst in a flow apparatus under pressure (giving mixed tetra- and deca-hydroquinolines),[504, 505] and a homogeneous catalyst made from borohydride and [(pyridine)$_3$RhCl$_3$].[506]

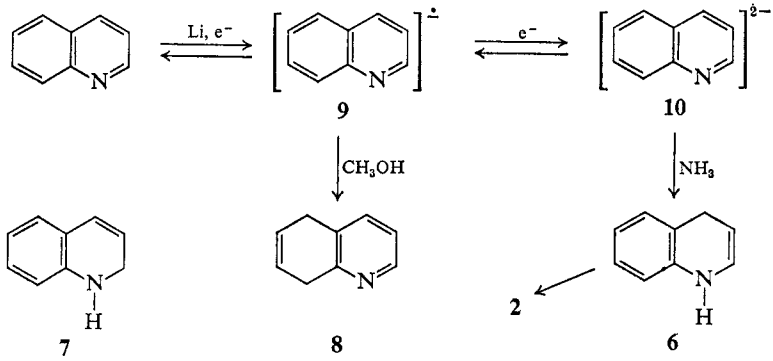
Catalytic hydrogenation would not normally be the method of choice for the preparation of 5,6,7,8-tetrahydroquinoline (**3**; R = H), although there is a patent recording the production of 5,6,7,8-tetrahydroquinoline in a ratio of 47 : 2 against the more normal 1,2,3,4-tetrahydroquinoline.[507] The only hydrogenations in which appreciable quantities of 5,6,7,8-tetrahydroquinoline have been obtained involve a platinum catalyst;[492, 507, 508] there is no obvious reason for the preferential reduction of the benzene ring in these cases.

Vierhapper and Eliel, using platinum oxide and concentrated hydrochloric acid at room temperature and hydrogen pressure of 50 p.s.i., obtained 70% of 5,6,7,8-tetrahydroquinoline, which was further reduced by sodium in ethanol to give *trans*-decahydroquinoline.[508] The use of 12N-sulphuric acid gave 75% of tetrahydroquinoline, while trifluoroacetic acid gave 84% in 45 minutes. Careful examination of the hydrogenation products after use of a nickel catalyst[497] or a molybdenum sulphide catalyst[509] have shown the presence of small amounts of 5,6,7,8-tetrahydroquinoline. It seems probable that modern analytical methods, notably gas chromatography,[510] would have shown such small quantities to be present even in the supposedly quantitative yields of 1,2,3,4-tetrahydroquinoline mentioned above. The presence of 3-alkyl or 3-aryl substituents in quinoline has been shown to lead to an increased proportion of product reduced in the benzenoid ring even on use of a nickel catalyst giving compounds (**3**; R = Et, CH_2Ph, or Ph).[494] There is one report of the preparation of an octahydroquinoline (in 98% yield) by reduction over ruthenium oxide, but no structure was given.[501] The production of decahydroquinolines requires high temperatures and pressures if nickel,[497] copper,[500] or ruthenium[511] catalysts are used, or alternatively a platinum catalyst, preferably in an acid medium. The classic studies on the decahydroquinolines were by Hückel and Stepf;[512] the mixture isolated after reduction of quinoline in aqueous acetic acid was 80% of *trans*- (**5**) and 20% of *cis*-decahydroquinoline (**4**); the structures were assigned partly by a comparison of physical properties (density and refractive index) and partly by oxidation of the *N*-benzoyl derivatives. Addition of concentrated hydrochloric acid to the hydrogenation mixture gave a *trans* : *cis* ratio of 35 : 65; reduction of quinoline oxalate gave a *trans* : *cis* ratio of 90 : 10. The former ratio may be compared with that reported by Booth and Bostock for reduction with platinized charcoal and concentrated hydrochloric acid, giving decahydroquinolines containing less than 3% of the *trans*-form.[513]

A number of studies of the destructive hydrogenation of quinoline have been made. High-pressure and high-temperature hydrogenation over iron oxide,[514] cobalt sulphide,[515] molybdenum sulphide,[516-518] tungsten sulphide,[519] or various mixtures of cobalt, molybdenum, tungsten, nickel, and aluminium[520-523] were reported to give ammonia and hydrocarbon mixtures. Such procedures have been used to "denitrogenate" paraffins contaminated with quinoline. Another study, in which molybdenum sulphide and hydrogen were used at 360 °C and 100 atm., showed the presence of the two tetrahydroquinolines, *trans*-decahydroquinoline, 2- and 3-methylindole, indene and octahydroindene, anilines (parent, *o*-Me, *o*-Et, and *o*-Pr^n), benzene, toluene, ethylbenzene, *n*-propylbenzene, hexane, and the corresponding cyclohexanes.[510]

Quinoline is generally accepted as being more reactive towards hydrogenation than benzene; competitive experiments showed pyridine and quinoline to be approximately equally reactive.[524] A kinetic study showed that the hydrogenation of quinoline with platinum oxide as catalyst, was first-order in hydrogen and zero-order in the hydrogen acceptor.[525]

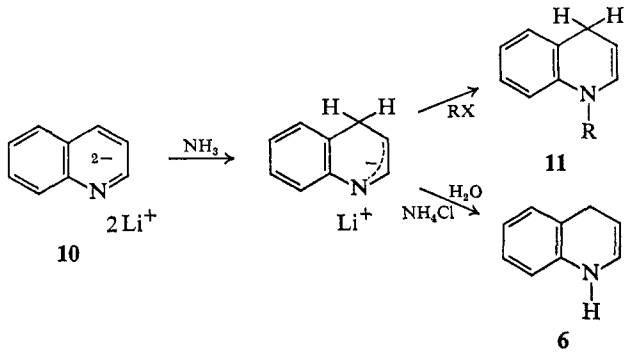
Chemical reducing reagents are much more satisfactory for the preparation of the dihydroquinolines. An early report[526] on the reduction of quinoline by sodium in liquid ammonia recorded the isolation of a benzoyldihydroquinoline and of a diacetyldihydroquinoline dimer, and suggested that 1,4-dihydroquinoline (**6**) was the likely product.[526] A subsequent paper by Hückel and Hagedorn[527] claimed that an 84% yield of 1,2-dihydroquinoline (**7**) could be obtained after reduction with sodium in liquid ammonia; their *N*-benzoyl derivative melted at 89 °C, whereas that reported earlier had a melting point above 100 °C (see below). Lithium reduced quinoline in liquid ammonia with no proton source present, giving mainly, 1,2,3,4-tetrahydroquinoline (**2**); with methanol present throughout the reduction, the product was 5,8-dihydroquinoline (**8**).[528, 529] The results of parallel studies on 6-methoxyquinoline



led to the suggestion that reduction without methanol proceeded through the dianion (**10**) and 1,4-dihydroquinoline (**6**), while methanol, if present during the reduction, protonates the radical anion (**9**), reversibly on nitrogen but irreversibly on C-5.

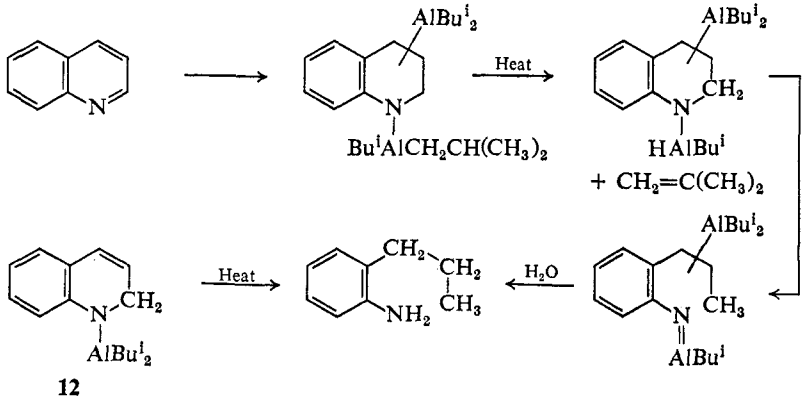
Birch and Lehman isolated 1,4-dihydroquinoline from reductions when using lithium (2 equivalents) in anhydrous ammonia, the reaction mixture being quenched by ammonium chloride.[530] They showed that the 1,4-dihydroquinoline was unstable at room temperature, though stable at −15 °C in ether solutions and that it was identical with Hückel and Hagedorn's "1,2-dihydroquinoline". Addition of alkylating

agents to a solution of quinoline in liquid ammonia previously treated with 2.5 mol-equiv. of lithium gave 1-alkyl-1,4-dihydroquinolines (**11**);[531] the intermediacy of the dianion (**10**) was shown by isolation of some 1,4-dialkyl-1,4-dihydroquinoline, and



the action of ammonia in providing the proton by the use of ^2H_3N, giving a 4-^2H-substituted dihydroquinoline.

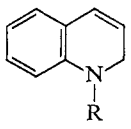
Hydride reduction offers an attractive route to 1,2-dihydroquinoline (**7**); some reports of reduction of quinoline by lithium aluminium hydride in ether gave low melting points (40–41 °C,[532] 57 °C,[533] or 62–66 °C,[534] instead of 72 °C [527]). Nevertheless, it has been reported that pure 1,2-dihydroquinoline (**7**)[535] or its *N*-benzoyl derivative[536] can be obtained by lithium aluminium hydride reduction. A reported 95% yield of 1,2-dihydroquinoline (**7**) was obtained by the use of dialkylaluminium hydrides (ethyl or isobutyl)[537] When heated, the intermediate aluminium complex (**12**) gave 2-*n*-propylaniline and isobutene, products which could also be obtained by



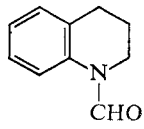
direct treatment of quinoline in boiling xylene with di-isobutylaluminium hydride. A suggested mechanism for this decomposition is illustrated. Either of the trialkylaluminium groups might break down to isobutene, generating a further dialkylaluminium hydride for the reductive ring opening.

Sodium hydride is not normally used as a reducing agent, but it has been reported[538] that treatment of quinoline in hexamethylphosphorotriamide (HMPT) gave a mixture (2 : 3) of 1,2- and 1,4-dihydroquinoline, trapped by acylation.

A variant of hydride reduction is the reported reaction between quinoline and sodium borohydride in dimethylformamide with added ethylchloroformate; the product was ethyl 1,2-dihydroquinoline-1-carboxylate (**13**).[534] Since there is no report of borohydride reduction of the free base it seems likely that a quaternary intermediate was formed. Reduction of quinoline by formic acid, with triethylamine and Raney nickel[539] or sodium formate[540] added, gave good yields of 1-formyl-1,2-dihydroquinoline (**14**); a poorer yield was obtained by using formic acid and formamide.[540] Very high yields of 1-formyl-1,2,3,4-tetrahydroquinoline (**15**) have been obtained by using high-temperature reduction with formic acid.[541–543] In one case,[541] small amounts of 1,2,3,4-tetrahydroquinoline and of 1,2,3,4-tetrahydro-1-methylquinoline were also obtained. Possibly related to these reactions involving formates is the catalytic methylation of quinoline by carbon monoxide and hydrogen over various oxide (copper, chromium, zinc) catalysts.[544]



13; R = $CO_2C_2H_5$
14; R = CHO



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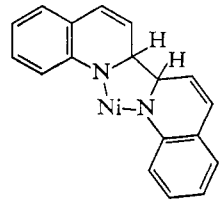

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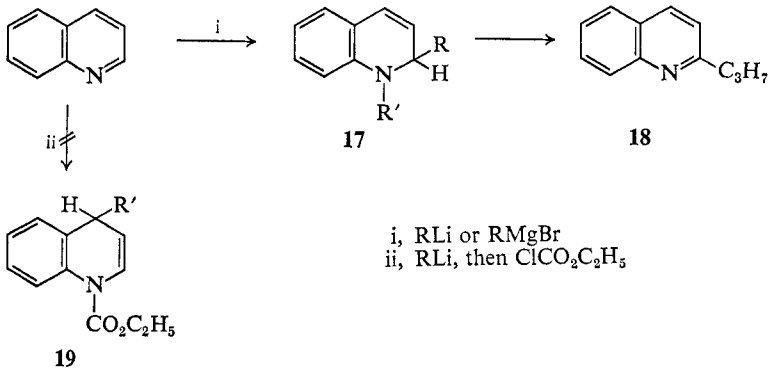
Sodium amalgam in ethanol converted quinoline into 1,2,3,4-tetrahydroquinoline (**2**),[545] which was also one of the products after reduction by tin[546] or zinc[547, 548] and hydrochloric acid. During such reductions, and more prominently during reduction by zinc and ammonia[545] or by zinc and acetic anhydride,[549, 550] reduced biquinolines were also formed. The only satisfactorily characterized material was a tetrahydrobiquinoline reported by Koenigs.[545] The formation of 2,2′-biquinoline from quinoline and nickel can be regarded as a 1,2-addition, as the mechanisms proposed postulate an intermediate derivative of tetrahydrobiquinoline (**16**) which is dehydrogenated before desorption.[551, 552]

When quinoline reacts with Grignard reagents the initial product is probably always the 2-substituted 1,2-dihydroquinoline but the intermediate is very rarely isolated. Gilman, Eisch, and Soddy have reported the isolation of the 2-allyl derivative (**17**; R = allyl, R′ = H) from allylmagnesium bromide and quinoline;[553]



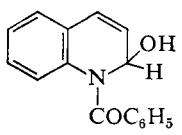
17 **18**

19

i, RLi or RMgBr
ii, RLi, then $ClCO_2C_2H_5$

this product was never completely pure, possibly because of the extremely easy oxidation to the corresponding allylquinoline, but also because of the thermal bond isomerization giving 2-*n*-propylquinoline (**18**). There are more cases of the isolation of 2-substituted 1,2-dihydroquinolines (**17**; R′ = H) from reaction between quinoline and alkyl-[553, 554] or aryl-lithium[555, 556] reagents; typical products were (**17**; R = Pr^n, Bu^n, *m*-(trifluoromethyl)phenyl, and *o*-methoxyphenyl). A suggestion that certain addition products formed from quinolines with *n*-butyl- or phenyl-lithium and trapped by addition of ethyl chloroformate had 1,4-dihydroquinoline structures (**19**; R = *n*-C_4H_9 or C_6H_5)[557] were subsequently disproved by examination of the nmr spectra of the adducts.[558–560] The compounds were shown to be of general type (**17**; R′ = $CO_2C_2H_5$).

The chemistry of the quinoline Reissert compounds will be the subject of a later section, but as they represent formal 1,2-addition products, the various compounds available from quinoline itself will be discussed here. Reissert's original observations were that crystalline compounds could be obtained from quinoline and an aqueous mixture of benzoyl chloride and sodium hydroxide (or sodium cyanide).[561] The compound obtained from quinoline, benzoyl chloride, and sodium hydroxide was formulated by Reissert first as 1-benzoyl-1,2-dihydro-2-hydroxyquinoline (**20**)[561] and subsequently as *o*-benzamido-*cis*-cinnamaldehyde (**21**).[562] Elliott, from a study of the spectroscopic properties, has concluded that the compound is best represented as the *trans*-cinnamaldehyde (**22**) and not as a tautomeric mixture of the pseudo-base (**20**)



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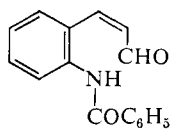

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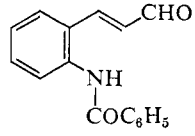

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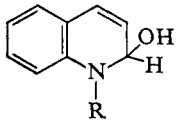

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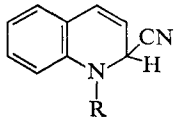

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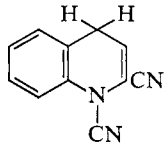

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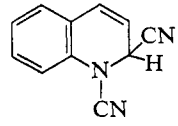

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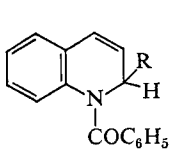
and the *cis*-cinnamaldehyde (**21**).[563, 564] The true 1,2-dihydro-2-hydroxyquinoline form was obtained in products from reaction between quinoline, ethyl chloroformate, and potassium hydroxide[565] (**23**; R = $CO_2C_2H_5$) and from quinoline and cyanogen bromide in moist ether (**23**; R = CN).[566–568] The compound (**23**; R = CN) was also obtained by reaction between quinoline, bromine, and potassium cyanide and shown to have no spectral characteristics of the cinnamaldehyde form.[569] Much more work has been done on the second type of compound such as that prepared by Reissert from quinoline, benzoyl chloride, and potassium cyanide (**24**; R = COC_6H_5).[561] By the use of methylene chloride as solvent, with a minimum of water to dissolve the potassium cyanide it has been possible to use more reactive acid chlorides such as acetyl chloride,[570] which gives compound (**24**; R = $COCH_3$); although the yields are generally inferior to those achieved by using anhydrous hydrogen cyanide in benzene,[571] the gain in convenience is obvious. The reaction between quinoline, cyanogen bromide, and hydrogen cyanide was reported to give a dicyanohydroquinoline, readily converted into an isomer;[572] the first-formed compound has been assigned the 1,4-dihydroquinoline structure (**25**) and the isomer the

1,2-dihydroquinoline structure (**26**), mainly on the basis of their electronic absorption spectra.[573].

Among other nucleophiles that can enter position 2 during a Reissert reaction, are the phenylethynyl anion, giving (**27**; R = PhC≡C);[574] dimethylaniline, giving (**27**, R = *p*−$Me_2NC_6H_4$);[575] indoles, giving for example (**27**, R = indol-3-yl);[576] 1-methylindoline, giving (**27**, R = 2,3-dihydro-1-methylindol-5-yl);[577] and 1-alkyl-1,2,3,4-tetrahydroquinolines.[578] von Dobeneck and Goltzsche have studied the reaction between quinoline, acid chlorides (aryl, acyl, and tosyl), and a variety of compounds containing active methylene groups;[576] all these gave 2-substituted 1,2-dihydroquinoline derivatives similar to (**27**) except for diethyl malonate which gave the 1,4-dihydro-derivative (**28**). It has subsequently been shown that, while



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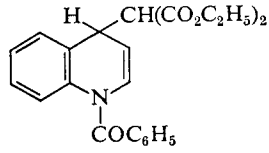

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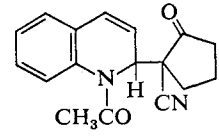

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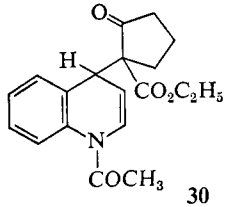

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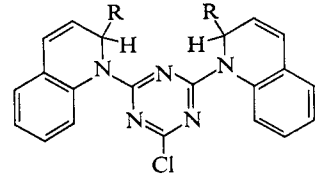
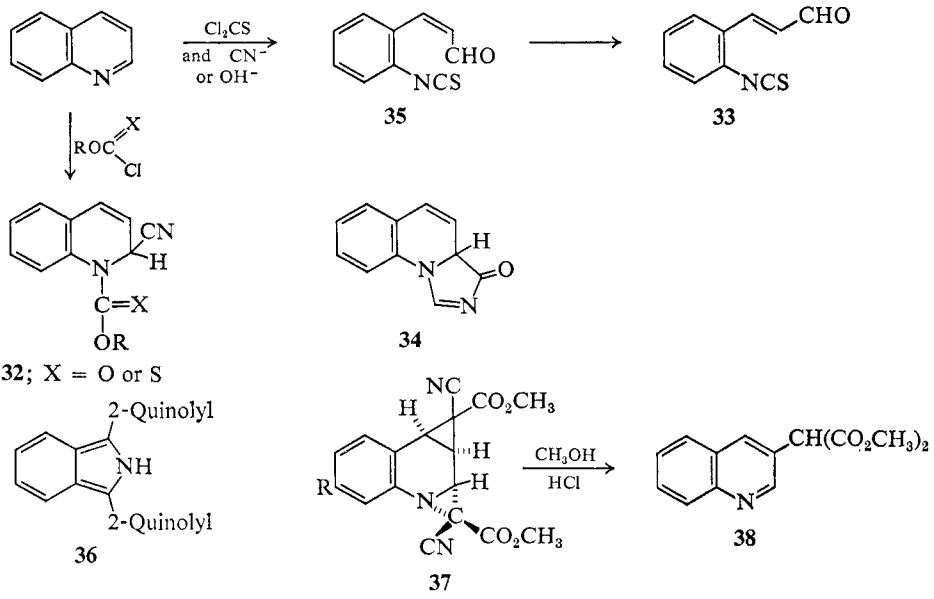


31; R = *p*-$(CH_3)_2NC_6H_4$

quinoline, acetyl chloride, and 2-cyanocyclopentanone gave the 1,2-dihydroquinoline (**29**), a similar reaction with ethyl 2-oxocyclopentanecarboxylate gave the 1,4-dihydroquinoline (**30**).[579] Instead of acid chlorides, Sheinkman and his co-workers have used vinylogous acid chlorides (R—COCH=CHCl)[580] and 2,4,6-trichloro-*s*-triazine,[581] the latter, with dimethylaniline, giving the bis(dihydroquinolyl)triazine (**31**).

Ethyl chloroformate and potassium cyanide gave compound (**32**), R = C_2H_5, X = O).[582] Ethyl or phenyl chloro(thioformate) reacted with quinoline and potassium cyanide to give the normal Reissert addition compound (**32**); R = C_2H_5 or C_6H_5, X = S). More interesting was the reaction between quinoline, thiophosgene, and potassium cyanide, where the products were the *trans*-cinnamaldehyde (**33**) and the tricyclic compound (**34**).[583] Predictably, the substitution of sodium hydroxide for potassium cyanide gave a much improved yield of the aldehyde (**33**), and by using barium carbonate it was possible to isolate the *cis*-cinnamaldehyde (**35**), which is presumably the first product of ring opening. The production of both ring-opened and tricyclic compounds was interpreted by means of the principle of "hard" and "soft" acids and bases.

A reaction that may belong to this class is that between quinoline, benzoyl chloride, and phthalimidine to give 1,3-di-(2-quinolyl)isoindole (**36**).[584] Equally unusual is the reaction reported between quinoline (in excess) and methyl bromocyanoacetate, giving the 1,2,3,4-tetrahydroquinoline (**37**; R = H) which with methanol and hydrogen chloride gave dimethyl 3-quinolylmalonate (**38**).[585, 586] The stereochemistry of compound (**37**; R = H) was established by nmr data and by

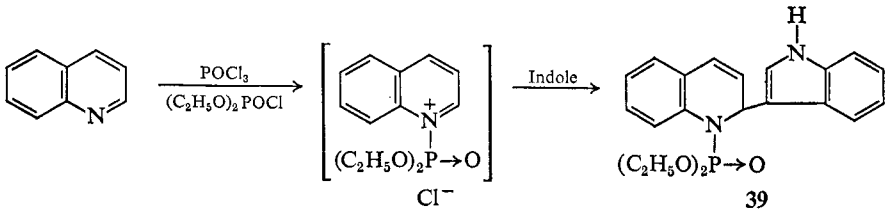


comparison with the bromo-derivative (**37**; R = Br) whose molecular structure was established by X-ray crystallography.

Thiocyanate ion does not substitute in the 2-position of quinoline under Reissert conditions, giving instead quinolinium thiocyanate.[587]

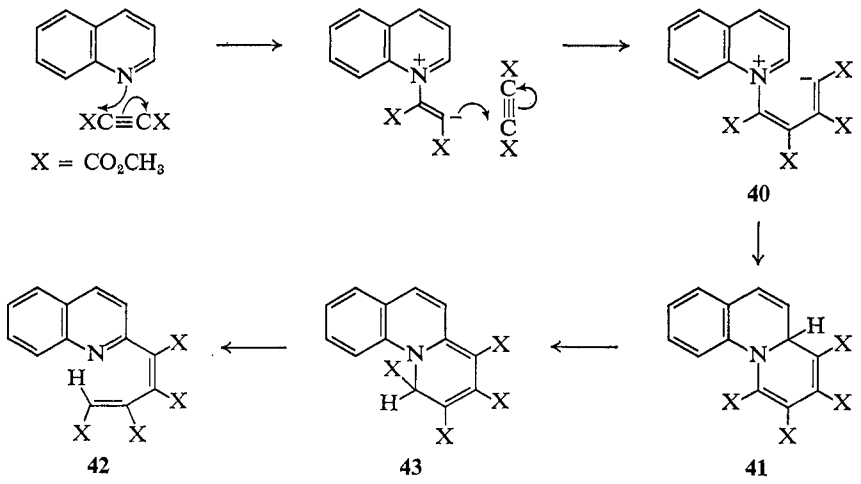
All the types of Reissert reaction have been interpreted in terms of an initially formed 1-acylquinolinium salt, which has enhanced reactivity towards nucleophilic attack at position 2. Johnson and Ridd have shown that a Reissert product can be obtained from 1-cyanoquinolinium fluoroborate.[569] Although 1-acylquinolinium compounds cannot normally be isolated, there is a report of a complex from oxalyl chloride and two molecules of quinoline[588] and of the presence of 1-acetylquinolinium bromide in solution[589] and as a solid.[590].

Quinoline was reported to react with phosphoryl chloride and a phosphorochloridate to give a quaternary compound, which with indole gave the 1,2-dihydroquinoline derivative (**39**).[591]

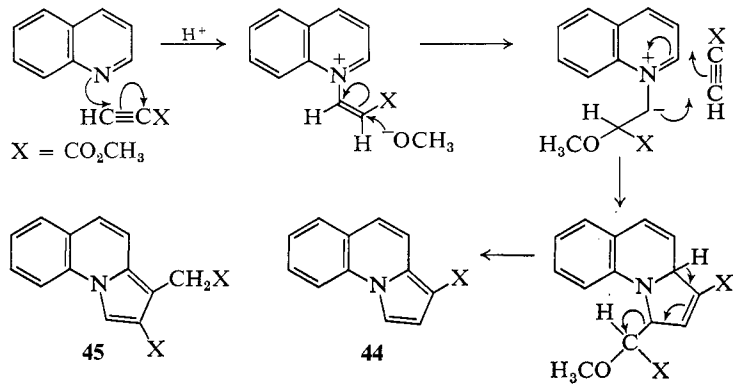


A number of species react with quinoline to give 1,2-cycloaddition products. Diels, Alder, and their co-workers noted that quinoline reacted with acetylenedicarboxylates in a manner similar to that of pyridine.[592, 593] Two products were obtained, a labile and a stable isomer, each made up of one quinoline and two acetylenedicarboxylate molecules. Diels and Alder thought of them as an intermediate dipolar species (**40**;

X = CO_2CH_3) (labile), and a tricyclic system (**41**; X = CO_2CH_3) (stable). Later authors have suggested that the labile isomer is in fact the 4a*H*-benzoquinolizine (**41**);[594, 595] initial disagreement as to the structure of the stable isomer, which was

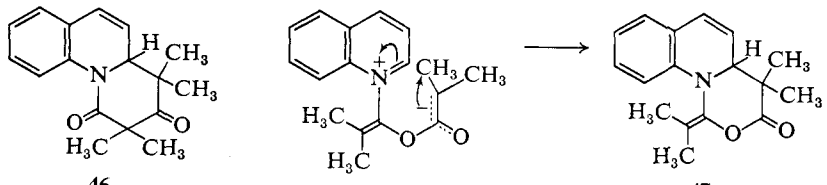


formulated both as the quinolylbutadiene (**42**)[594] and as the 1*H*-benzoquinolizine (**43**),[595] has been resolved in terms of the latter structures.[596] The dipolar intermediate (**40**) has not been isolated. Methyl propiolate behaves differently on reaction with quinoline, giving small yields of the benzindolizines (**44**) and (**45**); the mechanism suggested for this reaction is shown (X = CO_2CH_3).[597]

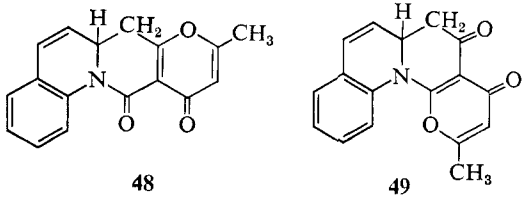


Staudinger and Klever first reported the cycloaddition reaction between quinoline and dimethylketen, giving an adduct formulated as (**46**).[598] Later workers pointed out more likely structures for the adduct, and on the basis of spectral and degradative evidence preferred the oxazino quinoline structure. (**47**)[599, 949] Another group has examined the adducts formed between quinoline and diketen in boiling benzene and obtained a product of formula $C_{17}H_{13}NO_3$; this corresponds to the addition of two molecules of diketen, with elimination of one molecule of water. The structure

suggested for the adduct was (**48**) or (**49**);[600] the former seems more likely. The mechanism of addition must be different from that followed by dimethylketen.



46 **47**



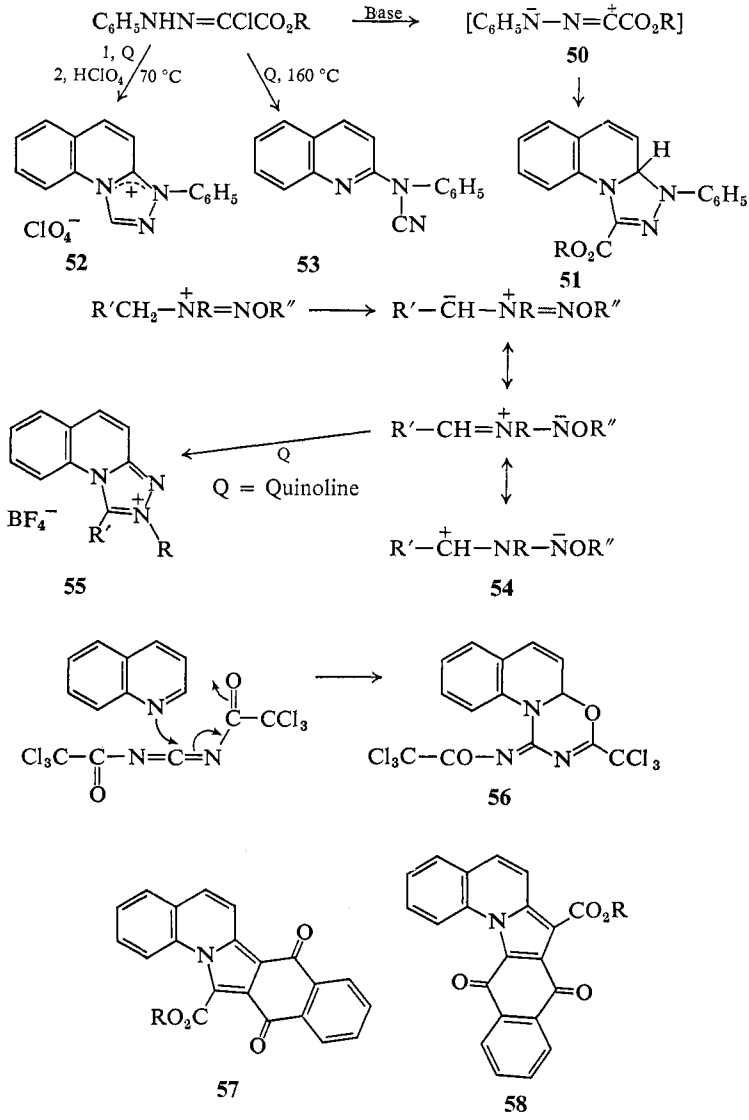
48 **49**

Staudinger also reported the formation of adducts from quinoline and diphenylketen[601, 602] or diphenyleneketen.[603] The reported properties of these adducts, notably their complete dissociation in hot chloroform or benzene, suggest that they are more likely to be molecular complexes than compounds in which new nitrogen-to-carbon or carbon-to-carbon bonds have been formed, such as those described above.

s-Triazoloquinolines have been obtained by reaction between suitable 1,3-dipolar species and the C=N bond of quinoline. Fusco, dalla Croce, and Salvi[604] used arylhydrazonochloroacetic esters, ClC(OR)=NNHAr, which with the heterocyclic base or added triethylamine could give the 1,3-dipolar species (**50**); after addition to quinoline the [1,2,4]triazoloquinoline (**51**) was obtained. After reaction at higher temperatures (70 °C) the CO_2R-free triazoloquinolinium salt (**52**) could be isolated after addition of perchloric acid to the reaction mixture; reaction at still higher temperatures (160 °C) gave the cyanamide (**53**), either directly from quinoline and *tert*-butylhydrazonochloroacetate or from compound (**52**) by treatment with more quinoline. Hünig and his co-workers used alkoxydiazenium salts (**54**) as 1,3-dipolar species and obtained, from quinoline, triazoloquinolinium salts of general type (**55**).[605] The reaction between quinoline and trichloroacetyl isocyanate gave first a dimer of the isocyanate and then, by cycloaddition of this dimer with loss of CO_2, a tricyclic compound (**56**).[606]

The yields of the triazoloquinolinium salts of type (**55**) were on the whole inferior to those obtained with isoquinoline; in a direct competition between quinoline and isoquinoline only the triazoloisoquinolinium salt was isolated. It is not clear whether this is a reflection of the relative steric hindrance of the nitrogen atom in quinoline, its weaker basicity, or other factors. It is noteworthy that isoquinoline gave a diaryl tricyclic 1,2-adduct with diphenylcyclopropenone but quinoline did not.[607]

A 1,2-cycloaddition product formed by reaction between quinoline, ethyl acetoacetate, and 2,3-dichloro-1,4-naphthoquinone is shown below (**57**; R = C_2H_5).[608] The same compound was obtained in poorer yield from diethyl malonate; the corresponding methyl ester (**57**; R = CH_3) was obtained from dimethyl malonate or from methyl acetoacetate. No detailed mechanism has been given; a dipolar mechanism would lead to the isomeric structure (**58**).

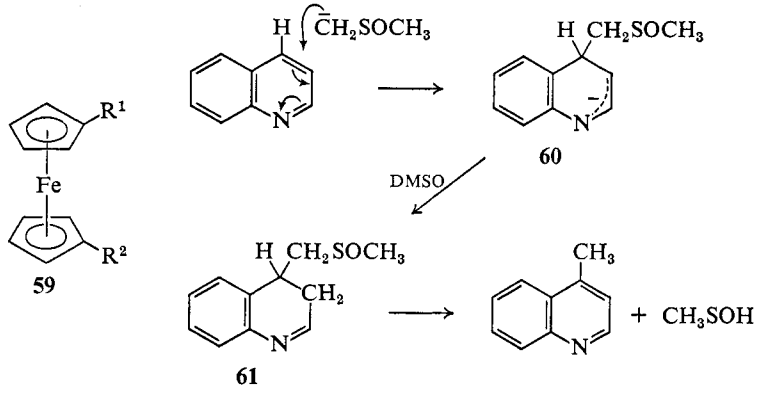


Addition of bromine to the heterocyclic ring of quinoline has been suggested as a mechanism for the bromination of quinoline under neutral conditions; such additions are considered in the section on electrophilic addition. The only example of halogen addition similar to that commonly observed with benzenes and naphthalenes is provided by the isolation of heptafluorodecahydroquinoline in 2% yield after passage of quinoline over cobalt fluoride at 400 °C, fractionation, and passage of one fraction over uranium hexafluoride;[609] much decomposition occurred, with production of various fluorinated cyclohexenes. Hexachlorobenzene and hexachloroethane were isolated after treatment of quinoline with antimony pentachloride.[610]

2. Nucleophilic Substitution Reactions

In many respects the 1,2-addition reactions of quinoline and the nucleophilic substitution reactions merge into one another; the commonly accepted mechanism for nucleophilic substitution involves a 1,2-dihydroquinoline as an intermediate. Reactions that commonly give as the isolated products a 2-, or more rarely, a 4-substituted quinoline are dealt with in this section.

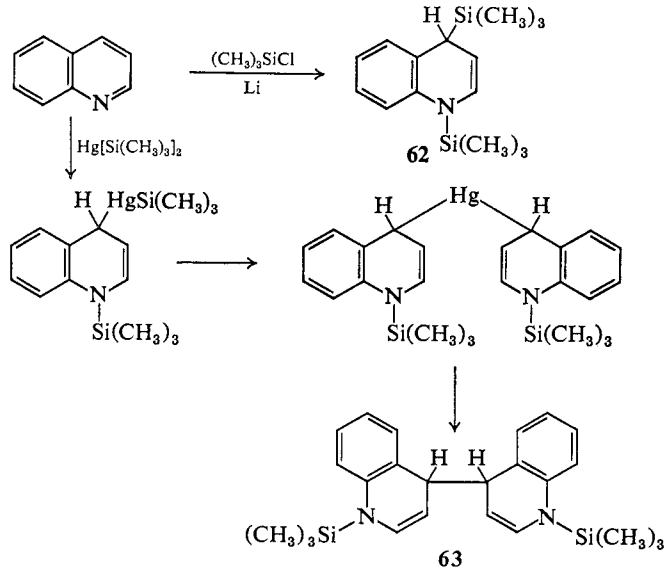
The reaction between quinoline and an alkyl- or aryl-lithium reagent, or between quinoline and a Grignard reagent, have been referred to previously (p. 30). The majority of reactions between quinoline and organometallic reagents of these types appear to give 2-substituted quinolines and fall within the scope of this section. Thus 2-phenylquinoline is obtained from quinoline with phenylsodium[611] (67%), phenyllithium[554, 612, 613] (85%), or phenylmagnesium bromide,[614–617] (66%). The reaction with phenyl-lithium provides the only report of the isolation of some 4-substituted quinoline as well as the normal 2-substituted product,[554] but Abramovitch and his co-workers subsequently reported that no 4-phenylquinoline could be identified among the products.[613] Two groups have reported an uncharacterized intermediate in the reaction between quinoline and phenylmagnesium bromide. Gilman and Gainer obtained 2-(4-biphenylyl)quinoline from quinoline and 4-lithiobiphenyl without the nitrobenzene oxidation that was necessary with the products from quinoline and 2- or 3-lithiobiphenyl.[618] A very poor yield (2.9%) of 2-ferrocenylquinoline (**59**; R^1 = 2-quinolyl, R^2 = H) from ferrocenyl-lithium and quinoline was



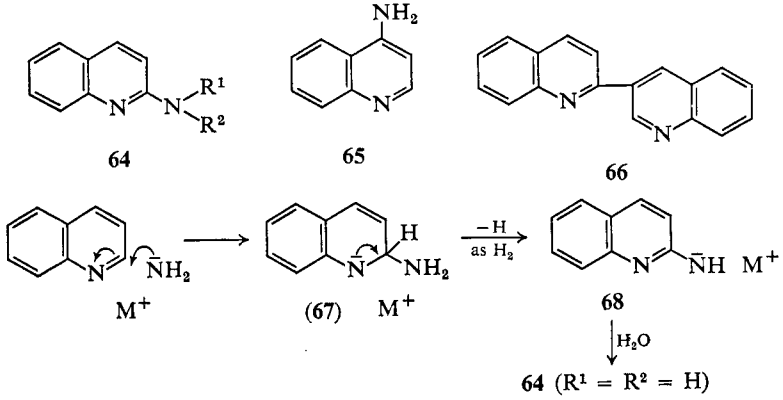
accompanied by an even smaller yield of the di-(2-quinolyl)ferrocene (**59**; $R^1 = R^2$ = 2-quinolyl).[619] The methylsulphinyl carbanion causes nucleophilic substitution (the suggested mechanism is shown, **60** → **61**) to give only 4-methylquinoline;[620] this reaction is so far unique in its production of only the 4-substituted quinoline.

Quinoline and lithium di-isopropylamide, with added hexamethylphosphorotriamide, gave 2,2′-biquinoline in 74% yield; the reaction was thought to involve α-metallation, the quinoline 2-anion adding to a second molecule of quinoline.[621] The reaction of lithium with trimethylchlorosilane, followed by quinoline, gave 1,4-dihydro-1,4-bis(trimethylsilyl)-quinoline (**62**), which is a useful silylating agent.[622] Bis(trimethylsilyl)mercury at 50 °C gave a 4,4′-dihydroquinoline dimer (**63**), silylated on nitrogen; the product was not completely purified, but the structure was clearly established by the ^{1}H-nmr spectrum.[623]

Probably the best known nucleophilic substitution reaction of quinoline is the Chichibabin amination. Originally reported[624] as giving a 2-aminoquinoline (**64**;

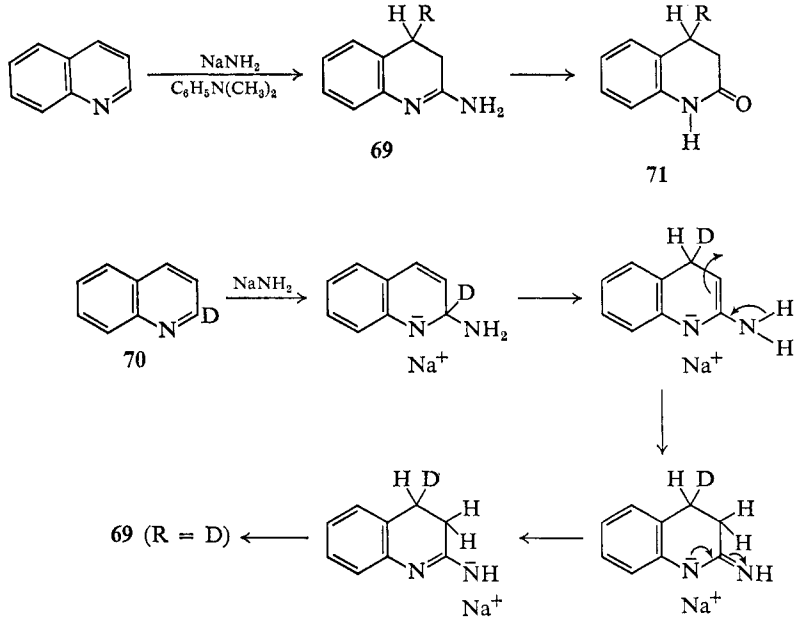


$R^1 = R^2 = H$) it was subsequently noted[625] that the products included 4-aminoquinoline (**65**); the reagent was sodium amide in boiling toluene. Another minor product was a dihydroquinoline, oxidized to 2,3′-biquinoline (**66**). A very thorough study of the amination reaction by Bergstrom[626] showed that for solutions of quinoline in liquid ammonia at 20 °C the reaction was very slow, or did not proceed at all, with the amide of lithium, sodium, potassium, or strontium; in a later paper Bergstrom reported the isolation of up to 50% yield of 2-aminoquinoline, with some 4-aminoquinoline, if potassium nitrate was added to a solution of quinoline and



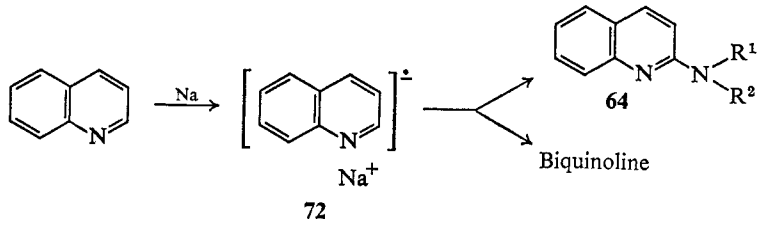
sodium amide in liquid ammonia.[627] The best results were obtained by using barium amide (80% of 2-aminoquinoline, with no 4-aminoquinoline), and the reaction was catalysed by the addition of barium salts, notably the thiocyanate or nitrate.[626] Hydrogen was collected during the reaction and Bergstrom suggested that the initial addition product (**67**) lost hydrogen to give the anion (**68**). The importance of particle size in non-homogeneous reactions has been emphasized.[628]

A detailed examination has been made of the reaction between quinoline[629, 630] (or some alkylquinolines[631–633]) and sodium amide in dimethylaniline. Kametani and his co-workers were able to isolate appreciable quantities (up to 24%) of 2-amino-3,4-dihydroquinoline (**69**; R = H) in dimethylaniline as solvent; no dihydro-product was obtained in benzene or toluene. When the reaction was performed with 2-deuterioquinoline (**70**) hydrolysis of the product yielded 4-deuterio-3,4-dihydrocarbostyril



(**71**; R = D) via the intermediate 2-amino-4-deuterio-3,4-dihydroquinoline (**69**; R = D); their suggested mechanism is shown above. Zoltewicz and his co-workers found that the kinetic product of amide addition in liquid ammonia at −45 °C was the 2-amino-1,2-dihydroquinoline anion, while the thermodynamic product was the 4-amino-1,4-dihydroquinoline anion.[634] They also showed that quinoline is covalently aminated in liquid ammonia.[635]

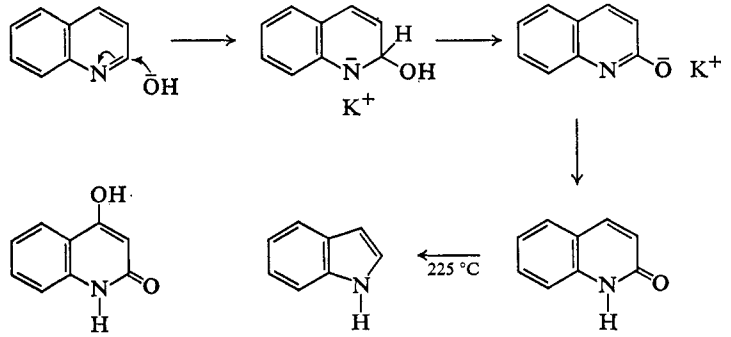
Attempts to extend the scope of the Chichibabin amination by the use of substituted ammonias (hydrazines, amines) have met with variable success. Sodium hydrazide reacted with quinoline to give 2-hydrazinoquinoline (**64**; R^1 = H, R^2 = NH_2) provided that no free hydrazine was present.[636] Lithium methylamide and quinoline gave 2-(methylamino)quinoline (**64**; R^1 = H, R^2 = CH_3);[637] the same product was reported to be formed from sodium methylamide and quinoline.[638] Primary amines and a fused eutectic of sodium amide and potassium amide also gave 2-(alkylamino)quinolines.[639] However, a different mechanism may be involved in the reaction between quinoline and a primary amine with sodium; it was suggested that the radical anion (**72**) was formed, and that this in turn reacted with the primary amine (butylamine or 2-(dimethylamino)ethylamine) to give the 2-substituted quinoline (**64**; R^2 = Bu^n or $(CH_3)_2NCH_2CH_2$, R^1 = H).[640] In this case no 2-substitution was achieved by using phenylhydrazine or morpholine; in general the use of secondary or tertiary amines gave only biquinolines.[641]



72

There is no report of the production of 2-(dialkylamino)quinolines by any variant of the Chichibabin reaction. Of uncertain mechanism is the reaction between quinoline and ammonia with Raney nickel under high pressure; a 15% yield of 2-aminoquinoline was reported.[642]

Chichibabin was also responsible for the observation that high yields of carbostyril (**73**) could be obtained if quinoline was heated with absolutely dry potassium hydroxide; lower yields were obtained by using barium oxide.[643] Since one mole of hydrogen was collected for each mole of quinole used, it was assumed that the mechanism of the reaction was similar to that of amination. The only by-product after reaction at 225 °C was tentatively identified as indole (**74**), which is known[644] to be formed as a product from alkali fusion of carbostyril. Some 4-hydroxy-2(1*H*)-

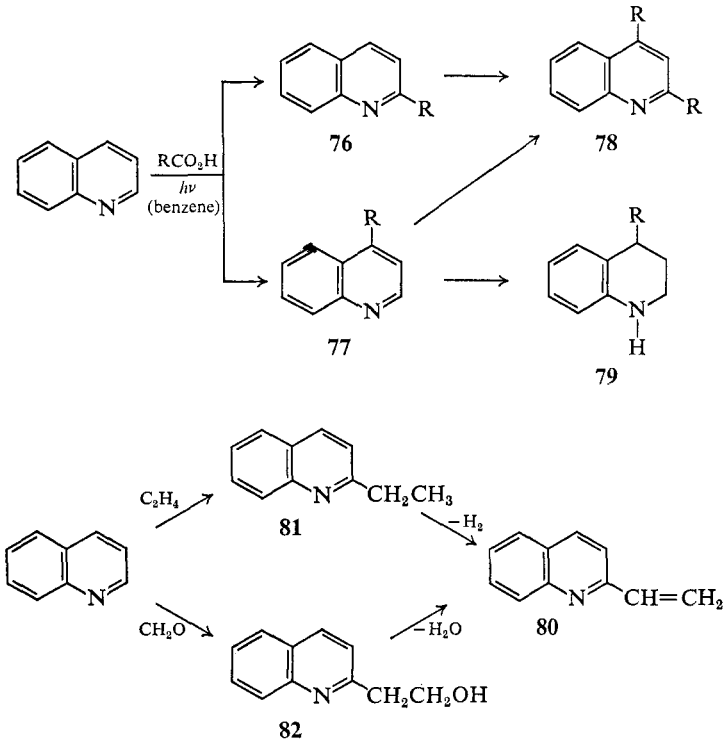


75 74 73

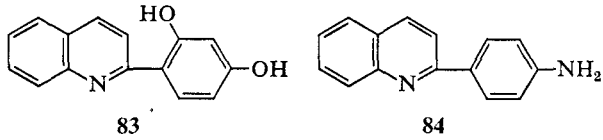
quinoline (**75**) was thought to be formed at higher temperatures. Carbostyril is also produced when quinoline is treated with hypochlorites or with hypochlorous acid; this may involve attack on the nitrogen atom by positive halogen, with subsequent attack by nucleophile at position 2.[645–648]

There are a number of reactions other than by organometallic reagents that lead to 2- or 4-substituted quinolines; some are of indeterminate mechanism but are grouped here for convenience. In the photochemical alkylation of quinoline by means of carboxylic acids, attack by an anion has been suggested[649] (contrast the alkylations described on p. 58). The products obtained, in varying proportions, were the 2-alkyl- (**76**) and 4-alkyl-quinolines (**77**), 2,4-dialkylquinolines (**78**) and the appropriate 4-alkyl-1,2,3,4-tetrahydroquinoline (**79**); a radical mechanism was excluded because of the success of the reaction when R was *tert*-butyl.

In two routes to 2-vinylquinoline (**80**), quinoline was alkylated either with ethylene over a silicon–alumina catalyst[650] or with formaldehyde in boiling alcohol.[651] The intermediates were 2-ethylquinoline (**81**) or 2-(2-hydroxyethyl)quinoline (**82**), respectively.



There is an account of reaction between quinoline and aromatic amines[652] or phenols[653] in which, for example, 2-(2,4-dihydroxyphenyl)quinoline (**83**) was formed; the conditions of the reaction and the mechanism are obscure. Equally obscure is the alkylation of quinoline by alcohols or amines with added ruthenium chloride and

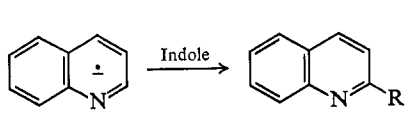


83 **84**

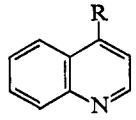
triphenylphosphine.[654] Much earlier, quinoline hydrochloride had been shown to react under drastic conditions with aniline to give 2-(*p*-aminophenyl)quinoline (**84**).[845] Quinoline gave a 5% yield of 2-(3-indolyl)quinoline (**86**) when heated with indole in dimethylformamide;[655] higher yields were obtained with quinoline, aluminium powder, mercuric chloride, and indole were heated in benzene to 190–200 °C.[656] Since 2,2′-biquinoline was formed when the indole was omitted[657] this is not certainly a nucleophilic substitution. The quinoline radical anion reacted with indole to give the products summarized (**85**) to (**90**) in the yields shown.[658]

Quinoline reacts with benzophenone and lithium to give two products, 2-benzhydrylquinoline (**91**) and the tricyclic compound (**92**).[659, 660] The mechanism advanced for the production of 2-(α-hydroxybenzhydryl)quinoline is shown and involves

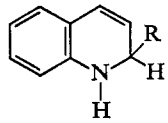
attack by the anion; it was suggested that the production of compound (**92**) may involve radical anions.



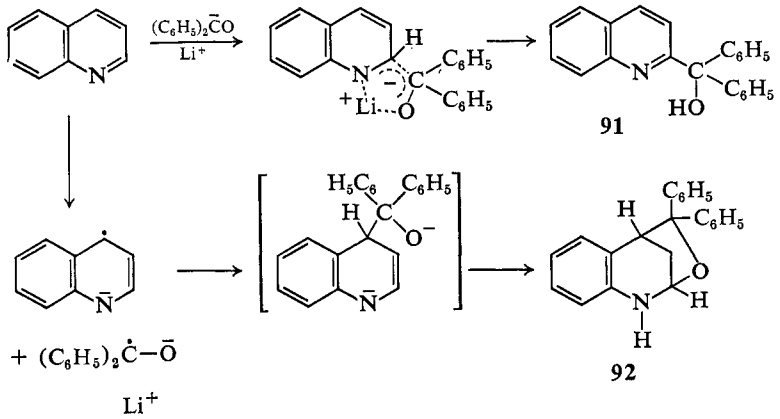
85; R = 2-Indolyl, 3.5%
86; R = 3-Indolyl, 26.5%
87; R = 3-Quinolyl, 15%



88; R = 2-Indolyl, 9%



89; R = 2-Indolyl, 12.5%
90; R = 3-Quinolyl, 12%



3. Electrophilic Substitution Reactions

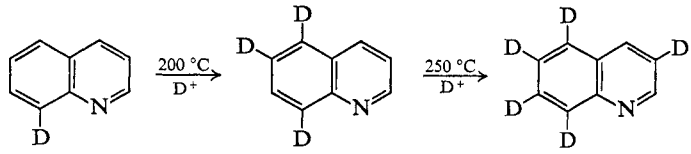
The major part of mechanistic and synthetic effort has been expended on studies of electrophilic substitution. The general pattern of electrophilic substitution shows preferred attack at nitrogen, and at positions 5 and 8 or 3, 6, and 8. Taylor has used the pyrolysis of 1-(*x*-quinolyl)ethyl acetate to obtain a direct measure of the electrophilic reactivity at position *x*.[661] By this method he derived some general conclusions:

1. All positions in quinoline are less reactive than naphthalene.
2. All positions in the nitrogen-containing ring of quinoline are more reactive than ring positions in pyridine.
3. With the exception of the 5-position, all quinoline positions are deactivated relative to benzene.
4. Apart from positions 2 and 4, all quinoline positions differ from those of benzene by only a slight amount.

He arrived at the order of reactivity:

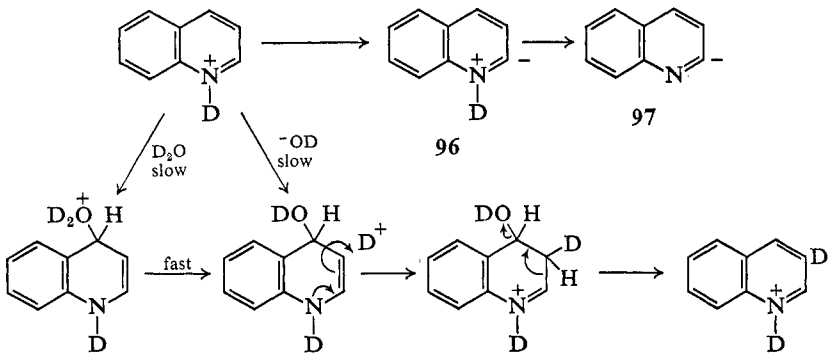
$$5 > \text{phenyl} > 8 = 6 > 3 > 7 \gg 2 > 4$$

The simplest electrophile is the proton; studies of deuteriation by deuteriosulphuric acid showed that at 150 °C, with 70% acid, 8-deuterioquinoline (**93**) was formed.[204, 662] Raising the temperature (to 200 °C) or increasing the concentration of the acid (to 96.5%) gave 5,6,8-trideuterioquinoline (**94**); finally, by using 90% acid at 250 °C, 3,5,6,7,8-pentadeuterioquinoline (**95**) was obtained. A careful study of the reaction



93 **94** **95**

between quinoline and deuteriosulphuric acid was made by Bressel, Katritzky, and Lea, using nmr spectroscopy to follow the deuterium exchange.[663] At 180 °C, over the range $H_0 - 4$ to -9, substitution occurred first at position 8, then at positions 5 and 6. At 245 °C, over the range pH $+0.5$ to $H_0 - 3$, the rate profiles were complex; at low acidity the exchange occurred first at position 2, then position 3, then at positions 8 and 5, with very slow exchange at position 6; at increased acidities the rate at positions 2 and 3 decreased, while those at positions 8, 5, and 6 increased, with some exchange at position 7; no exchange at position 4 was observed. Exchange on the benzene ring, whether at 180 or 245 °C, was thought to occur on the conjugate acid. At lower acidities the exchange at position 2 was thought to involve proton abstraction, giving (**96**). Substitution at position 3 was suggested to proceed through covalent hydration (at high acidities by D_2O, at low acidities by OD^-) as shown in Scheme 1.



96 **97**

SCHEME 1

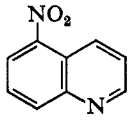
A suggested procedure for the standardization of acid-catalysed hydrogen exchange rates to 100 °C and pH 0 has been suggested and applied to quinoline.[664] However, standard K_0 rate constants for hydrogen exchange and for nitration have shown such wide variations that it has been suggested that there is no unique order of susceptibility to electrophilic attack and that no single reactivity index can be used as a measure of electrophilic reactivity.[951] Zoltewicz and Sale used nmr measurements to study base-catalysed exchange of quinoline with CH_3OD and sodium methoxide.[665]

The second-order rate constants were:

Position	2	3	4	8
Rate constant (mol l^{-1} s^{-1})	4.5×10^{-5}	3.0×10^{-4}	9.4×10^{-4}	4.5×10^{-5}
Ratio	1	6.7	21	1

Here again the preferred mechanism involved deprotonation, giving an anion such as (**97**) which was inhibited for position 2 and position 8 by the influence of the nitrogen lone pair. There was, however, no large effect on the *peri*-position 8. These results may be contrasted with catalytic deuteriation or tritiation with heavy water over a platinum catalyst, where incorporation was predominantly in the 4-position.[666, 667] Here a charge-transfer–no-bond adsorption mechanism appeared to operate.[666] On nickel catalysts, exchange was found at positions 2, 7, and 8.[205, 668] Treatment of quinoline with a labelled carboxylic acid, RCO_2D or RCO_2T, in the presence of a Friedel–Crafts catalyst, was reported to give deuterium- or tritium-labelled quinoline.[669]

Early papers on the nitration of quinoline were concerned with maximization of the yield and with methods for separating the mixed 5-nitroquinoline ("*meta*" or "*ana*"-nitro) (**98**) and 8-nitroquinoline ("ortho"-nitro) (**99**). Königs reported that cold fuming nitric acid failed to nitrate quinoline, but that a mixture of fuming nitric acid and "englischer" sulphuric acids at 100 °C produced a mixture.[670] Claus and Kramer observed that the mononitroquinoline mixture was complicated by the presence of two dinitroquinolines,[671] and Dufton was able to show that by using quinoline nitrate and adding the salt to a cooled mixture of sulphuric acid and oleum an 87% total yield of mononitroquinolines could be obtained, in a ratio 5-nitroquinoline to 8-nitroquinoline of 4 : 3;[672] a minor product in this reaction was a hydroxydinitroquinoline; the mononitroquinolines were easily separated by virtue of the much greater insolubility of 5-nitroquinoline nitrate;[672] the dinitroquinolines were subsequently shown to be 5,7- (**100**) and 6,8-dinitroquinoline (**101**),[673] and the minor



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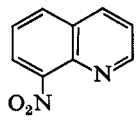

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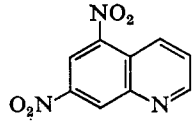

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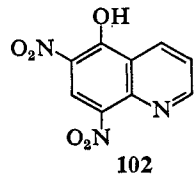

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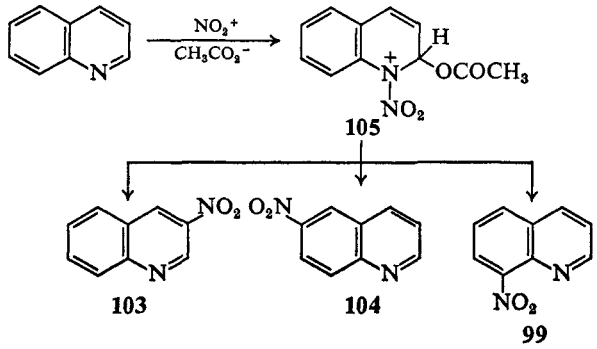
product obtained by Dufton was shown to be 5-hydroxy-6,8-dinitroquinoline (**102**).[674] Later workers have reported[675–677] the isolation of various ratios of 5- to 8-nitroquinoline, but all agree that these are the major products when mixed acid or fuming nitric acid is used.

In an investigation of the action of other nitrating agents on quinoline (not all of electrophilic character, see p. 60), Dewar and Maitlis were able to devise chromatographic methods for the separation of the various mononitroquinolines.[56] The

major product from nitrations by metal nitrates or nitric acid in acetic anhydride was 3-nitroquinoline (**103**), not as had been previously reported[678] 7-nitroquinoline; the other products formed, in lower yield (the overall yield of mononitroquinolines was poor). were 6- (**104**) and 8-nitroquinoline (**99**). As the production of 3-nitro-



quinoline was unexpected, the reaction was rationalized in terms of a 1,2-dihydroquinoline intermediate (**105**). If a cupric nitrate–quinoline complex was treated with sulphuric acid, however, the product was reported to be a mixture of 5- and 8-nitroquinoline.[679]

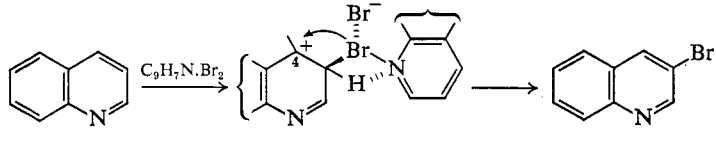
There have now been reported several studies of the nitration of quinoline by mixed acid. Ridd and his co-workers have examined[680, 681] the nitration of quinoline in 85–100% sulphuric acid and showed it to be of the second order, described by the equation $v = k_2$[quinoline] [nitric acid]. The reaction profiles for nitration of quinoline base and of the quinolinium ion were calculated and compared with the experimental results; the quinolinium ion profile was found to be very similar to that determined experimentally. This suggestion was confirmed by Schofield and his co-workers,[682] who showed that logarithms of the rate constants for the nitration of quinoline, 1-methylquinolinium perchlorate and many other substrates showed a closely parallel dependence on acidity (80–84% sulphuric acid); the free base would be expected to show a much shallower dependence on acidity owing to decreasing concentration of free bases with increasing acidity. Figures for the ratio of reactivity of quinoline to benzene (1.2×10^{-7})[682] and to naphthalene (10^{-10})[681] have been derived. By the use of ^{14}C-labelled quinoline Crout, Penton, and Schofield were able to obtain partial rate factors for five positions in the quinoline nucleus;[683] these were:

Position	3	5	6	7	8
Partial rate factor	4.57×10^{-12}	1.74×10^{-7}	5.58×10^{-9}	4.76×10^{-11}	1.47×10^{-7}
Ratio	1	38,100	1220	10.4	32,200

Attempts to nitrate quinoline by nitryl fluoride gave only intractable tars.[684] Nitration of quinoline by tetranitroatotitanium(IV) gave low yields (6–10%) of 3-nitroquinoline; tetranitratotozirconium(IV) at room temperature gave a 90% yield of 7-nitroquinoline.[950] Products were not isolated but were identified by gas–liquid chromatographic comparison with authentic specimens.

The direct bromination of quinoline in inert solvents has been the subject of discussion since the early 1880's when, for example, Claus reported the preparation of a "tetrabromoquinoline" by interaction of quinoline and bromine in carbon

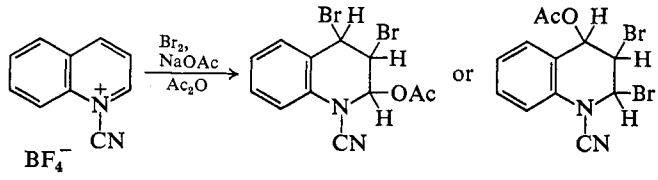
disulphide.[685] A number of other "polybromoquinolines" were prepared in different solvents;[686, 687] the structures have been clarified by the work of Eisch.[688-691] In practical terms, quinoline can be converted into 3-bromoquinoline (**106**) in 41% yield by treatment of the hydrochloride with bromine in nitrobenzene,[692, 693] in 70–75% yield by bromine in carbon tetrachloride,[694] or in up to 80% yield if the initial complex from quinoline and bromine is heated in carbon tetrachloride with added bromine.[688, 689] The change in the electronic absorption spectrum observed on mixing quinoline and bromine in carbon tetrachloride, combined with the observation that no extra maxima appear in the spectrum of 8-methylquinoline or 8-bromoquinoline on similar addition of bromine, led to the suggestion[691] that an *n*-donor complex was initially formed. Similar evidence for quinoline–iodine complexes is available.[695] The complex $C_9H_7N.Br_2$, when heated dry, gave 3-bromoquinoline and quinolinium tribromide.[477] Further bromination products observed were 3,6-dibromoquinoline (**107**), 3,8-dibromoquinoline (**108**), and 3,6,8-tribromoquinoline (**109**).[686, 696] If bromination to give 3-bromoquinoline proceeds through di- or tetrahydroquinoline intermediates (as suggested by Johnson, see below), the benzenoid ring in these intermediates can be viewed as a derivative of aniline, and 6- or 8-substitution would be the logical pattern. Eisch has suggested that direct electrophilic attack by the quinoline–bromine complex on position 3 will be favoured by the possibility of 3,4-bromonium ion formation [intermediate (**110**)] in which the incipient positive charge is particularly well sited on position 4.



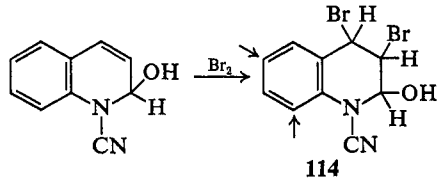
110 **106**

107 **108** **109**

The suggestion that dihydro- or tetrahydro-quinoline intermediates were involved in bromination was advanced by Johnson and Ridd.[569, 697] They observed that 1-cyanoquinolinium fluoroborate (**111**) not only added bromine in a mixture of acetic anhydride and sodium acetate to give the dibromotetrahydroquinoline (**112**) [or less probably its isomer (**113**)], but that the 1-cyanoquinolinium salt in perchloric acid was brominated to 3-bromoquinoline (**106**), with an appreciable quantity of 3,6-dibromoquinoline (**107**), some quinoline, and some 3,6,8-tribromoquinoline (**109**). The same products could be obtained by the action of bromine on 1-cyano-1,2-dihydro-2-hydroxy-quinoline (**23**; R = CN); a possible intermediate was compound (**114**) which could either lose hydrogen bromide and water or undergo further bromination (as a substituted aniline) in the 6- or in the 8-position. Some kinetic data are available on the direct bromination of quinoline; the reaction was said to be of the first order in bromine and of the second order in quinoline when the concentrations were comparable; when an excess of quinoline was present the reaction was first-order for both.[698]



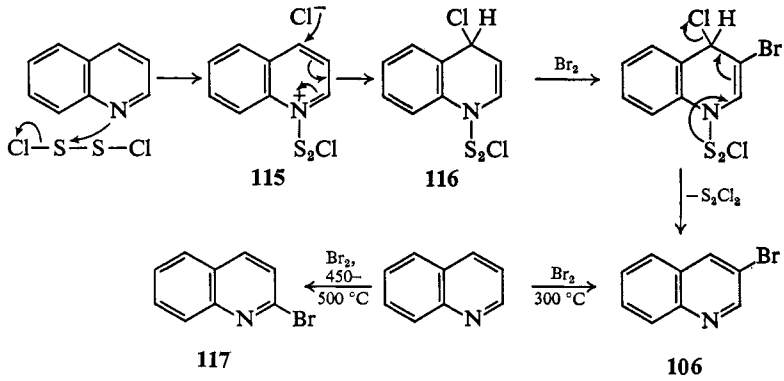
111 112 113



114

106 + 107 + 109

Before high yields of 3-bromoquinoline were achieved by use of bromine alone, the most satisfactory brominating agents were sulphuryl bromide or bromine and elementary sulphur. Edinger reported the isolation of 3-bromoquinoline (**106**) (55%) and a tribromoquinoline, probably 3,6,8-tribromoquinoline (**109**) from its melting point.[699, 700] More recent work[701] showed that an improved yield of 3-bromoquinoline (**106**) followed from use of sulphur monochloride and bromine with added pyridine. A dihydroquinoline intermediate (**116**) was proposed, obtained from a quaternary compound (**115**); the vinylamine system would be expected to undergo rapid bromination with subsequent loss of S_2Cl_2.

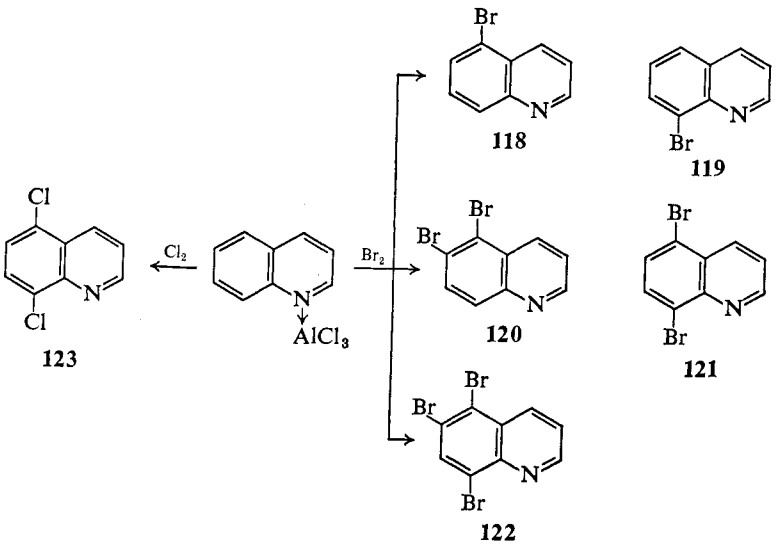


115 116 117 106

Direct bromination in the vapour phase at 300 °C gave (as with pyridine) bromination in the 3-position.[702] The yield was low (25% on the quinoline used) with much recovery of starting material; a small yield of dibromoquinoline (possibly the 3,4- or the 3,5-isomer) was also recorded. At 450 °C the main product was 2-bromoquinoline (**117**) although some 3-bromoquinoline was still obtained; at 500 °C a good yield of 2-bromoquinoline (**117**) could be achieved, especially when the vapours were

diluted with nitrogen. Suggestions have been made that radical bromination predominates at the higher temperature. Eisch has noted[691] that 3-bromoquinolinium bromide can decompose at 300 °C (although it must be noted that 4-bromoquinoline and not 2-bromoquinoline is formed), and he has suggested that the differing patterns of substitution at 300 and 500 °C may indicate different stabilities of the isomers rather than differing mechanisms.

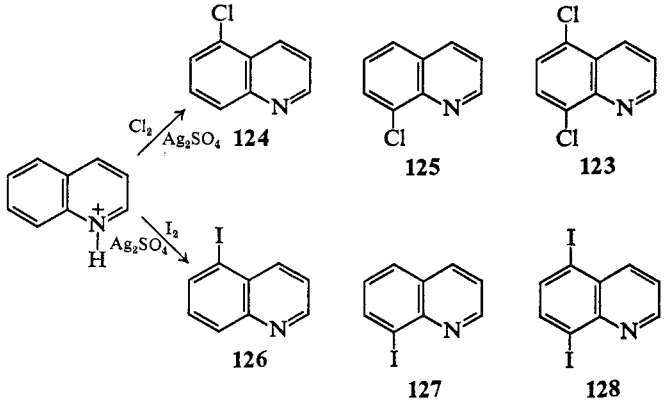
True electrophilic substitution by halogens is probably only shown by the quinolinium ion, or by quinoline in the presence of a strong complexing agent. Quinoline formed a complex with aluminium chloride which reacted with bromine to give a mixture of 5-bromoquinoline (**118**) with small amounts of 8-bromo (**119**), 5,6-dibromo (**120**), 5,8-dibromo- (**121**), and 5,6,8-tribromo-quinoline (**122**); increased



molar ratios of quinolines raised the proportion of dibromoquinolines (particularly of 5,8-dibromoquinoline) to a maximum of 62%.[703] Gaseous bromine reacting directly with the complex gave up to 70% of purified 5,8-dibromoquinoline (**121**); the use of gaseous chlorine gave a similar yield of 5,8-dichloroquinoline (**123**).[704]

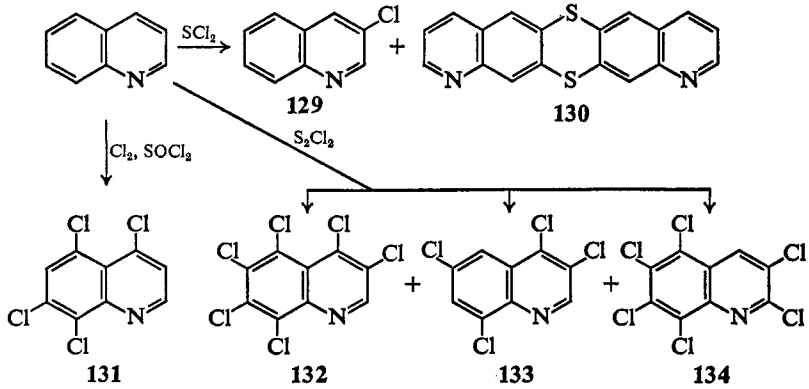
Halogenation in sulphuric acid (of concentration greater than 95%) would be expected to involve the quinolinium ion, and hence, as in nitration, should lead to substitution in the 5- and the 8-position. In practice, bromination with bromine and silver sulphate in sulphuric acid shows good agreement with nitration[705, 706] although appreciable quantities of 5,8-dibromoquinoline (**121**) were also obtained. No bromination of quinoline was observed on using bromine and sodium acetate in acetic acid, or using bromine and silver nitrate in concentrated nitric acid.[706] The suggested electrophilic species was $BrH_2SO_4^+$ or $BrSO_3^+$. Subsequent work showed that chlorination by chlorine and silver sulphate in sulphuric acid gave 5-chloro- (**124**), 8-chloro- (**125**), and 5,8-dichloro-quinoline (**123**);[707, 708] similarly, iodine added to a mixture of silver sulphate and sulphuric acid at 150–200 °C gave 5-iodo- (**126**), 8-iodo- (**127**), and 5,8-di-iodo-quinoline (**128**).[709, 710] In the latter case it was established that 3-iodoquinoline was stable under the reaction conditions, so a rearrangement is unlikely: the electrophilic species suggested was I^+. A mixture containing some 5-bromoquinoline was obtained when the complex $(C_9H_7N)_2Br^+ClO_4^-$ was allowed

to decompose in aqueous media; this may also involve true electrophilic attack by some positive species.[711]



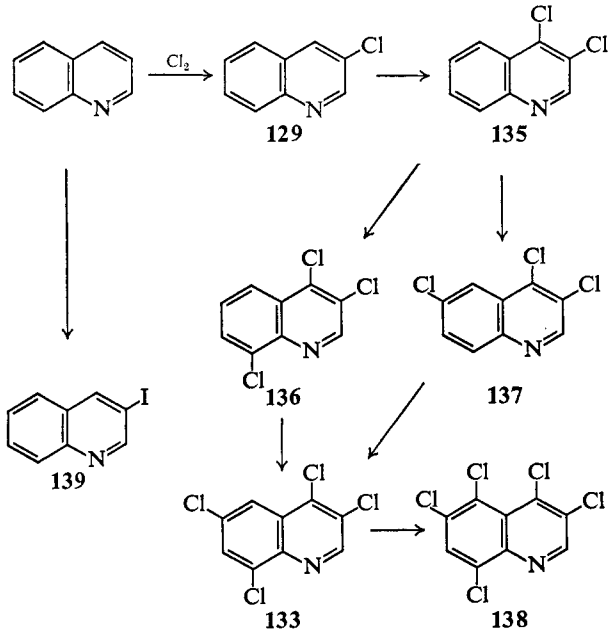
A very thorough comparative study of various methods of bromination has been made by Butler and Gordon;[936] they have confirmed that high yields can be obtained by Eisch's method[689] and by that of Kress and Costantino.[692] They provided corrected figures for product ratios in many of the other bromination procedures by the use of improved analytical techniques, and in one experiment were able to obtain appreciable amounts of 7-bromoquinoline, which had not been previously reported in direct bromination experiments.

Chlorination follows the same general pattern as bromination, although it has been less intensively studied. Attempts at chlorination by antimony pentachloride at temperatures raised gradually to 400 °C converted quinoline into hexachloroethane and hexachlorobenzene.[610] Chlorination by sulphur dichloride at 160 °C gave 3-chloroquinoline (**129**) (20%) and a trichloroquinoline, but the major product was a "quinolylbisulphide",[700] later formulated as a thiaquinanthrene (dipyrido[3,2-*b*:2′,3′-*i*]thianthrene) (**130**),[712] this compound was also formed when quinoline was heated



with sulphur and concentrated sulphuric acid.[713] The sulphur-containing product (**130**) seemed to be derived from quinoline and elemental sulphur, and lowering the reaction temperature gave a better yield of 3-chloroquinoline (30%).[700] Chlorination

with gaseous chlorine and thionyl chloride gave 4,5,7,8-tetrachloroquinoline (**131**).[714] With sulphuryl chloride at 55–60 °C, the major product was 3,4,5,6,7,8-hexachloroquinoline (**132**) with a substantial amount of 3,4,6,8-tetrachloroquinoline (**133**) and a small amount of a compound tentatively identified as 2,3,5,6,7,8-hexachloroquinoline (**134**).[715] Direct chlorination of quinoline in the liquid phase at 100 °C gave a low yield of 3-chloroquinoline (**129**); when the reaction temperature was raised to 160–190 °C ten products were obtained;[716] the identified products are shown in Scheme 2



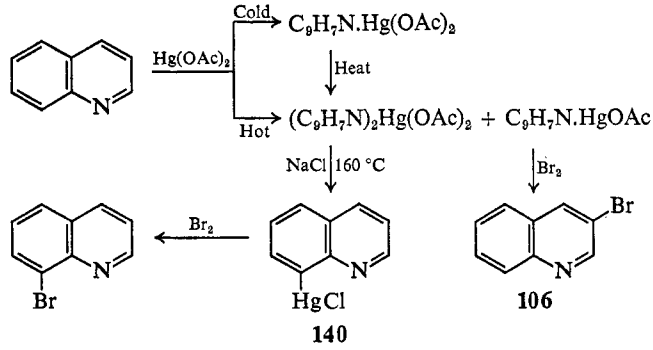
SCHEME 2

in the order in which they were assumed to be formed. With chlorine in carbon tetrachloride quinoline gave 3,4,6,8-tetrachloroquinoline (**133**),[717] and quinoline hydrochloride with chlorine and hydrogen chloride at temperatures of 80 to 225 °C gave polychlorinated products.[718] There is an early report that quinoline reacted with chlorine in acetic acid to give a small yield of a trichlorohydroxyquinoline which could be reduced to carbostyril;[719] no further information as to the structure of this chlorination product is available.

Direct iodination of quinoline was reported by LaCoste in 1885, using iodine either with potassium iodide and mercuric oxide at 160–170 °C, or with iodic acid and potassium iodide at 240 °C.[720] The melting point of LaCoste's monoiodoquinoline agrees well with that reported, much later, for 3-iodoquinoline (**139**).[721] Examination of the reaction between quinoline and iodine at ambient temperature showed evidence for complex formation, with subsequent attack upon the quinoline to give iodinated products that were not identified;[722] the suggestion was advanced that the initial complex led to substitution in the quinoline ring system with simultaneous formation of tri-iodide ion which was spectroscopically detected; tri-iodide ions themselves appeared capable of causing substitution. Similar results were obtained when solutions of quinoline and iodine were irradiated.[723] A tri-iodoquinoline, m.p.

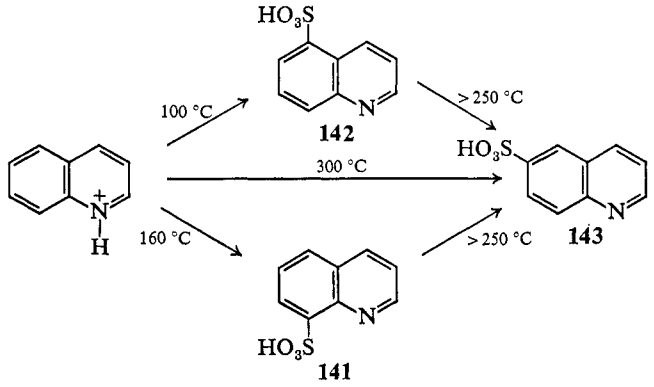
189 °C, reported to be obtained by treatment of quinoline in fuming sulphuric acid with iodine remains unidentified;[724] it is worth noting that Kiamud-din and Haque were unable to introduce a third iodine atom into their di-iodoquinoline (**128**).[709, 710]

Mercuric acetate has been reported to form a complex $C_9H_7N.Hg(OAc)_2$ with quinoline; heating the complex or the components on the water-bath gave a mixture. One component was a complex formulated as $(C_9H_7N)_2Hg(OAc)_2$, from which



8-(chloromercuri)quinoline (**140**) was obtained;[725] the second component was $C_9H_7N.HgOAc$, from which 3-bromoquinoline (**106**) was obtained.[726]

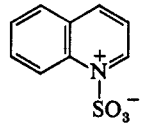
Early attempts to sulphonate quinoline gave the 8-sulphonic acid (**141**) which is the major product at water-bath temperature.[727, 728] The 5-sulphonic acid (**142**) was shown to be present in increasing quantities with increased reaction temperature;[729] when fuming sulphuric acid was used at temperatures up to 170 °C, separating the isomeric acids through their calcium salts characterized both acids adequately.[730] A number of published procedures give details of increased yields of quinoline-8-sulphonic acid (**141**);[731–736] a patent describes[737] sulphonation with 20% oleum at 150 °C, leading to a 60% yield of that isomer. One patent[732] also reported an increase in the proportion of the 5-sulphonic acid (**142**) on use of a mercury catalyst in oleum



at 175 °C. There are no reports of direct sulphonation of quinoline in the 3-position; this accords with the general pattern of electrophilic attack on protonated quinolines. The possibility of migration of the sulphonic acid group from the 3-position seems

not to have been investigated; both quinolines-5- (**142**)[738] and quinoline-8-sulphonic acid (**141**)[739] isomerize to the 6-sulphonic acid (**143**) at temperatures above 250 °C. Attempts at direct sulphonation of quinoline by fuming sulphuric acid at 300 °C gave the 6-sulphonic acid (**143**) in 60% yield.[740]

The betaine, 8-sulphonioquinolinium (**144**), gave a mixture of quinoline-5- (**142**) and -8-sulphonic acid (**141**) on treatment with sulphur trioxide and mercury.[741] Chlorosulphonation of quinoline gave quinoline-8-sulphonyl chloride (**145**) in high yield.[742, 743]



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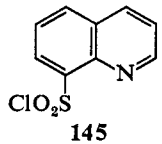

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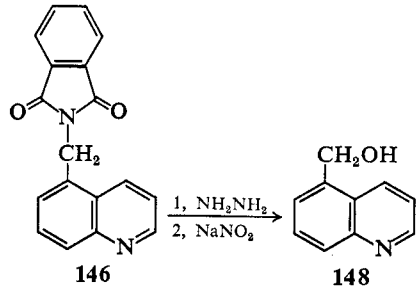
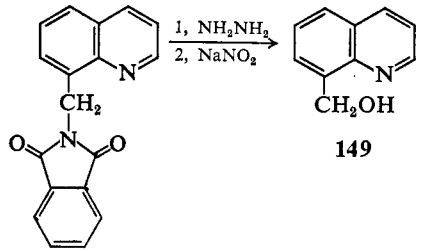
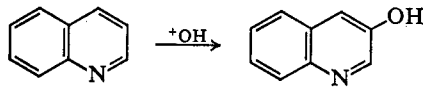


146 **148**



147 **149**

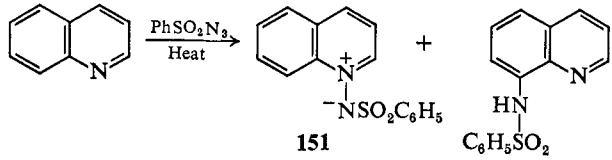
An apparent electrophilic substitution is that reported between quinoline and *N*-(hydroxymethyl)phthalimide in the presence of concentrated sulphuric acid.[744] The products were shown to be the 5- and the 8-(phthalimidomethyl)quinolines, (**146**) and (**147**), since treatment with hydrazine and subsequently with sodium nitrite gave the 5- and the 8-(hydroxymethyl)quinolines (**148**) and (**149**).



150

Quinoline has been converted in 6% yield into 3-hydroxyquinoline (**150**) by ascorbic acid and oxygen in the presence of ferrous iron.[745] The reactive species was said to be "electrophilic hydroxyl" rather than hydroxyl radicals.

The attack on quinoline by phenylsulphonylnitrene (electrophilic singlet from the azide) gave a mixture of the ylide (**151**) and the 8-(phenylsulphonamido)quinoline (**152**).[746]



151 **152**

A reaction that may be electrophilic is the alkylation of quinoline by alcohols over alumina at 450 °C; methanol gave up to 41% of 3-methylquinoline, and ethanol gave 3-ethylquinoline.[747] Quinoline was reported to give a mixture of octylquinolines when treated with octyl alcohol, ruthenium trichloride, and triphenylphosphine; the reaction was said to be general.[748] Chloramine in its reaction with tertiary amines has been described as electrophilic;[749] however, in view of the observation that yields of up to 92% of 2-aminoquinoline (**64**; $R^1 = R^2 = H$) (and its hydrochloride) have been claimed from the reaction between quinoline and chloramine,[750] the description of the reaction as electrophilic substitution is unconvincing.

In summary, substitution involving electrophiles that takes place on the quinoline as free base gives 3-, 6-, and 8-substituted products, probably by an addition–elimination reaction. When the quinolinium ion or a strongly complexed quinoline is used, substitution is invariably directed to the 5- or to the 8-position.

4. Homolytic Substitution Reactions

The reactions between quinoline and free radicals have received less attention than the other, ionic, substitution procedures, probably because of the multiplicity of products formed in low yields. Some of the more recent procedures, particularly the photochemical substitution reactions, show sufficient selectivity to encourage further work on homolytic substitution.

Alkylation and arylation procedures have received most attention. In 1893 Möhlau and Berger described the decomposition of phenyldiazonium chloride in quinoline and reported the isolation of a phenylquinoline, said to be 8-phenylquinoline.[751] The melting point recorded for their "8-phenylquinoline picrate" was much higher than that now generally accepted,[752] and the identity of their product (if indeed it was a single compound) remains obscure. Quinoline was also reported to be *p*-nitrophenylated by treatment of a mixture of quinoline and sodium *p*-nitrophenylisodiazotate with acetic acid; again the position of entry of the substituent is uncertain.[753] Hey and Walker isolated 4- and 5-phenylquinoline after phenylation with benzoyl peroxide.[754] With more efficient methods of separation available, Pausacker was able to show the presence of all seven monophenylquinolines;[752] his estimates of the proportions are given in Table 17. No change in proportions of the various isomers was found in an acid medium;[755] both reports emphasized the poor correlation between highest reactivity and the calculated figures for localization energy.[752, 755]

The work of Dou and Lynch was repeated by Vernin, Dou and Metzger;[756] their figures for neutral and for acid conditions are also given in Table 17. They found that the figures for neutral quinoline were parallel to those described for methylation (p. 54).

Szwarc and his co-workers have studied the affinity of a number of aromatic compounds, including quinoline, towards methyl,[757, 758] ethyl,[759] and *n*-propyl[760] radicals. The affinity increased with increased conjugation and also with the introduction of a ring nitrogen atom; thus quinoline was more reactive than naphthalene.

TABLE 17. Percentage Composition of the Mixtures from Phenylating Quinoline and Quinolinium Salts

Phenyl substituent	2	3	4	5	6	7	8
% of monophenylquinoline fraction in neutral medium[a]	6 (11)	14[b]	20 (18)	12 (22)	8[b]	8[b]	30 (32)
Ditto in acid medium	35	[c]	38	8	[c]	[c]	13

[a] Ref. 752 (ref. 756). [b] Combined total 17% (ref. 756). [c] Combined total 6%.

The reaction between quinoline and benzyl radicals[761] or methyl radicals[762, 763] has been studied in detail: in a non-acidic medium the total amount of benzylquinolines was very small (benzyl radicals generated thermally from dibenzylmercury); the proportions of 2- (**153**) and of 4-benzylquinoline (**154**) are given in Table 18. In an acidic medium a very considerable increase in the yield of benzylquinolines was observed; in neither case could any 3-benzylquinoline be observed.[761]

TABLE 18. Yields of 2-Benzylquinoline and 4-Benzylquinoline after Homolytic Benzylation[761]

Reagent	Medium	2-Benzylquinoline (%)	4-Benzylquinoline (%)
$(PhCH_2)_2Hg$	Quinoline	0.6[a]	0.8[a]
$(PhCH_2)_2Hg$	Acetic acid	17.5[a]	15.7[a]
$(PhCH_2CO_2)_4Pb$	Phenylacetic acid	2.4	1.8

[a] Calculated as % benzyl from dibenzylmercury.

The qualitative picture of the products derived from the thermal decomposition of benzyl phenyl ether in quinoline was also in accord with the suggestion that benzyl radicals were involved.[764] The products were 2-benzylquinoline (**153**), 4-benzylquinoline (**154**), 2-(*o*-hydroxyphenyl)quinoline (**155**), 2-(*p*-hydroxyphenyl)quinoline (**156**), and 2,2′-biquinoline. The suggested mechanism is shown on p. 55; subsequent reports of the decomposition of benzyl 1-naphthyl ether [765] and of benzyl 2-naphthyl ether[766] present a similar picture. A reaction of potential synthetic use was the alkylation (notably benzylation) of quinoline by radicals formed from alkyl halides, finely divided metals (iron, nickel, or zinc) and concentrated sulphuric acid.[767] When isopropyl iodide was used some alkyl tetrahydroquinolines were also formed.

In the methylation of quinoline the major products were again shown to be the 2-methyl- and the 4-methylquinoline. Again the proportion of these products increased markedly in an acidic medium, although the total yield of monomethylquinolines remained the same.[762] The proportional increase in the yield of 2-methylquinoline was greater than that of 4-methylquinoline, in accord with the prediction of Brown and Harcourt.[768] The product distributions for methylation under various conditions are given in Table 19.

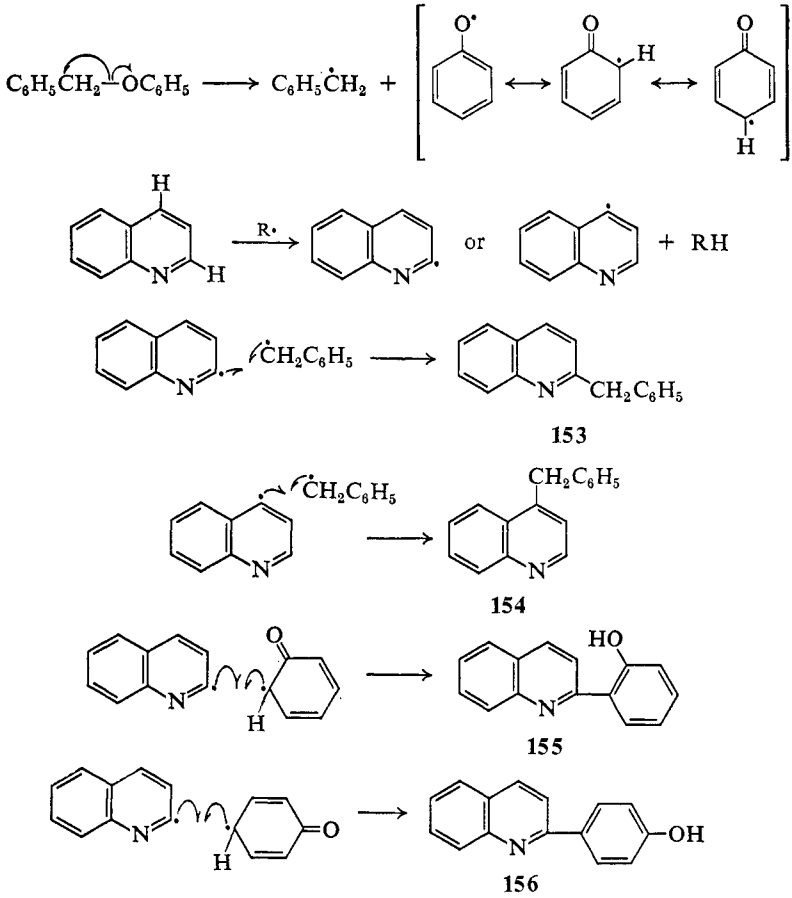


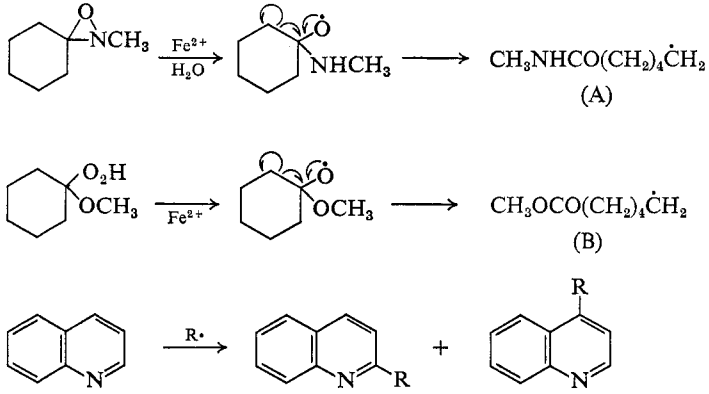
TABLE 19. Percentage Yields of Monomethylquinolines from Homolytic Methylations[762, 769]

Reagent	Medium	Methyl substituent (%)[a]					Total[b]
		2	4	5	8	3,6,7	
$Bu^t_2O_2$	Non-acidic[c]	10.2	24.2	16.1	30.85	18.7	34.7
$Bu^t_2O_2$	Acetic acid[c]	33.6	38.7	8.8	13.2	5.7	34.2
$Bu^t_2O_2$	Acetic acid/HCl[c]	49.0	50.0	←	1.0	→	15.7
$Pb(OAc)_4$	Non-acidic[c]	8.6	23.4	17.7	32.0	18.3	19.0
$Pb(OAc)_4$	Acetic acid[c]	34.4	40.7	8.4	10.7	5.8	24.9
$(CH_3)_2SO/H_2O_2/Fe^{2+}$	[d]	15	10	←	20	→	

[a] Percentage of the monomethylquinoline fraction. [b] Calculated on radical source consumed. [c] Ref. 762. [d] Ref. 769.

The apparent nucleophilic character of free radicals, as shown by their tendency to substitute in the 2- or the 4-position of quinoline, was indicated by experiments with a range of radicals formed by ferrous oxidation procedures.[763] In the examples shown

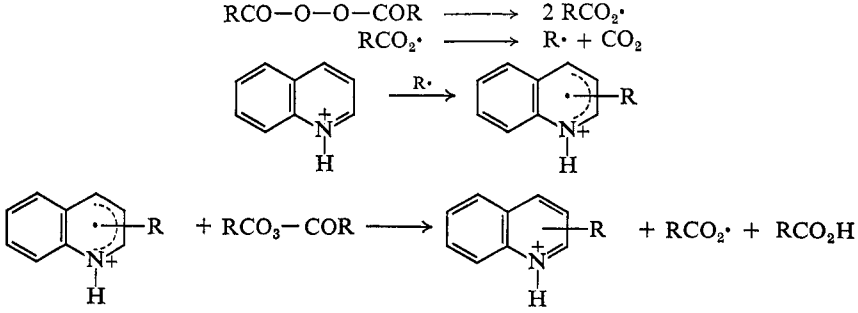
the total yields of alkylated quinolines were 80% (radical A) and 60% (radical B), calculated on the radical source. With methyl radicals derived from ferrous oxidation of *tert*-butyl hydroperoxide the proportions of 2- and 4-methylquinoline were in fair agreement with those quoted in Table 19; an excess of radical source gave some 2,4-dimethylquinoline. Ethylation was reported to give poor yields.



R = (A); 2- : 4-Ratio = 53 : 47
R = (B); 2- : 4-Ratio = 54 : 46

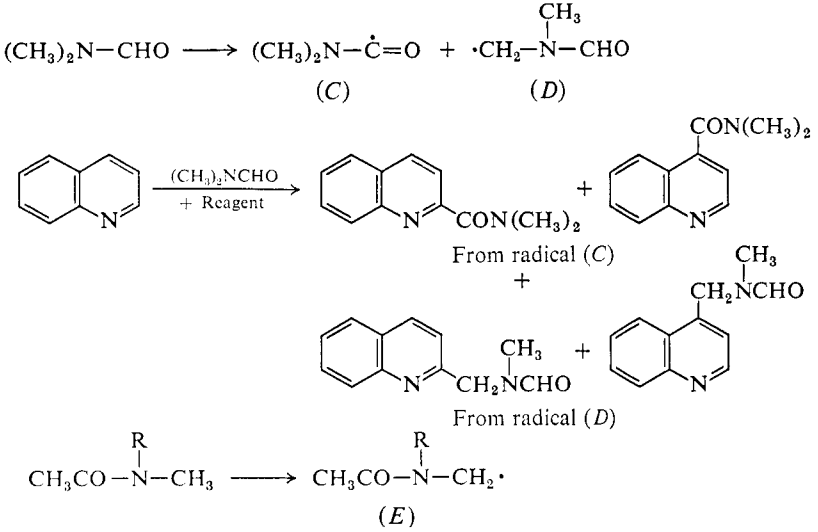
This work was subsequently much developed by Minisci and his co-workers.[770-778] By using radicals derived from lead tetra-acetate oxidation of carboxylic acids, or by ferrous ion oxidation of aryl peroxides, the ratio of 2- to 4-substitution was determined for different radicals and found to vary, the more hindered alkyl radicals giving more 4-substituted quinoline.[770] A second study, with radicals generated by silver-catalysed oxidative decarboxylation of carboxylic acids with peroxydisulphate,[771] gave very high conversions producing typically 2-, 4-, and 2,4-substituted quinolines. One notable anomaly was the production of 2-*tert*-butylquinoline in very high yield, where the previously reported ratio[770] was 1.4 (4- : 2-). A more intensive study of the decomposition of decanoyl peroxide in benzene, heptane, acetic acid, quinoline, and quinoline in acetic acid showed that the reaction was much simplified by using quinolinium ions.[772] First-order kinetics in peroxide showed cross-termination in a radical chain, by a mechanism shown in Scheme 3.

The ratio of activity benzene : quinoline was 1 : 60, but for quinolinium ion very large indeed, emphasizing the nucleophilic character of the radicals.



SCHEME 3

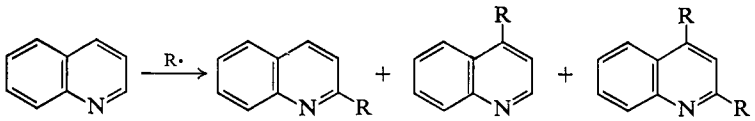
An investigation of the substitution of quinoline by carbamoyl radicals derived from formamide and from dimethylformamide as in Scheme 4 provided interesting results, involving tautomerism in the attacking species.[773, 774] With dimethylformamide and *tert*-butyl hydroperoxide the radical formed was predominantly (*C*) (81 : 19), while peroxydisulphate gave predominantly radical (*D*) (12 : 88), and



SCHEME 4

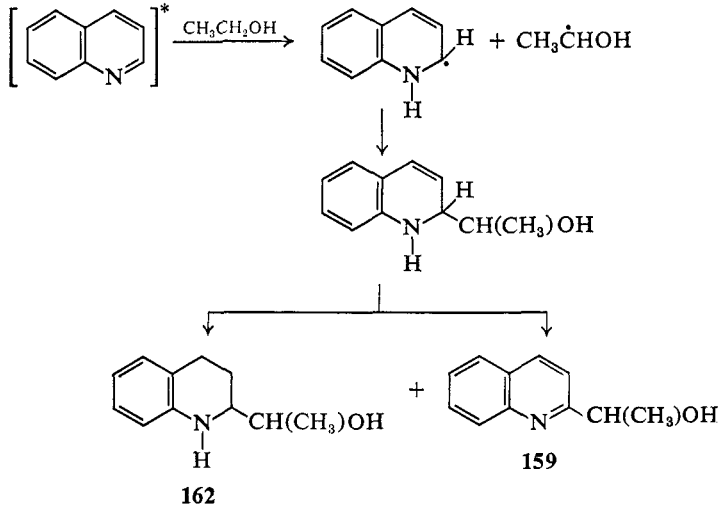
the proportion of radical (*D*) was increased even further by using ferrous catalysis of the peroxydisulphate reaction (2 : 98). On the other hand, *N*-methyl- or *N,N*-dimethyl-acetamide gave the same radical type (E; R = H or CH_3) under either set of conditions.

Further preparatively interesting radical substitutions are those using α-oxyalkyl radicals, which have been generated chemically or photochemically (p. 59). Minisci and his co-workers reported that α-oxyalkyl radicals derived from methanol or ethanol by various oxidative methods gave mixtures of equal proportions of 2- and 4-(α-oxyalkyl)quinolines.[775] The best yield of 2- and 4-(hydroxymethyl)quinolines (53% based on unrecovered base) was obtained by using peroxydisulphate; substituted quinolines were reported to react with α-oxyalkyl radicals derived from ethers, but no statement was made about such reactions with quinoline. Ethoxycarbonyl radicals from ethyl pyruvate and Fenton's reagent gave mainly diethylquinoline-2,4-dicarboxylate with some 2- and 4-esters.[776] Acyl radicals, formed from aldehydes by reaction with *tert*-butyl hydroperoxide and ferrous ions, gave 2,4-diacylquinolines when acidified quinoline was used;[777] acetyl radicals generated from pyruvic acid by silver ion-catalysed decomposition of peroxydisulphate gave a mixture of 2-acetyl-, 4-acetyl, and 2,4-diacetyl-quinolines.



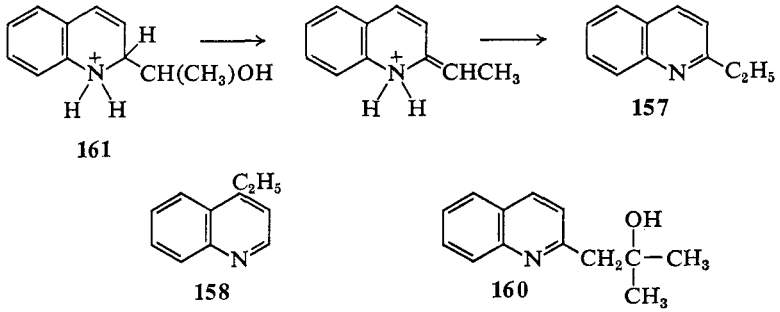
R = CH_2OH, $CH(CH_3)OH$, $CO_2C_2H_5$, or COR′

There are accounts of photochemical alkylation of quinoline and of simple substituted quinolines. Irradiation of quinoline in acidified ethanol through Pyrex gave 2-ethylquinoline (**157**) and 4-ethylquinoline (**158**) in yields of 7 and 10%, respectively.[779, 780] In neutral ethanol the product was 2-(1-hydroxyethyl)quinoline (**159**) (20%). No identified product was obtained from quinoline in propan-1-ol; *tert*-butyl alcohol gave 2-methylquinoline (3%) and 2-(2-hydroxy-2-methylpropyl)-quinoline (**160**). The mechanism proposed for the alkylation in neutral medium is shown in Scheme 5; it was assumed that a $\pi \rightarrow \pi^*$ excited state was involved, although



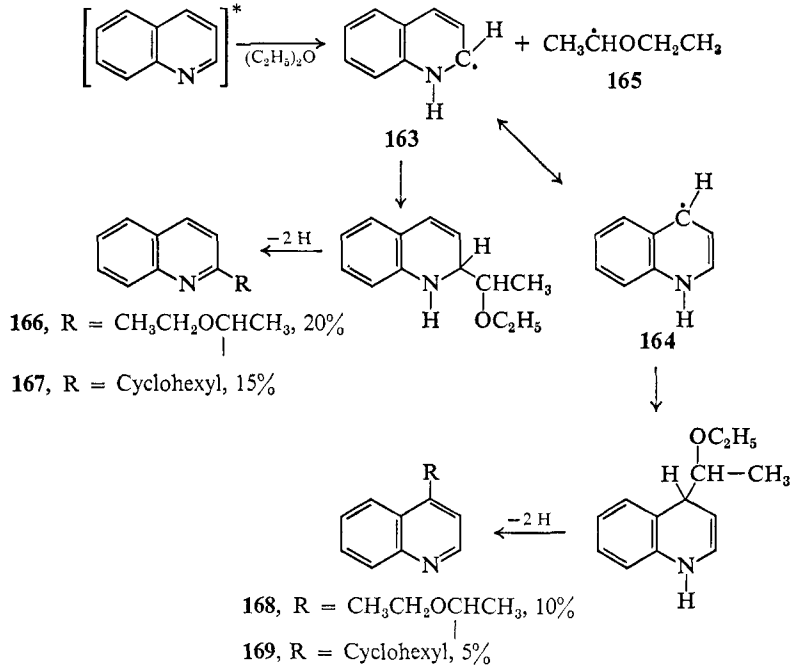
SCHEME 5

it has been suggested[781] that hidden $n \rightarrow \pi^*$ states may be involved in addition to heterocycles. In the protonated intermediate (**161**) elimination is favoured, (yielding (**157**). A tetrahydro-derivative of type (**162**) was isolated in the reaction of 8-methyl-quinoline; the yield was similar to that of 2-(1-hydroxyethyl)-8-methylquinoline. In the reaction of quinoline, only a trace of the tetrahydroquinoline (**162**) was obtained.

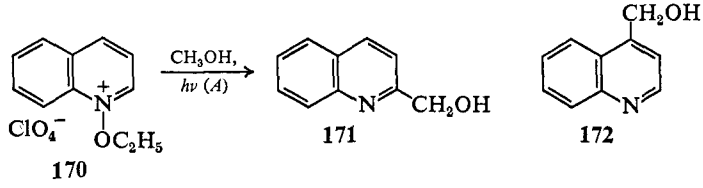


Irradiation of quinoline in neutral ether[782, 783] or cyclohexane,[782] sensitized by benzophenone, gave the 2- and 4-substituted quinolines (**166**)–(**169**) in the proportions shown.[782] Experiments in different solvents at 77 K and 113 K led to a suggested

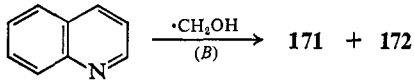
mechanism, via an excited quinoline (which was thought to be due to $\pi \rightarrow \pi^*$ transition). The radicals (**163**) and (**164**) could combine with the α-oxyalkyl radical (**165**) to give, by subsequent dehydrogenation, the observed products (**166**) and (**168**).



1-Ethoxyquinolinium perchlorate (**170**) was photochemically hydroxymethylated in good yield in methanol, giving a mixture of 2-(hydroxymethyl)quinoline (**171**) and 4-(hydroxymethyl)quinoline (**172**) in the proportions shown (*A*).[784] Palmer and McIntyre have suggested[785] that the reaction between quinoline and hydroxylamine-*O*-sulphonic acid in methanol was also a homolytic substitution in which the



$$\cdot NH_3 + HCH_2OH \longrightarrow NH_4^+ + \cdot CH_2OH$$

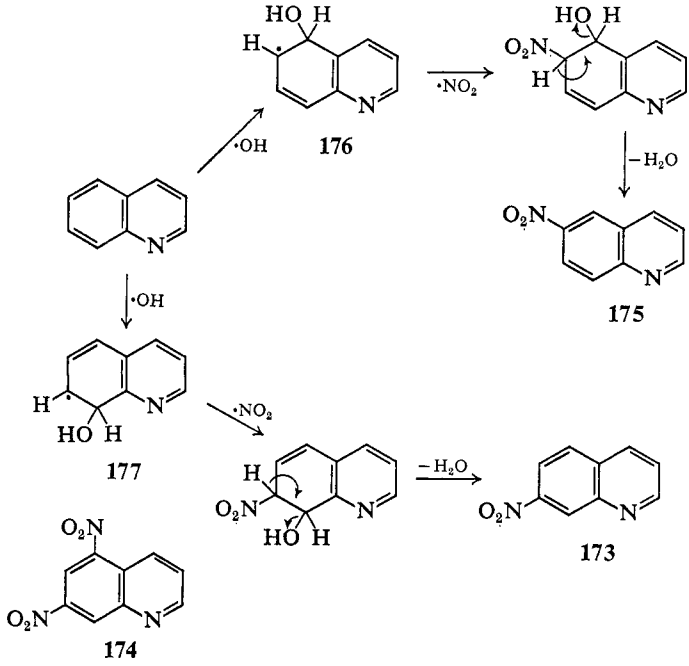


Yields (%) in (*A*) = (**171**) 43%; (**172**) 14%
Yields (%) in (*B*) = (**171**) 55%; (**172**) 25%

hydroxymethyl radical was formed by homolysis of the N—O bond giving $^{\bullet}NH_3^+$ with subsequent attack by this radical on methanol.

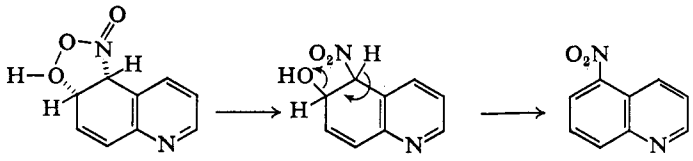
High-temperature vapour-phase bromination of quinoline has been commonly assumed to be homolytic, although, as mentioned above (p. 48), Eisch has suggested[691] that the variation of pattern of substitution with reaction temperature may be due to differing stabilities of the intermediates. However, bromination at 500 °C does give 2-bromoquinoline in 53% yield.[702] No substitution of quinoline was achieved on treatment with *N*-bromosuccinimide or *N*,2,4,6-tetrachlorobenanilide.[786]

Schorigin and Toptchiev reported that quinoline was nitrated by dinitrogen tetroxide to give 7-nitro- (**173**) and 5,7-dinitro-quinoline (**174**);[787] the reaction of quinoline with pernitrous acid was reported by Laville and Waters to give an equal amount of 6- (**175**) and of 7-nitroquinoline.[788] From the products of nitration by dinitrogen tetroxide Dewar and Maitlis[56] could isolate only 3-, 6-, and 8-nitroquinoline and concluded that this reagent followed the normal pattern of electrophilic substitution on the free base (see p. 45). By reaction with pernitrous acid



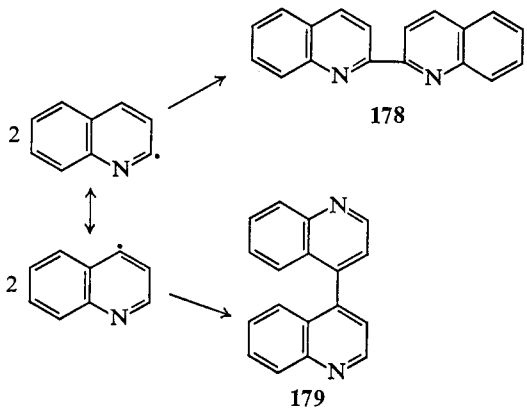
Dewar and Maitlis isolated a mixture of 5-, 6-, 7-, and 8-nitroquinoline.[56] The mechanism suggested by Laville and Waters[788] involved attack by hydroxyl radicals to give intermediates (**176**) or (**177**) followed by combination with nitro-radicals and elimination of water; the localization at positions 6 and 7 was interpreted on the basis of preferential attack by hydroxyl radicals at the "α" positions, as in naphthalene.

Dewar and Maitlis pointed out that the products were not those to be expected from a homolytic substitution; they suggested addition to the benzenoid double bonds by analogy with ozonolysis, as, for example, in Scheme 6.



SCHEME 6

The production of biquinolines during free-radical phenylation and alkylation has been noted (p. 96); thus 2,2′-biquinoline (**178**) was formed in substantial amounts during reactions between quinoline and benzyl radicals,[761, 764] with smaller amounts of 4,4′-biquinoline (**179**).



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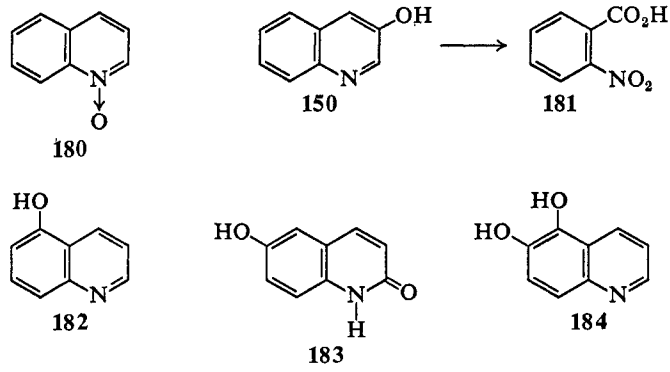
It is possible that a radical mechanism is involved in the reported synthesis of 2,2′-biquinoline by treatment of quinoline with sodium at 192 °C,[789] as there is evidence for the existence of dimeric dianions from quinoline and sodium.[100]

Quinoline was not aminated by *N*-chloro-amines under homolytic conditions,[790] although chloramine itself gave substantial yields of 2-aminoquinoline and its hydrochloride.[750]

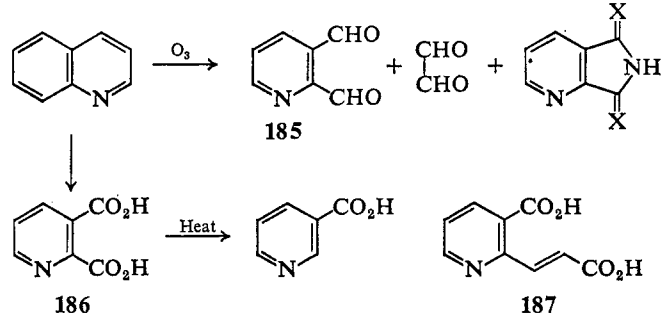
5. Oxidation Reactions

The mildest oxidation of quinoline, by peracids, leads to the valuable synthetic intermediate quinoline 1-oxide (**180**) which was first reported by Meisenheimer in 1926—he used perbenzoic acid in benzene;[791] a more convenient procedure for large-scale preparations is that using hydrogen peroxide in glacial acetic acid.[792] The rate constant for oxidation by perbenzoic acid in aqueous dioxan at 25 °C is 5.9×10^{-3}.[793] A number of other oxidation products have been isolated from the hydrogen peroxide oxidation of quinoline, notably 3-hydroxyquinoline (**150**),[794, 795] and *o*-nitrobenzoic acid (**181**).[794, 796] By using hydrogen peroxide and sulphuric acid some 5-hydroxyquinoline (**182**) was obtained.[794] Other simple hydroxyquinolines formed by biological oxidation were 2-hydroxyquinoline (carbostyril) and 2,6-dihydroxyquinoline (**183**) (by quinoline dehydrogenase[797, 798] or rabbit-liver supernatants[799]), and a mixture of 3-hydroxyquinoline (**150**), 6-hydroxy-2(1*H*)-quinoline (**183**), and

5,6-dihydroxyquinoline (**184**) obtained from rabbits' urine after feeding with quinoline.[798]



Oxidations involving the opening of one or both rings of quinoline have been intensively studied, particularly those resulting in the production of nicotinic acid. Ozonolysis at −25 to −35 °C was used in an attempt to prove bond fixation; some 2,3-diformylpyridine (**185**) and glyoxal were obtained.[800] Later work showed the initial attack to be largely at positions 5, 6, 7, and 8; some derivatives of quinolinimide were also isolated.[801, 802] Ozonolysis in hot dilute acetic acid has been reported to give a



high output of nicotinic acid,[803] probably through the intermediate formation of quinolinic acid (**186**). Quinolinic acid is probably the intermediate in most oxidations that yield nicotinic acid; it has been isolated after oxidation of quinoline with chromic acid,[804, 805] manganese dioxide in oleum,[806] permanganate,[3, 807] and chromium(III) acetate.[952]

Other oxidizing reagents that have been used to convert quinoline into nicotinic acid are: nitric acid;[808] nitric with sulphuric acid;[809] nitric and sulphuric acid with added halogen;[810] sulphuric acid and selenium;[811] sulphuric acid and selenium oxychloride;[812] sulphuric acid, selenium, and chlorine[813] or nitrosyl chloride;[814] sulphuric acid, selenium, and selenium dioxide;[815] sulphuric acid, selenium dioxide, and dinitrogen tetroxide;[816] alkaline manganate;[817] and air-oxidation in a basic aqueous medium at 250 °C and above 1 atm. pressure.

Vapour-phase oxidation of quinoline over mixtures of tin and vanadium oxides have been reported to give nicotinic acid,[803, 819, 820] but quinoline was said to show

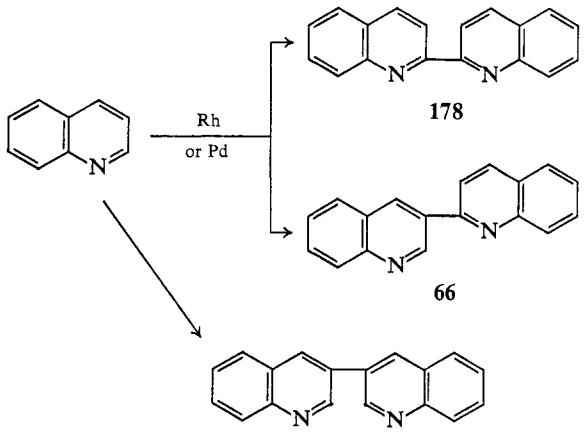
extreme stability to oxidation by oxygen over vanadium pentoxide at 400 °C.[821] Using an air–ammonia mixture over mixed vanadium pentoxide–molybdenum trioxide at 455–465 °C converted quinoline into 3-cyanopyridine.[820, 822] Hydrogen peroxide and acetic acid, with subsequent treatment with permanganate, converted quinoline into *o*-nitrobenzoic acid (presumably through the *N*-oxide);[823] chromic and sulphuric acid oxidation has been reported to give ammonia and nitrogen.[824, 825]

As with reduction, the most controlled oxidation procedure is electrolytic; the intermediate quinolinic acid (**186**) has been isolated in up to 77% yield. Most workers have used a sulphuric acid medium (sometimes with added ammonium sulphate); anodes used were platinum,[826, 827] lead,[827–829] or lead oxide coated,[473, 830–832] and technical quinoline can be used. In one case the unsaturated acid (**187**) was isolated from the oxidation products.

With anthraquinone in sunlight quinoline gave unidentifiable oxidation products.[833]

6. Formation of Biquinolines

Some reactions giving biquinolines have been mentioned (pp. 30, 37, 41 and 54). The reports of the formation of 2,2′biquinoline (**178**) by heating quinoline with nickel[834–839] include a so-called "mechanochemical" reaction with nickel powder in a ball mill, though the yield of 2,2′-biquinoline was 0.2% only.[839] The use of rhodium on carbon gave very high yields of 2,2′-biquinoline (**178**) (51%) with an appreciable quantity of 2,3′-biquinoline (**66**) (10%) if degassed catalyst was used and oxygen was excluded.[836, 840] Other dehydrogenation catalysts used to produce 2,2′-biquinoline (**178**) were palladium charcoal,[841–843] aluminium or zinc powder with mercuric chloride (nitrobenzene was used for subsequent oxidation),[844] and platinum asbestos.[845]



178 **66** **188**

Selenium has been reported to convert quinoline at 280–300 °C into 2,3′-biquinoline (**66**);[846] irradiation of quinoline in quartz with ultraviolet light gave 1% of 2,2′-biquinoline (**178**).[847] Passage of quinoline through a red-hot tube[848] or heating quinoline with benzoyl chloride at 240–250 °C[849] gave a biquinoline; the melting point in both cases was 191 °C, and this product seems likely to have been

also 2,2′-biquinoline (**178**). Calcium hydride at 220 °C was reported to convert quinoline into 3,3′-biquinoline (**188**);[850] the melting point differed from that reported elsewhere.

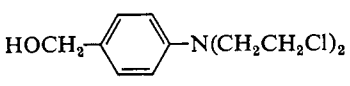
The preparation of other biquinolines (not directly prepared from quinoline) will be dealt with in the chapter on alkyl- and aryl-quinolines.

7. Complexes and *N*-Substituted Quinolines

Quinoline shows the usual properties associated with the lone pair of a tertiary amine, forming a variety of salts and quaternary compounds as well as complexes. No attempt will be made here to list the metal complexes in which quinoline acts as a ligand, or to tabulate the enormous number of quaternary salts. The common salts with inorganic acids are listed in Table 20, and the salts and complexes with organic compounds in Table 21, at the end of the chapter.

Quinoline reacts readily with the usual range of alkyl halides; the kinetics of alkylation have been studied by a number of workers. The rate constants for reaction between quinoline and methyl iodide in benzene were measured at various temperatures by Winkler and Hinshelwood and were compared with the rates for trimethylamine, triethylamine, and pyridine,[851] and other workers have studied the kinetics in benzene and in chloroform.[852] The energy of activation was calculated as 14.35 Kcal mol^{-1} (60.17 kJ mol^{-1}) from a study of the reaction between methyl iodide and quinoline in nitrobenzene at temperatures between 25 and 40 °C. Packer, Vaughan, and Wong calculated an activation energy of 14.79 Kcal mol^{-1} (71.97 kJ mol^{-1}).[853] Both groups were of the opinion that activation energy played the dominant part in accounting for the change in rate shown between pyridine and quinoline (or 2-methyl- or 8-methyl-quinoline);[853] the conclusion was that quinoline is sterically hindered in alkylation reactions relative to pyridine.[853] This conclusion has been further confirmed by a study of the methylation of quinoline and other heterocycles in dimethyl sulphoxide;[854] quinoline was found to be only one-eighth as reactive as predicted by its p*K* value. A detailed discussion has been made of the acceleration of quaternization of quinoline by ethyl iodide under increasing pressure.[855] The rate constant for quaternization by methyl iodide in acetonitrile at 24.8 °C was reported;[856] it is very similar to that in nitrobenzene solution.[853] Rate constants have also been reported for reactions between quinoline and isopentyl, isobutyl, and isopropyl bromide (the last of these rate constants being appreciably smaller)[857] between quinoline and allyl bromide,[858] and between quinoline and benzyl bromide.[858, 859]

Alkylating agents other than alkyl halides used with quinoline include: diazomethane (used on quinolinium fluoroborate),[860] triethyloxonium trinitrosulphonate,[861] the *para*-aminobenzyl alcohol derivative (**189**) in the presence of toluene-*p*-sulphonyl chloride;[862] ethylene chlorhydrin [which gave 1-(2-hydroxyethyl)quinolinium chloride];[863] chloroacetic acid[864] and ethyl chloroacetate,[865] either of which was used to make the zwitterion (**190**); 3-chloro-1-sulphopropionic acid, giving the zwitterion (**191**);[866] propiolactone, giving zwitterion (**192**);[867] acrylic acid,[868] acrylamide,[869, 870] and ethylenesulphonates,[870] giving the corresponding 2-(1-quinolylethyl) derivatives (**193**); *N*-(2-bromoethyl)phthalimide;[871] the cyclic sulphite (**194**), giving the quinoliniobutanesulphonate (**195**);[872] and various chlorosulphinates which can act as alkylating agents.[873] The azodioxide (**196**) gave 1-[2-(hydroxyimino)cyclohexyl]-quinolinium chloride.[874] Quinoline reacted slowly with a chloromethylated styrene–divinylbenzene copolymer, giving a low yield of quaternary centres, possibly again owing to steric hindrance.[875] Arylation of quinoline has been achieved by using picryl halides and also 3,4-dinitrophenyl iodide,[876] and with 1,4-benzoquinone and



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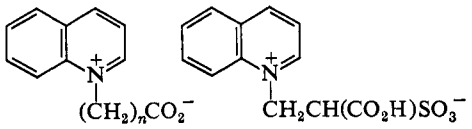

190, $n = 1$
192, $n = 2$

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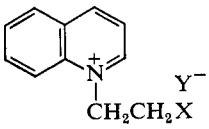
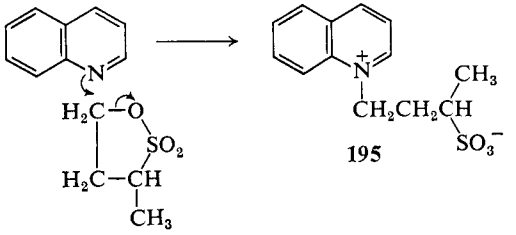


193

X	Y
CO_2H	Br
$CONH_2$	Br
$2,4\text{-}Cl_2C_6H_3SO_3$	CH_3SO_3
$2,4,5\text{-}Cl_3C_6H_2SO_3$	Cl



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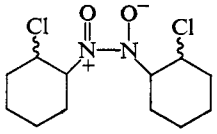
hydrogen chloride which gave the 1-(2,5-dihydroxyphenyl)quinolinium chloride (**197**).[877] The pentacyclic system (**198**) was obtained by treatment of a quinoline–2-methylquinoline mixture with iodine, presumably through the intermediate 2-(iodomethyl)quinoline.[878]



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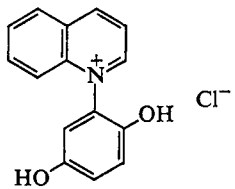
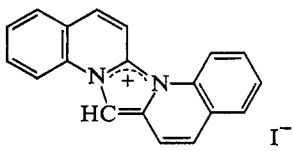


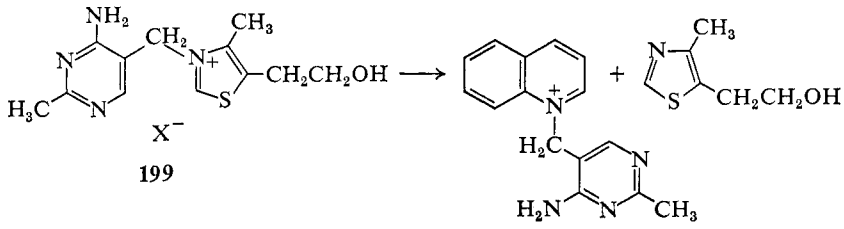
197



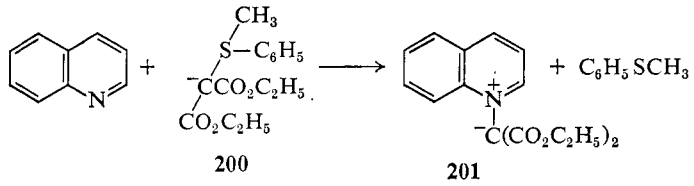
198

Thiaminase-I catalyses the transfer of the pyrimidinylmethyl (PM) group of thiamine (**199**) to bases; the kinetics of the transfer reaction to quinoline have been studied and were felt to suggest a "ping-pong" scheme where the PM group was transferred to enzyme and then to quinoline.[879] In a non-enzymic transfer, the sulphur ylide (**200**) gave, slowly, the quinolinium ylide (**201**).[880] The reaction between quinoline and *O*-(mesitylsulphonyl)hydroxylamine gave the 1-aminoquinolinium salt (**202**).[881]

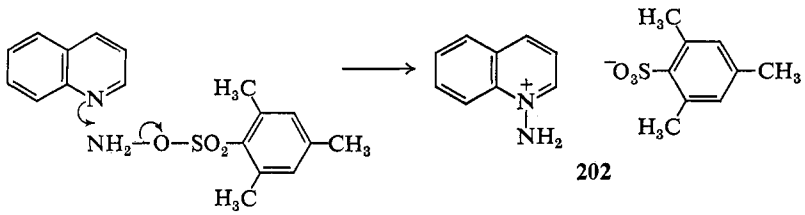
A number of early reports that quinoline forms quaternary salts with *gem*-dihalo-derivatives such as dichloroacetic acid,[882] methylene iodide,[883] and iodoform[884] or chloroform[884] have not been substantiated. Kröhnke and Leister have shown that the compounds were either simple salts or, in the case of iodoform, a molecular



199



200 201



202

complex.[885, 886] Quinoline does form diquaternary salts with 1,2-dibromoethane[883] or with *p*-di(bromoethyl)benzene (*p*-xylylene dibromide).[887] Evidence for the existence of complexes of quinoline with acyl chlorides (or of acylquinolinium salts) has been mentioned above (p. 33); also discussed previously were some of the spectra of complexes with halogens (pp. 9, 11 and 46), interhalogens (pp. 9 and 11), and some metal salts (pp. 11 and 48). Additional evidence for the complexes between quinoline and iodine monobromide (1 : 1 and 1 : 2) came from viscosity, density, conductivity, and freezing-point measurements.[888, 889] The electrical evidence favoured the presence of some 1-bromoquinolinium iodide complex.[888]

Quinoline also forms complexes with: sulphur dioxide[890] and selenium dioxide;[891] sulphur trioxide[892] and selenium trioxide;[893] sulphur monochloride with[894] and without[895] antimony pentachloride; sulphur monobromide[895] and sulphur dichloride;[895, 896, 897] selenium oxychloride;[898] boron trifluoride;[899] borane,[900] diborane,[901] and decaborane;[902] dinitrogen tetroxide (stable only below −25 °C);[903] phosphorus tri- and penta-halides[904] and phosphoryl bromide;[905] nitrosyl chloride;[906] silicon tetrafluoride (although not with silicon tetraiodide);[907] carbon tetrachloride;[908] stannic chloride and bromide, antimony trichloride and pentachloride, and titanium tetrachloride;[909, 910] bismuth trichloride;[909, 911] various tetracyanobenzene derivatives;[912] and with alcohols and phenols.[913–919]

Complexes with organic molecules that have been isolated are listed in Table 21. Additionally there are reports on various physical properties of such complexes in solution. Aromatic nitrocomopunds figure prominently; trinitrobenzene in carbon tetrachloride (1 : 1; $K_c = 3.5$);[920] trinitrotoluene in benzene (dielectric titration);[921] picric and styphnic acid in dioxan (Kerr constants);[922] styphnic acid (dipole moment);[923] 2,6-dichloro- and 2,6-dibromo-4-nitroquinoline (infrared spectra);[924] and 2,4,6,2′,4′,6′-hexanitrostilbene (2 : 1 quinolines to nitro-compound).[925]

Some solution properties of mixtures of quinoline and organic acids have been reported; dipole moment measurements on quinoline and benzene-1,3,5-tricarboxylic acid (1 : 3, 6.42 D)[926] or pyromellitic dianhydride (1 : 1),[927] and cryoscopic measurements leading to instability constants for dioxan solutions of quinoline with acetic, chloroacetic, and dichloroacetic acids (1 : 1; respectively 1.1, 6.6×10^{-1}, and 6.5×10^{-3}).[928] Complexes are formed with urea and thiourea,[929] and with various thiocyanates[930] and isothiocyanates.[930, 931] There is cryoscopic evidence for association between quinoline and aromatic amines,[932] and infrared evidence for the formation of complex cations between two molecules of quinoline,[933, 934] or one molecule of quinoline with another base.[934, 935] Donor–acceptor complexes between quinoline and hydrazyl radicals were detected by EPR measurements.[937]

8. Reactions Involving Pyrolysis, Degradation, or Irradiation

Ring opening and general degradation by reduction (p. 28) and by oxidation (p. 62) have been mentioned. A number of studies of the pyrolysis of quinoline have been made;[938–942] in one case a comparison was made of the degradation of quinoline by heat and by radiation.[943] Quinoline has been subjected to radium-radiation[944] and to neutron irradiation;[945–947] in the latter case there was no degradation but radioactive quinoline(^{14}C) was produced; the ^{14}C concentration was found to be at positions 4, 5, and 8; it has been said that π-electron distribution is important in determining the preferred points of neutron attack.[948]

TABLE 20. Salts and Molecular Complexes of Quinoline with Inorganic Compounds[a, b]

Arsenate 272 °C (dec.). Chlorate 66–67 °C. Dichromate 164–167 °C. Fluoroborate 94–96 °C. Hydrochloride 134.5 °C. Hydriodide 135 °C. Hydrogen sulphate 163.5–164.5 °C. Nitrate 121 °C. Perchlorate 130.2–131.0 °C. Platinichloride 227.5 °C. Selenocyanate 99.5–100.5 °C. Sulphamate 139–140 °C. Thiocyanate 141–141.5 °C.

$Q.Br_2$ 79–79.5 °C. Q.ICl 154–155 °C.
Q.IBr 128–129 °C. $Q.ICl_3$ 132 °C.

[a] Only salts with a reported m.p. are included.
[b] Q = Quinoline.

TABLE 21. Salts and Molecular Complexes of Quinoline with Organic Compounds[a]

(i) *Carboxylic Acids*: Acetylenedicarboxylate 210 °C (dec.). Acetylisatate 177.5 °C. Adipate 56.5 °C. Azaleate 58 °C. Bromomaleate 114–115 °C. Dibromocinnamate (inactive) 118 °C. 2,2-Dibromosuccinate (hydrate) 108 °C. Dichloroacetate 63–64 °C. 3,5-Dinitrobenzoate 148 °C. 4-Hydroxy-3,5-dinitrobenzoate 137 °C. 3,6-Dinitrophthalate 187.5 °C. Diphenylacetate 88 °C. Fumarate 153 °C. Furantetracarboxylate (monoquinolinium salt) 207–208 °C. Malate 152 °C (dec.). Oxanilate 122–123 °C. Oxalate (monoquinolinium salt) 105 °C. 4-Oxoparaconate 70 °C. Phthalate 98 °C. Pyromellitic anhydride 214–216 °C. β-Resorcylate 128 °C. Succinate 58 °C. Sulphosalicylate 220 °C. Tartranilate 129–130 °C. (+)-Tartrate 122 °C. (+)-Tartrate (diquinolinium salt, $5H_2O$) 131 °C. *Trans*-Cinnamylidenemalonate 114–115 °C. Trichloroacetate 100 °C.

(ii) *Sulphonic Acids*: Anthraquinone-1-sulphonate 225 °C. Benzenesulphonate 126–127 °C. Camphor-10-sulphonate (diquinolinium salt, $2H_2O$) 75–80 °C. Dibenzofuran-2-sulphonate 195–196 °C. Dimedonesulphonate 152–153 °C. 1,3-Dioxoindan-2-sulphonate 214 °C. "Methylenemonosulphate" (1,3,5,7,2,6-tetraoxadithiocane) 260–265 °C. Monopropyl sulphate 142 °C. *o*-Toluenesulphonate 115 °C.

[a] Only compounds with a reported m.p. are included.

TABLE 21 (*Contd.*)

(iii) *Miscellaneous Acids*: 2-Chloro-2-(hydroxyiminophenyl)acetonitrile 76 °C. 4-Chloro-2-(hydroxyiminophenyl)acetonitrile 111 °C. Dimyristophosphatidate (half-salt) 96.6–97.5 °C. Dipalmitoglycerophosphate 102–104 °C. Diphenylthioviolurate 176 °C. 5-Nitraminotetrazole (mono-salt) 85 °C, (disalt) 155 °C. 2-Nitroindan-1,3-dione 160 °C. 4-Nitro-2-(hydroxyiminophenyl)acetonitrile 172.5 °C. Tetraphenylborate 135–136 °C. Triphenylborate 92 °C. Triphenylmethylchlorophosphonate 181.5–182.5 °C.

(iv) *Polycyanohydrocarbons and Related Compounds*:

$(CN)_2C{=}C(CN)CH(CN)_2$	165–166 °C
$(CN)_2C{=}C(NMe_2)CH(CN)_2$	195–196 °C
$(CN)_2C{=}C(CO_2Et)CH(CN)_2$	111.5–112.5° (hydrate 52 °C)
$(CN)_2C{=}C[CH(CN)_2]_2$	(Diquinolinium salt) 206–208 °C
$(CN)_2C{=}C(CN)NHC(CN){=}C(CN)_2$	199–201 °C.

(v) *Complexes with Nitro-compounds and Cyano-compounds*: 3-Bromopicrate 243–244 °C. 3-*tert*-Butylpicrate 192–193 °C (dec.). 3-Chloropicrate 226–227 °C. 3,5-Dimethylpicrate 217–218 °C. 3,5-Dinitrobenzoate (1 : 2 = acid : quinoline) 102 °C. 2,4-Dinitro-*o*-cresol 114 °C. 1-Fluoro-2,4-dinitrobenzene 174–175 °C. 4-Hydroxy-3,5-dinitropyridine 1-oxide 172–174 °C. 3-Hydroxy-2,6-dinitropyridine 170 °C. 3,5-Dinitro-2-pyridone 149–150 °C. 2,3-Dinitro-4-(tosylamino)phenetole 94–96 °C. 3-Ethylpicrate 202–203 °C (dec.). 3-Iodopicrate 252–253 °C (dec.). 3-Methoxypicrate 150–151 °C (dec.). Picrate 203 °C. Styphnate 207–208 °C. 1,2,4,5-Tetracyanobenzene 262–265 °C. Tetracyano-*p*-xylylene (2 : 1 = cyano-compound : quinoline) > 250 °C. 3-(Trifluoromethyl)picrate 203 °C. 1,3,5-Trinitrobenzene 75 °C. 3,4,5-Trinitropyrocatechol 1-methyl ether 185 °C. 2,3,5-Trinitro-4-(tosylamino)-phenetole 102–103 °C.

(vi) *Miscellaneous Complexes*: *o*-Cresol 34.2 °C. *p*-Cresol 31.8 °C. 3-Cyano-4-hydroxy-6-(thiocarboxamido)azepin-5-one 192–193 °C. 2,2-Dichloro-1,1-di-(*p*-chlorophenyl)ethanol 97–98.5 °C. Diphenylboron chloride 212–213 °C. Di-(1-naphthyl)boron chloride 184–185 °C. Hydroquinone (2 quinoline) 98–99 °C. 2-Hydroxy-2,4,4,4′,7-pentamethylflavan 75–77 °C. Iodoform 63 °C. 4-Nitropyrogallol (2 quinoline) 74 °C. Pyrogallol (3 quinoline) 56–57 °C. Quinone (quinoline HCl) 144–146 °C. Thiourea (quinoline HI) 137 °C. Triphenylmethanol 52 °C.

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CHAPTER 2

Synthesis of the Quinoline Ring System

GURNOS JONES

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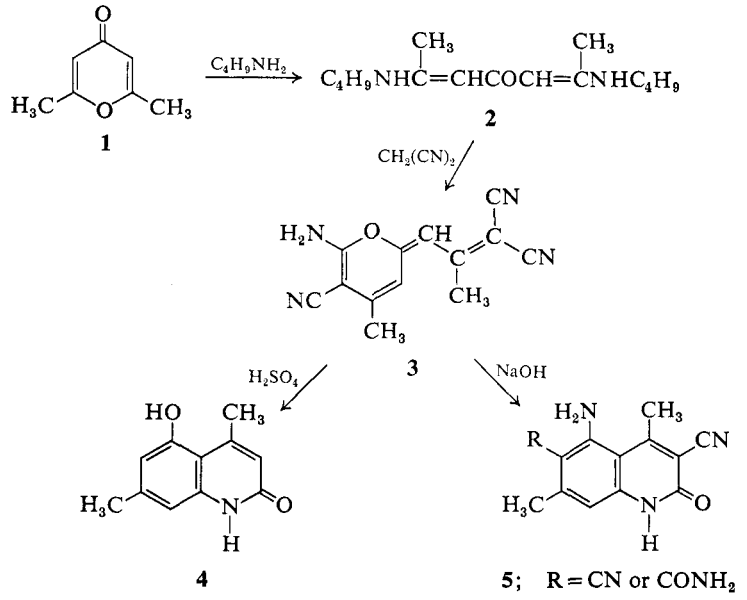
I. Introduction

The great majority of quinolines that have been prepared by ring formation, rather than by transformation from other quinoline derivatives, have been obtained by variants of two main routes. The first major class is that in which a monosubstituted benzene (or cyclohexane) is cyclized by a reaction involving a substituent on the side chain; this class includes Skraup, Doebner–von Miller, Knorr, Conrad–Limpach, and many variants of these, in which an *N*-substituted aniline is cyclized. There are a few examples of the alternative approach where a nitrogen species provides the cyclizing group. The second major class is that in which an *o*-disubstituted benzene (or α-substituted cyclohexane) undergoes intramolecular condensation or reacts with a second, two-carbon, fragment in an intermolecular condensation; this class includes the Friedländer and Pfitzinger syntheses; a minor variant of this group is provided by the synthesis of quinolines from some 2,3-disubstituted pyridines (or 2,3-pyridyne). Most quinoline syntheses can be squeezed into one or other of these two major classes—a few remain isolated (for example, syntheses involving ring expansion or contraction). This chapter, on quinoline syntheses, therefore deals with

the major classes in turn; the reader who wishes to discover the method of preparation of a particular class (such as quinoline-4-carboxylic acids) should refer to the Index or to the Tables, and thence to the appropriate section of the text. It should be re-emphasized that such a reference will yield only methods involving the synthesis of quinoline rings; on transformation reactions from other substituted quinolines (for example, oxidation of a 4-methylquinoline to a quinoline-4-carboxylic acid) information will be found in the appropriate chapter on substituted quinolines.

This brief introduction can close with a single example of a quinoline synthesis from one acyclic precursor.[1] The intermediate (**2**) obtained from the 4-pyrone (**1**) and *n*-butylamine gave with malononitrile the pyran (**3**). Treatment of the pyran (**3**)



1 **2** **3** **4** **5**;

with sulphuric acid gave the 5-hydroxy-2(1*H*)-quinolone (**4**); with sodium hydroxide, compound (**3**) gave the 5-amino-2-quinolones (**5**). Both reactions appear to proceed through an acyclic intermediate and hence provide an example of the most difficult route to a bicyclic aromatic system.

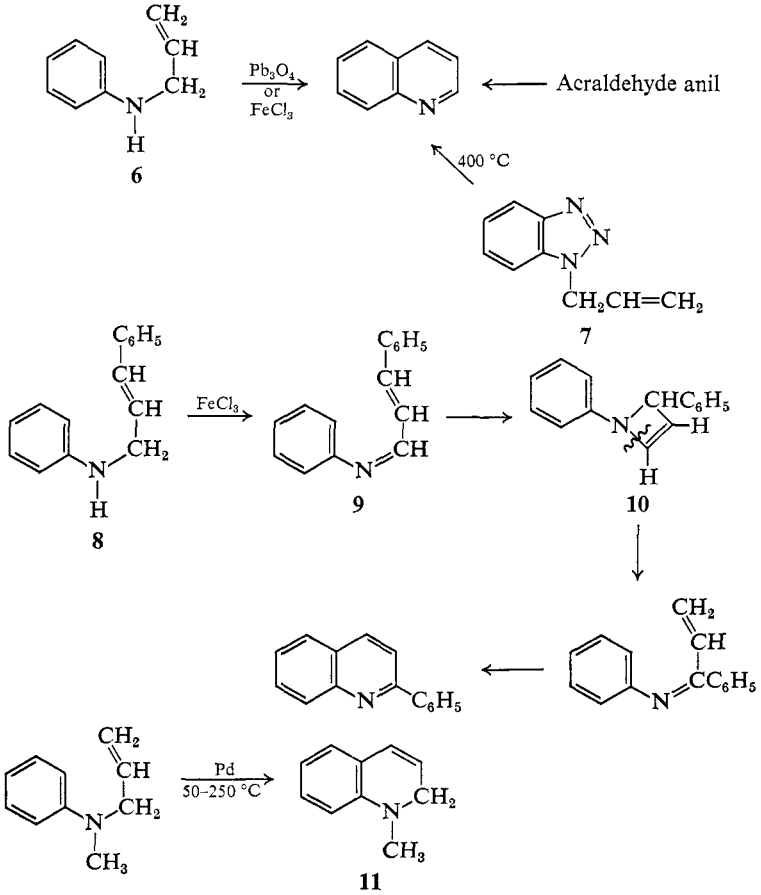
II. Syntheses Involving Cyclization of a Benzene or Cyclohexane in which One Substituent Forms the Heterocyclic Ring

1. Cyclization of Preformed *N*-Alkylanilines

The simplest, and earliest, synthesis in this class was due to Koenigs[2] when he passed *N*-allylaniline (**6**) over heated litharge. He subsequently[3] condensed aniline with acrolein and heated the condensation product.

The distillation of the Schiff base from acrolein, $CH_2{=}CHCHO$, was repeated by Mann[4] without success, nor was any quinoline obtained by sulphuric acid treatment or by the action of metal oxides. Small amounts of quinoline have been obtained from *N*-allylaniline by treatment with ferric chloride[5] and from the decomposition of

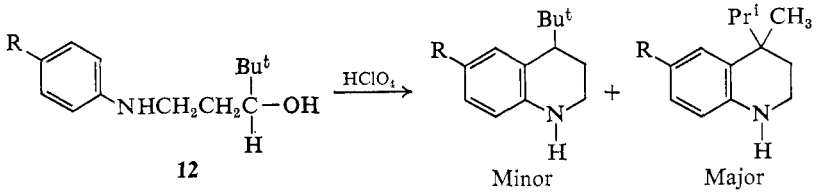
1-allylbenzotriazole (**7**),[6] in the latter case probably as a secondary product from *N*-allylaniline. The ferric chloride treatment was also applied to the substituted *N*-allylaniline (**8**) and to its "dehydrogenation product", the cinnamaldehyde anil



6 **7** **8** **9** **10** **11**

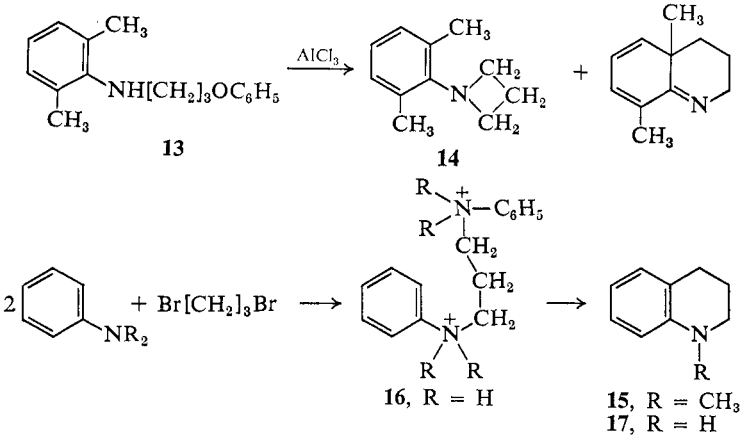
(**9**); the authors suggested an intermediate azetidine (**10**) to account for the formation of 2-phenylquinoline rather than the expected 4-phenylquinoline. Dehydrogenative cyclization of *N*-allyl-*N*-methylaniline gave 1,2-dihydro-1-methylquinoline (**11**).[7]

Most cyclizations of *N*-alkylanilines depend on the production of an electrophilic centre at the appropriate position in the alkyl chain. The most straightforward approach involves treatment of an *N*-(3-hydroxyalkyl)aniline[8–10] such as (**12**) or an



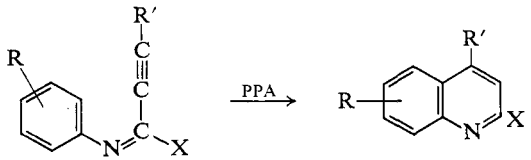
12

ether such as (**13**) with a proton acid or Lewis acid, thus generating a carbonium ion, which can substitute intramolecularly the adjacent benzene ring. The problems inherent in such an approach are the usual ones of alkyl migration (or elimination) illustrated by the dehydration of the alcohol (**12**)[10] and competitive attack by nucleophilic nitrogen which has been reported to give azetidines[9, 11] such as (**14**).[11] In cases where the developing carbonium ion would be primary, and hence unlikely, cyclization has been achieved by the use of a suitable leaving group which can be displaced by the nucleophilic benzene ring. Thus, Thorpe and Wood, in 1913,[12]



produced some 1,2,3,4-tetrahydro-1-methylquinoline (**15**) by heating dimethylaniline and 1,3-dibromopropane; an obvious intermediate would be the 1,3-diquaternary salt, with dimethylaniline as leaving group. Such an intermediate has been isolated from the reaction between aniline and 1,3-dibromopropane and converted on protonation into (**16**) and hence into tetrahydroquinoline (**17**) on cyclization.[13]

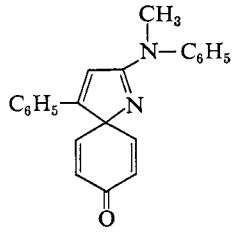
When further unsaturation is present in the side chain, quinolines can be formed rather than reduced quinolines. Of indeterminate mechanism is the reported conversion of *N*-(*n*-propyl)aniline into quinoline in 51% yield by treatment with iodine at 550 °C, followed by passage through a glass reactor containing calcium oxide



18, R = H, R′ = H, X = $N(CH_3)_2$ or morpholino
19, R = H, R′ = C_6H_5, X = $N(CH_3)_2$ or morpholino
20, R = 2-CH_3; R′ = H or C_6H_5; X = morpholino
21, R = 4-Cl; R′ = H or C_6H_5; X = morpholino

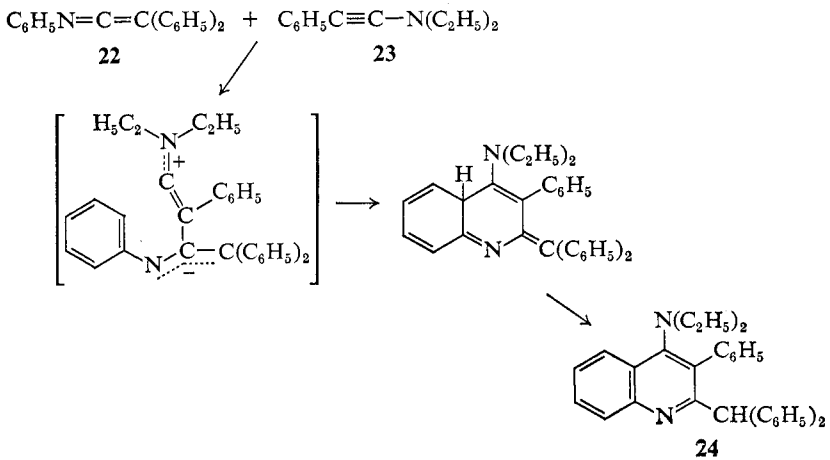
beads.[14] The acetylenic anils (**18**)–(**21**), prepared from the appropriate chloroformamidines and an acetylenic Grignard reagent, cyclized on treatment with polyphosphoric acid to give the corresponding 2-aminoquinolines in 55–95%

yields.[15] A further study of this reaction has shown[707] that the use of an electron-donating group (R = OCH_3 or OC_2H_5) in the *para*-position leads to much lower



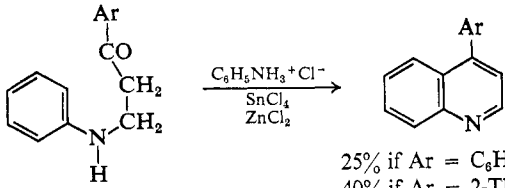
21A

yields with large amounts of the spiro compound (**21A**). Reaction between the ketene-imine (**22**) and the ynamine (**23**) generated a dipolar species which cyclized to produce the 4-diethylaminoquinoline (**24**) in 61% yield; other examples were given.[16]



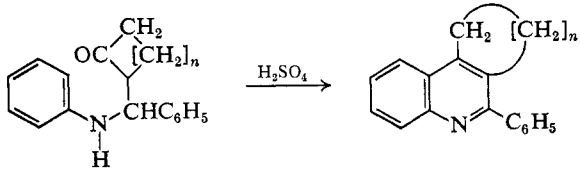
22 **23** **24**

In a further group of reactions, the electrophilic centre is developed from a carbonyl group rather than by protonation of an alkene or alkyne. The *N*-(2-aroylethyl)anilines of type (**25**) were cyclized by stannic chloride–zinc chloride with aniline hydrochloride to give 4-arylquinolines; the change in oxidation state was not explained.[17] With the same cyclization mixture 5-(arylamino)-1-phenylpent-1-en-3-ones gave 4-styrylquinolines[18] (or 1-methyl-4-styrylquinolinium salts if a secondary arylamine was used).[19] In an analogous cyclization of the substituted cyclanones (**26**) the dehydrogenation stage was said to be performed by free benzaldehyde anil;[20] a series of studies by Tilak and his co-workers[21–23] using polyphosphoric acid, and hence non-oxidative conditions, gave mixtures of quinoline and 1,2,3,4-tetrahydroquinoline. Cyclization of 3-anilinopropionic acids should give dihydro-4-quinolones. Clemo and Perkin studied the cyclization of the *N*-tosyl derivative (**27**) with phosphorus pentoxide and with phosphoryl chloride,[24] the former reagent gave 2,3-dihydro-*N*-tosyl-4-quinolone (**28**);[24, 25] the latter gave 4-chloro-1,2-dihydro-*N*-tosylquinoline (**29**)[26] and not the chloroquinolone (**30**) as Clemo and Perkin supposed.

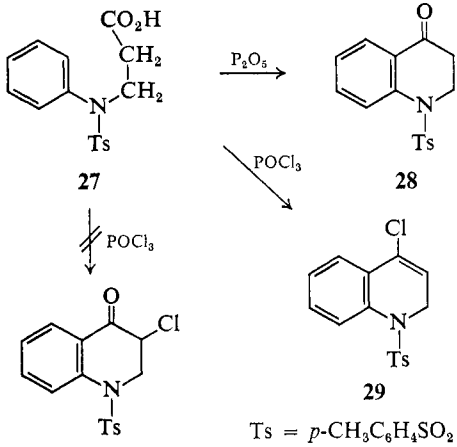


25

25% if Ar = C_6H_5
40% if Ar = 2-Thienyl

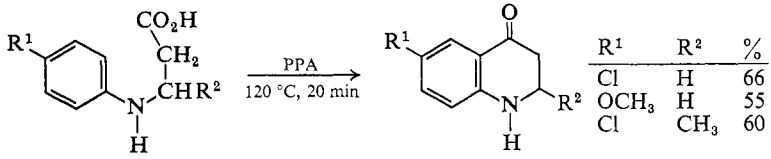


26, n = 2–5



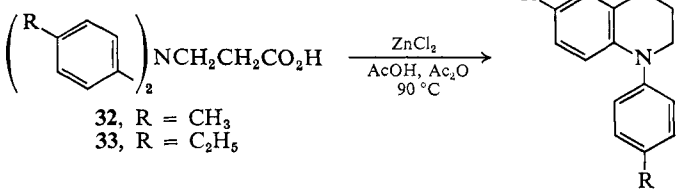
27 **28** **29** **30**

Ts = p-$CH_3C_6H_4SO_2$



R^1	R^2	%
Cl	H	66
OCH_3	H	55
Cl	CH_3	60

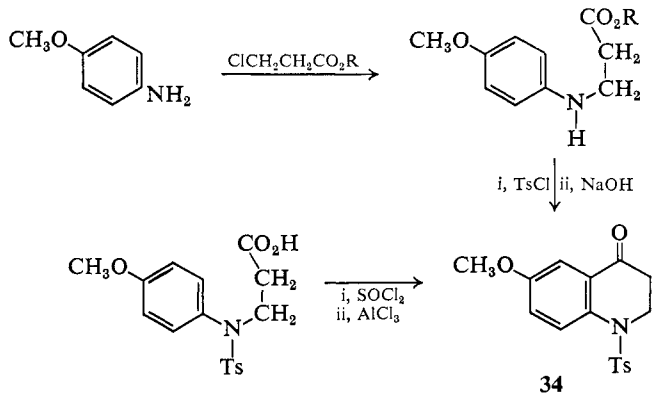
31



32, R = CH_3
33, R = C_2H_5

Considerable difficulties have been reported[27] with the Clemo–Perkin procedure, but it has subsequently been shown[28–30] that polyphosphoric acid provides good yields of dihydro-4-quinolones of type (**31**),[29] even when the nitrogen atom in the starting amine is unprotected by acylation or tosylation. The anilinopropionic acids can be prepared either by direct alkylation by chloropropionic acid,[24] by addition of an aromatic amine to an acrylic acid derivative,[27] or from a β-lactam.[31] Cyclization of (diphenylamino)propionic acids could give two possible products; cyclization of symmetrical (diphenylamino)propionic acids (**32**) and (**33**), by use of zinc chloride, gave reasonable yields.[32]

The alternative intramolecular cyclization of the acid chlorides under Friedel–Crafts conditions has been less used, although thoroughly studied.[33] Stannic chloride or aluminium chloride was used as catalyst; an example where inverse addition was a



34

useful improvement is provided by the synthesis of the 6-methoxy-4-quinolone (**34**) in reported 99% yield.

2. Syntheses in which Alkylanilines or Schiff Bases are Intermediates

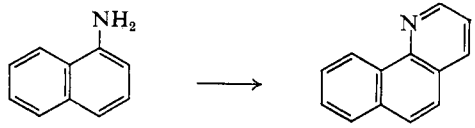
In this section the syntheses are derived from the interaction of an aromatic amine and an aldehyde or ketone; an alkylaniline or Schiff base is generally an intermediate but is rarely isolated. Well-known "named" syntheses dealt with in this section are the Skraup, Doebner–von Miller, Beyer–Combes, and Doebner cinchoninic acid syntheses. The similar syntheses that produce quinolones (Knorr, Conrad–Limpach, von Niementovski) are dealt with in Section I,3.

A. The Skraup and Doebner–von Miller Syntheses

To most organic chemists the Skraup reaction is the archetypal heterocyclic synthesis. From an apparently random mixture of starting materials a high yield of quinoline can be obtained; few books mention the reasonable basis on which Skraup devised his famous reaction. In a brief paper in 1880 Skraup[34] pointed out that alizarin blue had been shown[35] to be a quinoline derivative, and that alizarin blue was obtained from nitroalizarin and glycerol; therefore, reaction between nitrobenzene and glycerol should give quinoline itself. In fact from nitrobenzene, glycerol, and

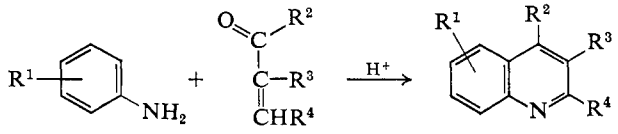
concentrated sulphuric acid a modest yield of quinoline was obtained. A yield of 10% of quinoline was obtained from aniline, glycerol, and sulphuric acid, but the best results were obtained from the classical Skraup reaction mixture of aniline, nitrobenzene, glycerol, and concentrated sulphuric acid. It is interesting that Skraup also hoped to produce pyridine from glycerol, nitroethane, and ethylamine.

In more detailed papers in the following year Skraup recorded a yield of 60% for quinoline and noted the violence of the initial reaction.[36, 37] By using *o*-toluidine or *p*-toluidine with the appropriate nitrotoluene, 8-methylquinoline and 6-methylquinoline were obtained in 45% and 47% yield, respectively, while α-naphthylamine gave the benzoquinoline (**35**). Quinolinecarboxylic acids were obtained from the aminobenzoic acids.



35

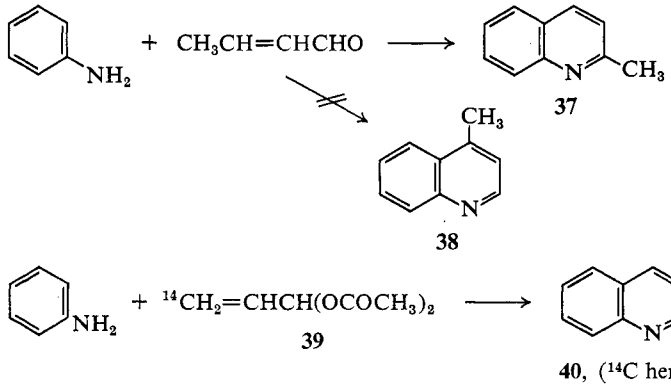
In 1881 Doebner and von Miller reported[38] the use of ethylene glycol in place of glycerol in a Skraup synthesis, obtaining a methylquinoline subsequently shown to be 2-methylquinoline. Correctly deducing that crotonaldehyde was an intermediate they improved the yield of 2-methylquinoline by using aniline, nitrobenzene, paraldehyde, and sulphuric acid, and opened the way for the more general synthesis that bears their names. It can be readily be seen that the two syntheses can lead to an enormous variety of substituted quinolines. Any group that is stable to the rather drastic acid conditions can be used as a substituent on the aromatic amine, and a variety of alkyl or aryl groups have been used on the unsaturated aldehyde or ketone, producing the general pattern of substitution shown in formula (**36**).



36

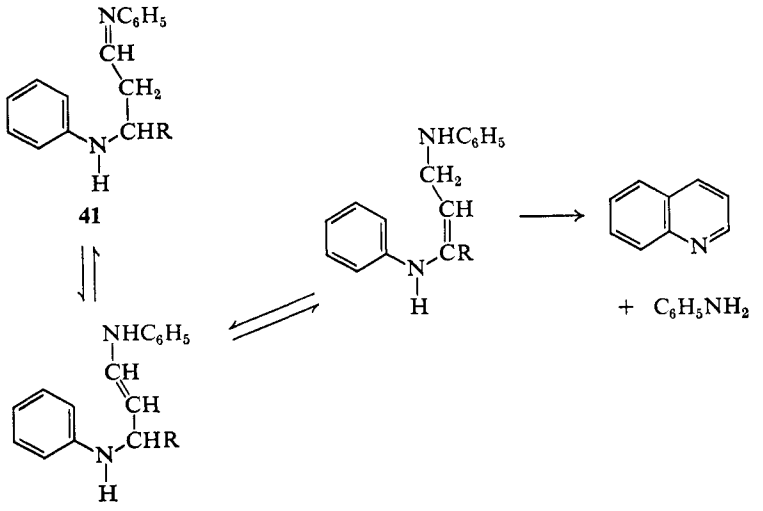
a. Mechanism of the Reaction. The Skraup reaction is often regarded as a specific example of the wider Doebner–von Miller synthesis, and the mechanism of the two reactions will be discussed together. Skraup suspected that acrolein (propenal) was the reactive species which provided the three carbon fragment needed to complete the "pyridine" ring; it was, of course, well known that acid treatment of glycerol gave acrolein. Skraup recorded a noticeable odour of acrolein in his original experiment in which nitrobenzene alone was used; the absence of such an odour when aniline was present could be due to formation of a Schiff base. Most attempts to use acrolein directly in a Skraup synthesis have given no quinoline or extremely low yields, which is not surprising in view of the rapidity of polymerization of acrolein in hot acids. Koenig's reported[3] synthesis of quinoline from acrolein anil could not be repeated by Mann[4] or by Barr.[39] However, Yale[40] was able to obtain reasonable yields of substituted quinolines using acrolein, and there are numerous examples of the successful use of α,β-unsaturated ketones in the Doebner–von Miller synthesis. In view of the notable instability of acrolein in acid media, it has been customary to suppose that the true intermediate was some derivative. The Schiff base or acrolein

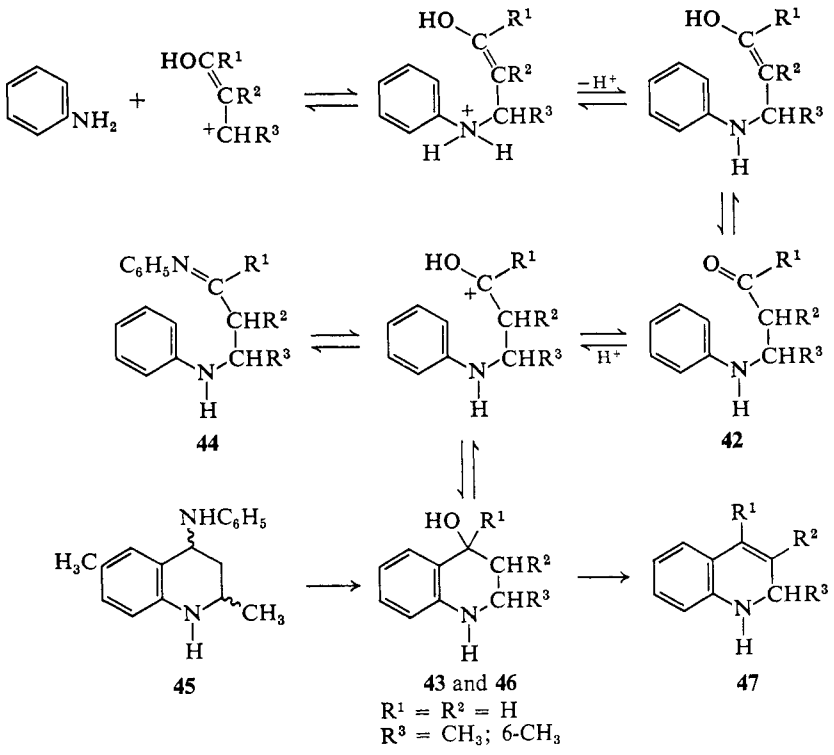
anil is the obvious candidate, but it has been shown that direct cyclization of a Schiff base other than that of acrolein provides a pattern of substitution in the "pyridine" ring that is at variance with what is observed. It was early observed[41] that the use of crotonaldehyde (but-2-enal) in the Skraup reaction gave 2-methylquinoline (**37**), not 4-methylquinoline (**38**), and hence the aniline reacts by β-addition to afford the intermediate α,β-unsaturated carbonyl compound. It has not proved



possible to establish the first stage of the reaction of acrolein itself, but the simple acrolein derivative (**39**) labelled on C-3 has been shown to give a quinoline (**40**) labelled at C-2.[42]

With the position of reaction between amine and aldehyde or ketone established, there has been much discussion of the details of the mechanism. Koenigs[43] elaborated a mechanism first proposed by Bischler[44] which involved the anilinopropanal anil (**41**) and numerous tautomers. Deuteriation studies of the condensation of aniline with acetaldehyde appear to confirm a substantial proportion of anil (**41**) which arises, not from crotonaldehyde, but directly from the Schiff base.[45] Badger and his co-workers,[46] in a very detailed examination, were able to isolate a number of β-arylamino-ketones from mixtures of aromatic amines and α,β-unsaturated ketones, of general type (**42**), and to show that the same mixture at raised temperatures gave quinolines. Their detailed mechanism, shown, arrives at the 1,2,3,4-tetrahydro-4-hydroxyquinoline intermediates (**43**) first isolated in 1910–1912 by Jones.[47, 48] An alternative approach, through a Schiff base (**44**) similar to that suggested by Koenigs (see above), has been disputed for one case which was suggested[49] to go through the tetrahydroquinoline (**45**) to the tetrahydrohydroxyquinoline (**46**). Such 1,2,3,4-tetrahydro-4-hydroxyquinolines are well documented,[47, 48, 50] and a detailed study of the relevant stereochemistry has been published.[51] The final stage of the reaction involves a dehydration to give the dihydroquinoline (**47**) which would be rapidly oxidized (for example by nitrobenzene) to the corresponding quinoline. A disproportionation of the dihydroquinoline (**47**) to quinoline and tetrahydroquinoline can be excluded. No tetrahydroquinoline has been isolated and Mills[52] has shown that saturated amines are obtained by reduction of Schiff bases, which were therefore thought to act as oxidizing agents when no oxidizing agent was added (for example in the simple Doebner–von Miller procedure). It has been shown[53] that in the Skraup reaction the quinoline-nitrogen atom is largely derived from the aniline, thus confirming the participation of the nitrobenzene at a late stage (presumably as an oxidant).




44
42
45
43 and 46
R¹ = R² = H
R³ = CH₃; 6-CH₃
47

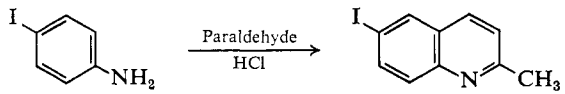
The observation that 1,2-dihydroquinoline disproportionates rapidly in acid solution, and that tetrahydroquinoline is not oxidized under the conditions of a Doebner–von Miller synthesis has led other workers to the conclusion that the dihydroquinoline (**47**) cannot be an intermediate in the synthesis.[54, 55] The alternative proposal was that oxidation occurs first and that the final stage is dehydration of 3,4-dihydro-4-hydroxyquinoline.

The other point in the mechanism that still requires some explanation is the nature of the cyclization step; although commonly shown as electrophilic it is noteworthy that the synthesis succeeds even with the extremely electron-deficient 2,4-dinitroanilines. The question of orientation of substituents (positions 5 or 7) in a synthesis involving a *m*-substituted aniline is dealt with later (pp. 105–106).

It is intriguing to note that interaction between aniline and α,β-unsaturated aldehydes, in the gas phase over an aluminosilicate catalyst, gave quinolines through an intermediate Schiff base in accord with Skraup's original suggestion—that is, crotonaldehyde gave mainly 4-methylquinoline (**38**).[56, 57]

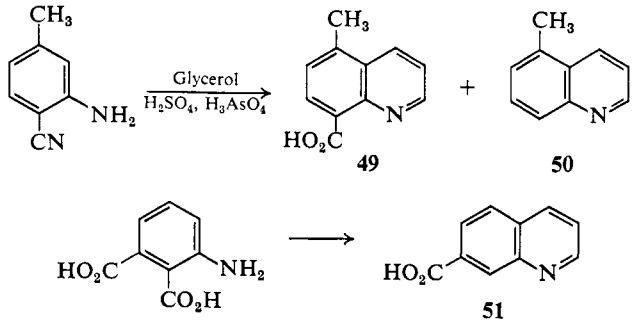
b. Scope of the Doebner–von Miller and Skraup Syntheses. The most obvious advantage of these two syntheses rests in the wide variety of substituents that can be used on the aniline component to give 6- or 8-substituted quinolines. The use of a *m*-substituted aniline leads generally to mixtures of 5- and 7-substituted quinolines; this is discussed below (pp. 105–106).

The extremely wide range of substituted anilines used in these syntheses is best appreciated from Table 1 (p. 247) which lists selected examples. Any group stable to hot concentrated sulphuric acid can be used in the Skraup reaction; the conditions are milder for the Doebner–von Miller procedure. Since the time of reaction can be short (90 seconds in an extreme case for a Skraup reaction)[58] there is less restriction than might appear. Of the halogens, iodine has been reported to fail to survive the Skraup conditions[59] although mixed 5- and 7-iodoquinolines were reported from *m*-iodoaniline.[60] 8-Iodo-5-(2-pyridyl)quinoline has been reported in a patent,[61] and a moderate yield of 6-iodo-2-methylquinoline (**48**) has been obtained in a Doebner–von

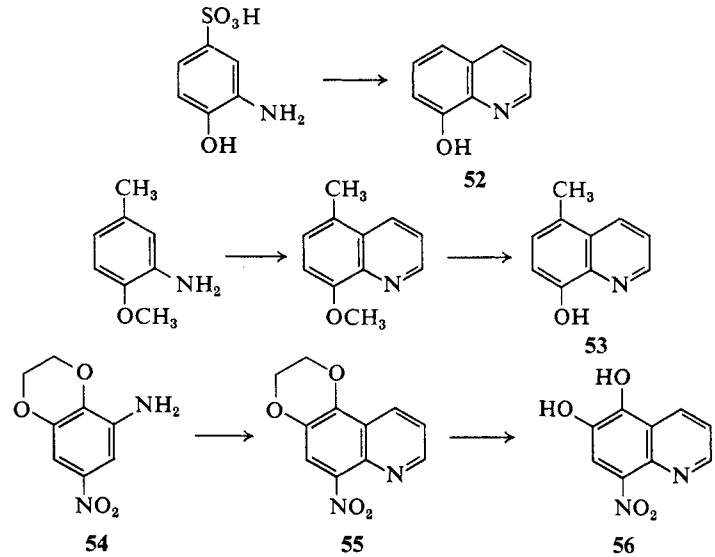


48; 20%

Miller reaction;[62] Mirek reported that better yields of bromoquinoline were obtained if reaction time was reduced to 1 hour from the more usual 3–4 hours.[59] Cyanoanilines gave quinolinecarboxylic acids, being hydrolysed under Skraup reaction conditions.[63, 64] The example illustrated makes obvious a further disadvantage; the products from a Skraup reaction on 2-cyano-5-methylaniline were the carboxylic acid (**49**) and 5-methylquinoline (**50**), obtained by decarboxylation during the synthesis.[64] It has been reported[65] that a carboxylic acid group in the 8-position of quinoline is particularly susceptible to decarboxylation; the product from 2-aminophthalic acid was quinoline-7-carboxylic acid (**51**). Other groups that are modified, or eliminated, during a Skraup synthesis are the sulphonic acid group, and ether or ester groups. In a reaction with 3-amino-4-hydroxybenzenesulphonic acid the product was 8-hydroxyquinoline (**52**);[66] this observation has been turned to advantage since the elimination has been reported[67] to give a moderated reaction, with a good yield of 8-hydroxyquinoline. While the use of ethers has been said to give improved yields of hydroxyquinolines (with a cleavage step after cyclization), as in the synthesis

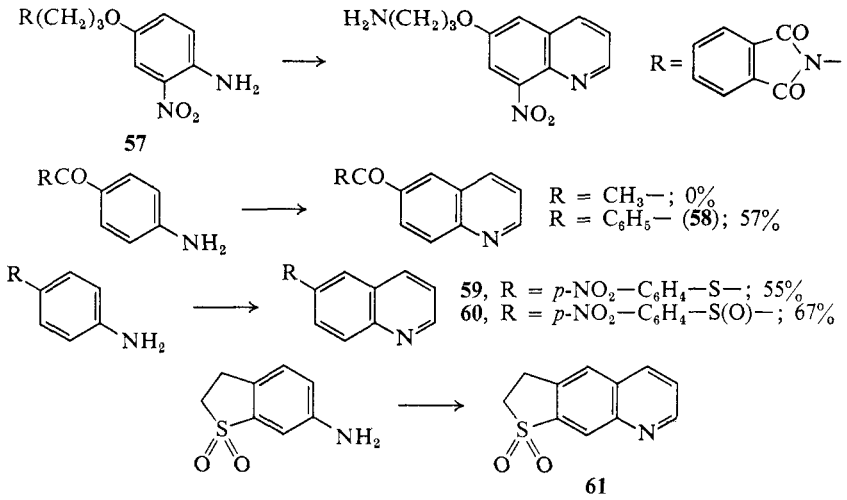


of 8-hydroxy-5-methylquinoline (**53**),[68] other ethers have been cleaved during the reaction,[27, 69] notably the more sensitive dioxo-derivatives such as (**54**) which gave a mixture of quinoline ether (**55**) and dihydroxyquinoline (**56**) even after 1 minute of reaction time.[70]



Although the presence of side-chain amino-groups has been reported to suppress Skraup cyclization, the phthalimido-derivative (**57**) has been successfully used.[71] No success was achieved with *p*-acetylaniline in the Skraup,[72] and very little in the Doebner–von Miller syntheses, although 4-aminobenzophenone gave a good yield of 6-benzoylquinoline (**58**).[73] Both *p*-acetylaniline[72] and *o*-benzoylaniline[74] reacted in the Doebner–von Miller synthesis to give 2-methylquinolyl ketones, but yields were poor. Sulphides, sulphones, and sulphoxides are stable under Skraup conditions; examples are provided by the synthesis of compounds (**59**) and (**60**),[75] and (**61**).[76, 77]

A major disadvantage of both the Skraup and the Doebner–von Miller synthesis is the production of mixtures of 5- and 7-substituted quinolines when a *m*-substituted aniline is used. The first detailed study of the ratio of 5- to 7-substituted quinolines from a variety of *m*-substituted anilines was made by Bradford, Elliott, and Rowe.[78]



Although the relative proportions were estimated on isolated material, and an analysis of the total quinolines by a physical method would be more accurate, some conclusions were drawn. The ratios are given in the annexed Table and are compared

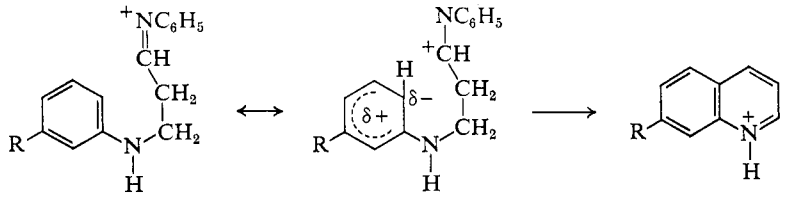
Ratio of 5- to 7-Substituted Quinolines in Skraup Reactions

m-Substituent	CH_3	OCH_3	OC_2H_5	OH	F	Cl	Br	I	NO_2	CO_2H	$N(CH_3)_2$	CF_3
Ratio (5 : 7)[78]	0[a]	0[a]	—	0[a]	—	0.25[b]	0.5	—	3.5	—	0.14	—
Ratio (5 : 7)[60]	0.66	0.282	0.23	—	0.33	0.85	0.85	0.75	3.6	5	0.33	0.7

[a] Only 7-substituted material isolated.
[b] Variable with concentration of sulphuric acid.

with those determined by Palmer,[60] who used infrared data and gas chromatography. Bradford, Elliott, and Rowe found[78] that strongly *o*- and *p*-directing groups gave only 7-substituted quinolines; that a strongly *m*-directing group led predominantly to 5-substitution, although the reverse was still true with weakly *o*- and *p*-directing groups; and that, except in the case of *m*-chloroaniline, variation in the concentration of the sulphuric acid had little effect on the product ratio. Palmer's ratios[60] seem more likely to be correct, since they do not depend on the isolation of what may be very soluble minor components. Palmer suggested[60] that in the halogen series the inductive effect was the more important; the formation of 5-substituted quinolines when *m*-aminobenzoic acids were used was ascribed to *p*-deactivation by the electromeric effect. Most of the observations appear to support attack by a fully charged carbonium ion (**62**) on the position of maximum electron density, and further support for this suggestion comes from the observation[79] that elimination of a group from the preferred *o*-position can occur if the group can leave as a positive ion, but not if a primary carbonium ion would have to be formed. Haigh, Palmer, and Semple have produced comparable ratios for the four pairs of haloquinaldines (**63**) and (**64**) obtained from *m*-haloanilines and crotonaldehyde.[80]

As mentioned in the Introduction (p. 100), the quinoline–nitrogen atom can be derived from nitrogenous precursors other than anilines. Skraup originally used



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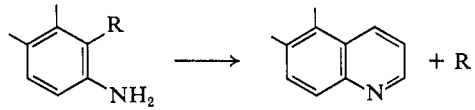
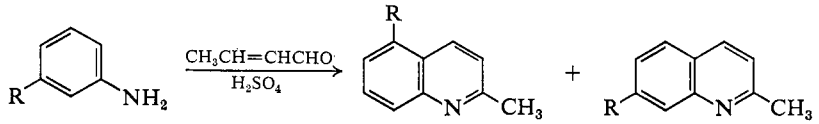


R = Cl, Br, NO_2, CO_2H, NHC_6H_5, SO_3H



63 64

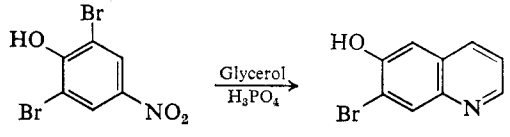
R = F, Cl, Br, or I

nitrobenzene, and a number of workers have subsequently reported the synthesis of quinolines from nitro-compounds and glycerol, although the yields are usually poor.[81-83] It has been suggested that the sulphuric acid used gave sulphurous acid, which reduced nitrobenzene to aniline. A few examples of practical yields are known; Das Gupta reported[84] a 60% yield of 5-chloro-8-hydroxyquinoline and Chichibabin[85] a reasonable yield of quinoline from nitrobenzene, sulphur trioxide, and sulphuric acid, with added acrolein.

An obvious disadvantage of the use of nitro-compounds in Skraup reactions is their enhanced activity towards nucleophiles. In reactions involving sulphuric or phosphoric acid this is normally unimportant, although there is one exception shown by the synthesis of compound (**65**).[86] In modified Skraup reactions using hydrochloric or hydrobromic acids there are a number of examples where nucleophilic replacement has taken place:[87-90] thus 1-isopropyl-2-nitrobenzene (**66**) gave chlorinated (**67**) and unchlorinated (**68**) quinolines with concentrated hydrochloric acid and glycerol;[87] nitrobenzene gave some 6-bromoquinoline with hydrobromic acid and glycerol;[88] and 1-iodo-2-nitrobenzene gave a mixture of quinoline itself and chlorinated quinolines (**69**), but no iodoquinoline. Hydrobromic acid leads to less substitution than hydrochloric acid; from 1-fluoro-2-nitrobenzene with hydrochloric acid the product was 6-chloro-8-fluoroquinoline (**70**), while hydrobromic acid gave only 8-fluoroquinoline (**71**).[90]

Azobenzenes have been used satisfactorily in place of aromatic amines in the Skraup synthesis,[91, 92] although there have been reports of biquinolines[91, 93] and of phenanthrolines[93] as by-products. Phenylhydroxylamine has been stated to give reasonable yields of quinoline when treated with acrolein diacetate and ferric chloride;[94] crotonaldehyde diacetate gave 2-methylquinoline in 31% yield. Much smaller yields of quinoline (less than 10%), of 2-methyl- and 2-phenyl-quinoline were obtained when phenylhydroxylamine was treated with sulphuric acid and acrolein, crotonaldehyde, or cinnamaldehyde, respectively. A Skraup reaction in which phenylhydroxylamine, glycerol, and concentrated sulphuric acid were used gave, as by-products, *p*-aminophenol and 6- and 8-hydroxyquinoline;[95] these

products obviously arise from an acid-catalysed rearrangement of phenylhydroxylamine to give *o*- and *p*-aminophenol before the cyclization.



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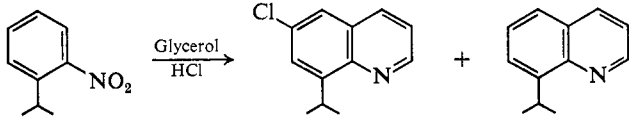
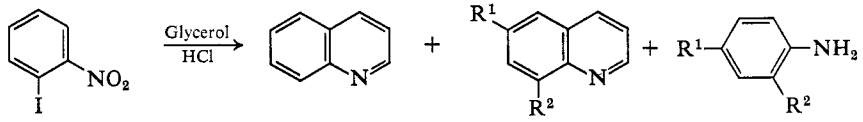
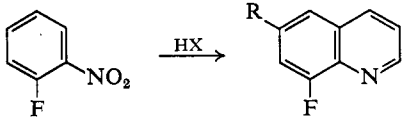


66 67; 25% 68; 10%

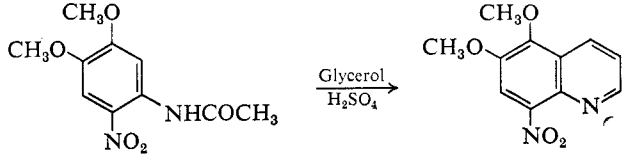


69, $R^1 = H$, $R^2 = Cl$
$R^1 = Cl$, $R^2 = H$
$R^1 = R^2 = Cl$



70, R = Cl (X = Cl)
71, R = H (X = Br)

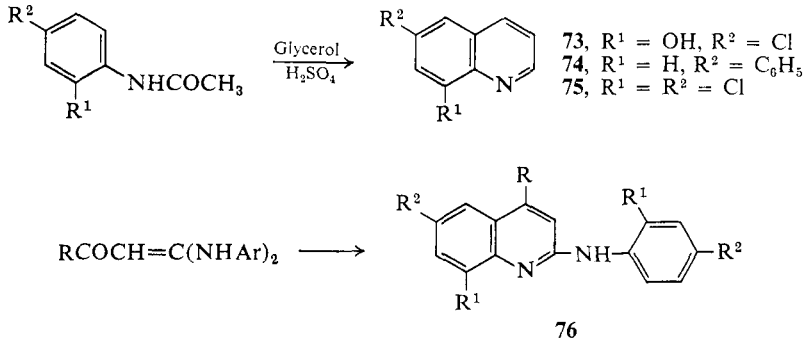
If an aromatic amine is unstable, a useful improvement in yield in the Skraup reaction can be obtained by using the *N*-acetyl derivative, so that the free amine is released slowly throughout the reaction. In the synthesis of quinoline itself, Manske, Leger, and Gallagher reported[96] a greatly improved yield over that reported in *Organic Synthesis*,[97] by using acetanilide. Other examples are provided by the



72; 40%

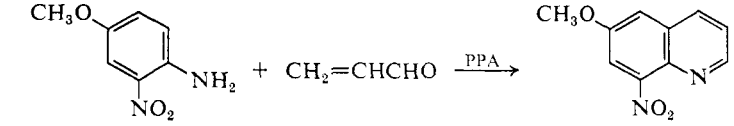
synthesis of compounds (**72**),[58] (**73**)[89] (where the *O*,*N*-diacetyl derivative was used), (**74**),[98] and (**75**).[99]

Other aromatic nitrogen compounds used include diphenylamines, dimethylaniline, and phenylhydrazine.[100] Cyclization of β,β-di(arylamino)-α,β-unsaturated ketones using polyphosphoric acid gave high yields of substituted quinolines (**76**).[101]



76

Variations in the three-carbon fragment which produces carbon atoms 2, 3, and 4 in the quinoline nucleus are more limited. Suspicions that acrolein was an intermediate in the Skraup synthesis led to attempts to use acrolein, or in general α,β-unsaturated aldehydes or ketones, in the Skraup and the Doebner–von Miller syntheses. Reasonable yields of mono- and of di-substituted quinolines have been obtained in modified Skraup reactions, using sulphuric or (preferably) polyphosphoric acids.[40, 102, 103] Thus 6-methoxy-8-nitroquinoline (**77**) was prepared in 60% yield. A number of acrolein derivatives, or acrolein precursors, have been used in Skraup syntheses, though rarely with any improvement over glycerol. The use of



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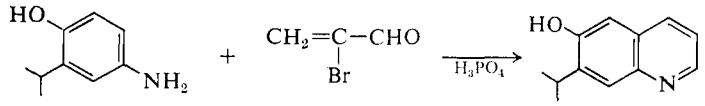

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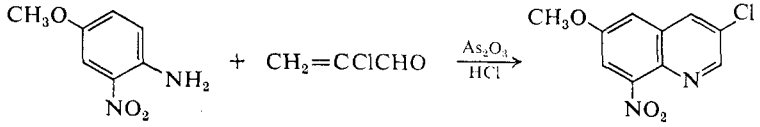
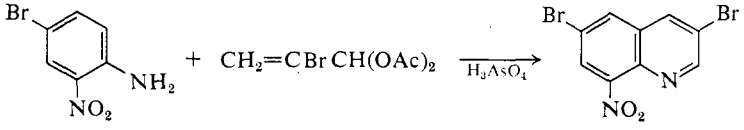


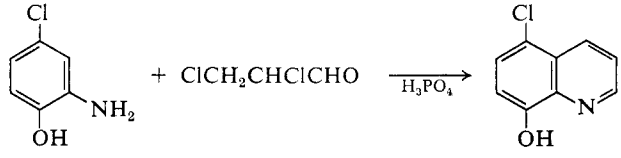
79; 22%



80

2-bromoacrolein has been reported to give good yields of the corresponding quinoline, not as might be expected, of the 3-bromoquinoline.[104–106] As shown in the synthesis of compound (**78**) there were cases where no oxidizing agent was added, and

elimination of hydrogen bromide have replaced the oxidation stage in the normal Skraup reaction.[104] In apparent confirmation of this suggestion, there is a report that the 3-chloroquinoline (**79**) was obtained when 2-chloroacrolein was used,[107] and the 3-bromoquinoline (**80**) from 2-bromoacrolein diacetate,[108] in both cases with added oxidant. Aromatic amines with 3-chloro- or 3-bromo-crotonaldehyde and added oxidizing agent gave corresponding 3-chloro- or 3-bromo-quinaldines, under the influence of a range of acids.[109] The use of 2,3-dichloropropionaldehyde or of 2,3-dibromopropionaldehyde may involve as an intermediate the corresponding 2-haloacrolein; again, in the synthesis of compound (**81**) no halogen appears in the



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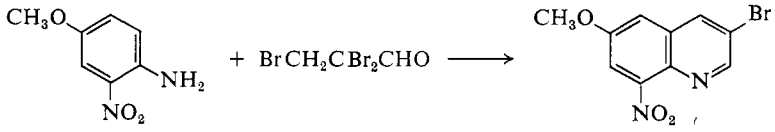


82

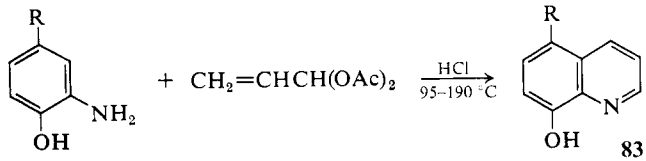
3-position of the quinoline.[110] Similarly 2,2,3-tribromopropionaldehyde gave the 3-bromoquinoline (**82**).[106]

In attempts to minimize polymerization, a number of compounds have been used that might release acrolein slowly during the reaction. Simple derivatives such as acrolein acetals[102, 111] and acrolein acetates[112-114] give yields that are reasonable but not generally superior to those obtained by using glycerol. Other compounds that could be converted into acrolein under the acid conditions are 3-chloropropionaldehyde,[115] 3-hydroxypropionaldehyde (mixed with acrolein),[114] 3-ethoxypropionaldehyde,[102] 3-ethoxypropionaldehyde diethylacetal,[116] and 3-ethoxyacrolein diethyl acetal.[117] Examples of some of these procedures are provided by the synthesis of compounds (**83**),[114] (**84**),[116] and (**85**).[117]

Quinolines substituted in the 2-, 3-, or 4-position can be prepared by using a suitably substituted α,β-unsaturated aldehyde or ketone (or such a precursor in the Doebner–von Miller synthesis as will produce a substituted α,β-unsaturated carbonyl derivative), or, less commonly, by using a substituted glycerol. In the original Doebner–von Miller synthesis paraldehyde was used, condensing *in situ* to crotonaldehyde, and thus giving a wide range of 2-methylquinolines. In the original experiment the medium was concentrated hydrochloric acid, and nitrobenzene was added as an oxidizing agent,[32] but this is unnecessary. Except for the simplest case (acetaldehyde) there are obvious disadvantages in preparing the α,β-unsaturated aldehyde *in situ*, since there will be a, possibly unwanted, substituent at position 3, as shown in the synthesis of compounds (**86**)[118] and (**87**)[119] from *n*-butyraldehyde and from isovaleraldehyde, respectively.

Wallach and Wüsten[120] used lactic acid and sulphuric acid to provide 2-methylquinoline, while Minkin and Ardashev used formanilide and acetaldehyde diethyl acetal to obtain a poor yield of quinoline, but a slightly better yield (30%) of 2,6,8-trimethylquinoline from the appropriate xylidine.[121] An obvious development of the

Doebner–von Miller route is to use a preformed α,β-unsaturated aldehyde, or some simple derivative, providing an unambiguous route to many 2-substituted quinolines; examples are compounds (**88**)[122] and (**89**).[123]



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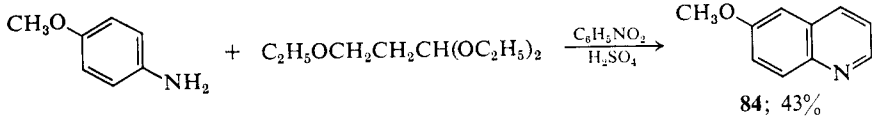
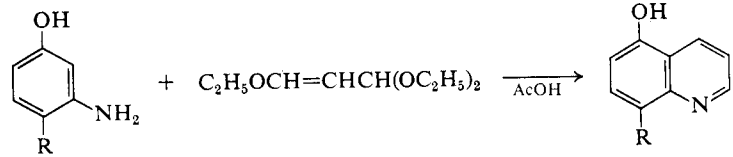
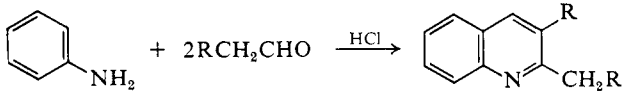


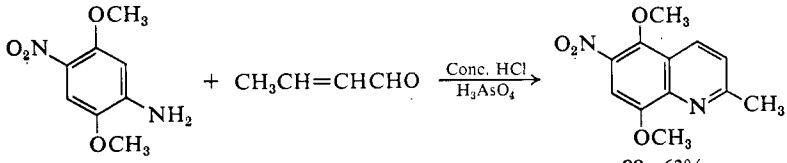
84; 43%



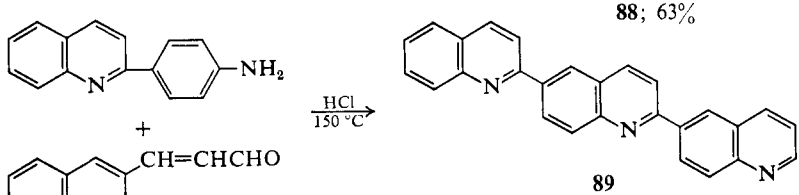
85, R = CH_3 or Cl



86, R = C_2H_5
87, R = $CH(CH_3)_2$



88; 63%



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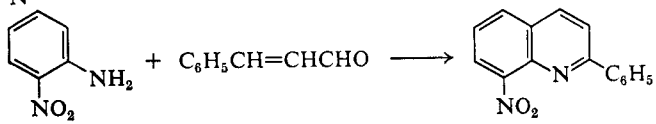
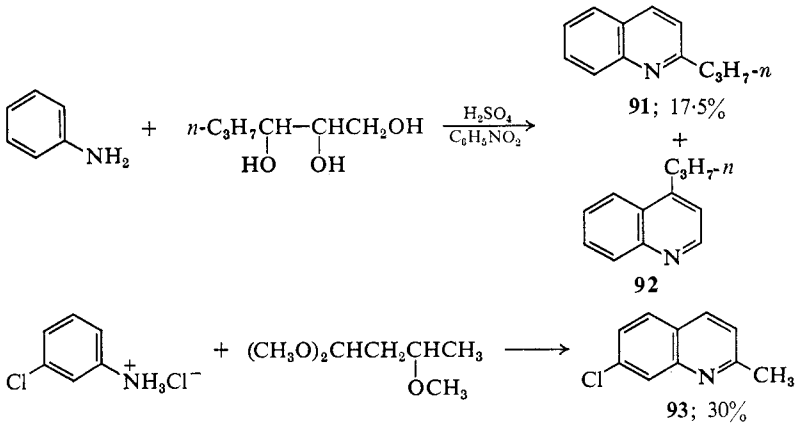


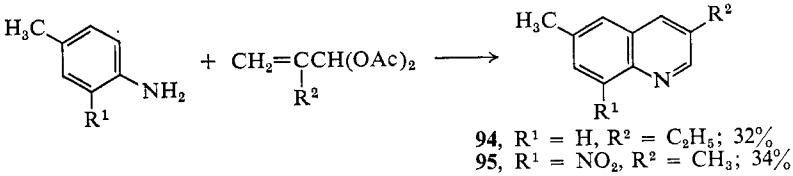
90

Yields of 2-phenylquinolines from cinnamaldehyde have been uniformly low.[124, 125] The yield of 8-nitro-2-phenylquinoline (**90**) was not improved by using cinnamaldehyde diacetate or by addition of an oxidizing agent, but crotonaldehyde diacetate has been shown to be superior to the aldehyde in a number of syntheses.[126] Substituted glycerols can be used to provide precursors for alkyl- or aryl-quinolines, but in the case of an unsymmetrical glycerol the synthesis is ambiguous. Thus α-alkylglycerols gave the 2-alkylquinolines in poor yield, e.g. (**91**), mixed with the 4-alkylquinoline



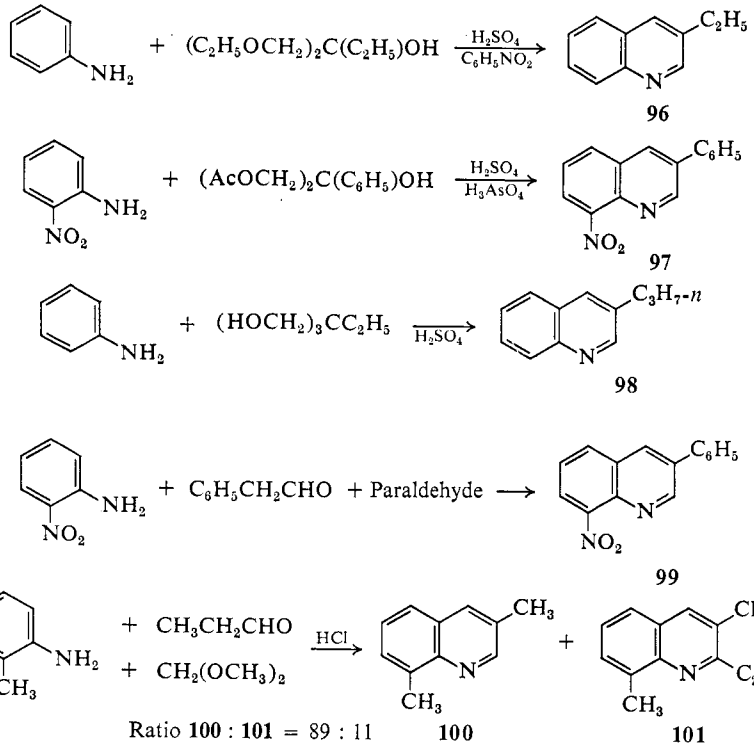
(**92**).[127, 128] Aromatic amine hydrochlorides and 1,1,3-trimethoxybutane have also given 2-methylquinolines such as (**93**).[129]

For the production of 3-substituted quinolines a 2-substituted acrolein or glycerol is required. The 2-substituted acroleins (or, better, their diacetates) gave reasonable yields in the Skraup synthesis,[107-109, 112, 126] of, for example, 3-ethyl- and 3-methylquinolines (**94**)[126] and (**95**).[108] The gas-phase reaction (p. 104) also gave 3-methyl-



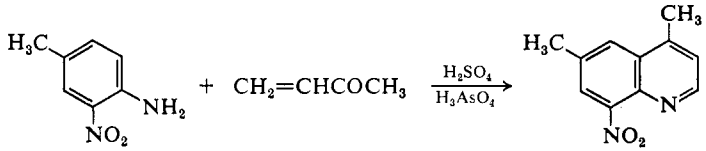
quinoline when 2-methylacrolein was used.[56] Few simple β-alkylglycerols are available. The 1,3-diethyl ether or 1,3-diacetate of appropriate glycerols gave poor yields of 3-ethylquinoline (**96**)[130] and the 3-phenylquinoline (**97**).[131] A series of 3-arylquinolines has been prepared from the 1,3-diethers of 2-arylglycerols.[132]

An interesting route involving carbonium ion rearrangement used the more readily available tri(hydroxymethyl) derivatives of aldehydes, giving for example 3-*n*-propylquinoline (**98**).[133] Any route to 3-substituted quinolines involving the classical Doebner–von Miller approach must use mixed aldehydes, one of which must be formaldehyde. The yields are low; examples are provided by the synthesis of 8-nitro-3-phenylquinoline (**99**)[131] and 3,8-dimethylquinoline (**100**).[134, 135] It is not surprising that in the latter case appreciable amounts of 2-ethyl-3,8-dimethylquinoline (**101**) were formed by self-condensation of the propionaldehyde; dimethyl formal was used.[135]

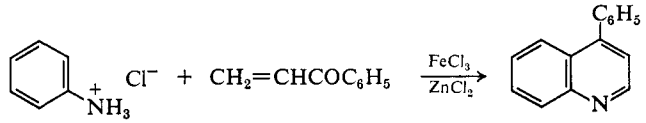


For the synthesis of a 4-substituted quinoline, the simplest approach would be through a vinyl ketone,[136-139] as in the synthesis of compounds (**102**)[137] and (**103**).[140] When more highly substituted α,β-unsaturated ketones were used, some alkyl groups were reported lost in the reaction; thus 3-methylpent-3-en-2-one gave, not the expected 2,3,4-trialkylquinoline, but the 2-methylquinoline (**104**).[141]

The notable instability of methyl vinyl ketone has led to the use of a number of compounds that could, by an elimination process, produce the unsaturated ketone during the reaction. For this purpose β-hydroxy-ketones[136, 142, 143] and β-chloro-ketones have been popular choices,[139, 144-148] used for example in the synthesis of quinolines (**105**)[143] and (**106**).[146] The use of 2,2,4-trimethoxybutane as a methyl vinyl ketone precursor has been advocated by Campbell and Schaffner.[149] By using the amine hydrochloride in conditions of low acidity, and ferric chloride as oxidizing agent, they were able to obtain yields of up to 75% in the preparation of 4-methyl-quinoline; yields of 55–60% were obtained in the preparation of the 4-methyl-8-nitroquinoline (**107**).[150] Good yields of 4-substituted quinolines have been claimed when β-dialkylamino-ketones (usually as hydrochlorides) were treated with aromatic amines in the presence of ferric chloride.[151-154] Tilak and his co-workers[154] made a careful study of the reaction and showed the β-arylamino-ketone to be an intermediate; cyclization of this ketone with polyphosphoric acid, without added oxidant, gave a mixture of the quinoline and the corresponding 1,2,3,4-tetrahydroquinoline. The synthesis of 4,8-dimethylquinoline (**108**) gives an example of the procedure.[152] A natural extension of this procedure was the use of β-trialkylammonium ketones, but there was no appreciable improvement in yield.[155]



102; 35%



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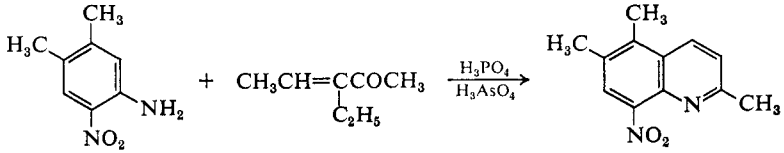

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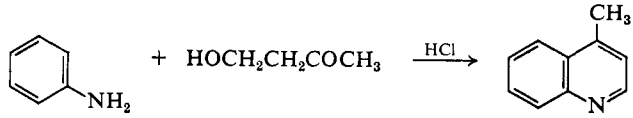

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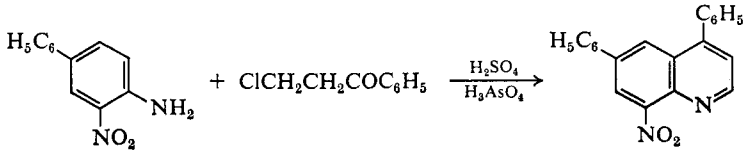

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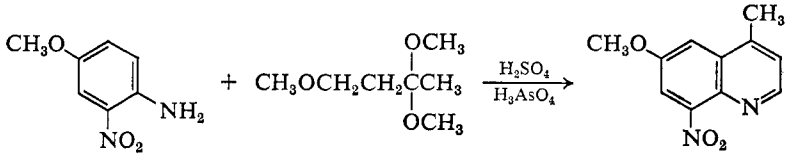
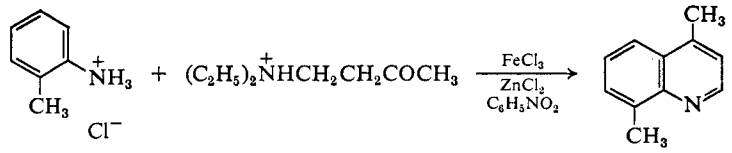
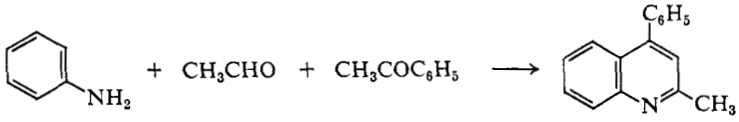


107; 55–60%



108; 65%

As a variant of the Doebner–von Miller synthesis, Beyer reported[156] in 1886 that a mixture of an aldehyde, a ketone, and an aromatic amine could condense under acid conditions to give a 2,4-disubstituted quinoline. Thus acetaldehyde, acetophenone, and aniline gave 2-methyl-4-phenylquinoline (**109**). In the usual procedure a mixture of paraldehyde with acetone or acetophenone is treated with dry hydrogen chloride and allowed to stand for some time, then the aromatic amine is added (with concentrated hydrochloric acid and possibly an oxidizing agent). Cases have been reported where the Combes procedure (p. 119) has failed but the Beyer method has succeeded—



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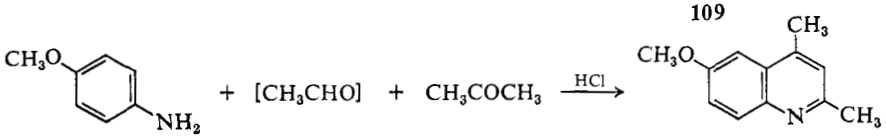

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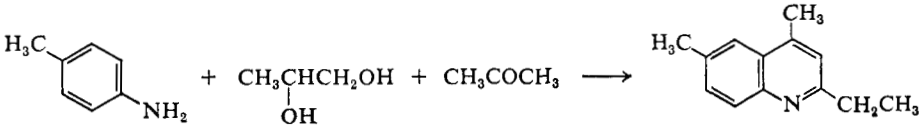
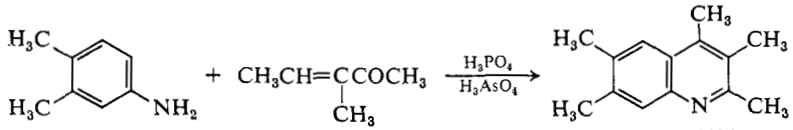
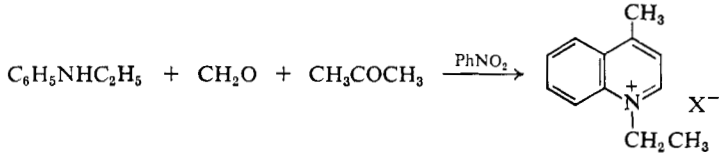


111

an example is the synthesis of the quinoline (**110**).[157] A substituted ethylene glycol with acetone has also been used to synthesize 2,4-disubstituted quinolines such as (**111**).[158] Further elaboration of the Doebner–von Miller synthesis to produce 2,3-, 2,4-, or 3,4-disubstituted quinolines will not be dealt with in detail, with the exception of the Combes synthesis (p. 119) of 2,4-disubstituted quinolines; a final example in this series is provided by the synthesis of the pentamethylquinoline (**112**).[141] The



112; 22%



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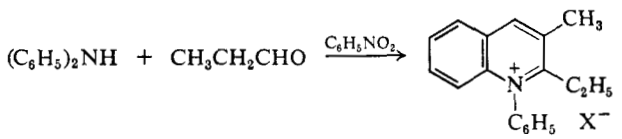
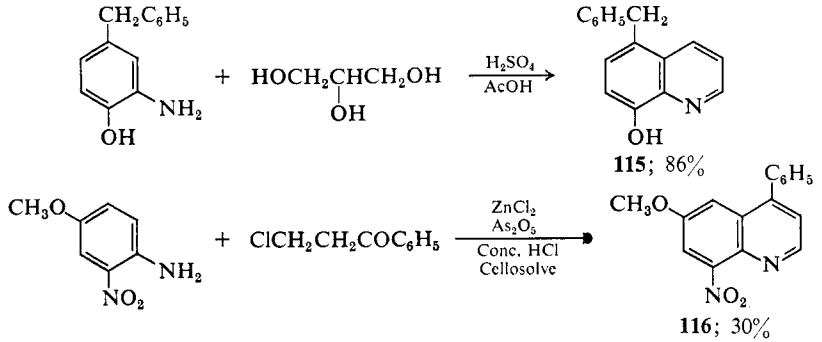


114

Beyer modification has been successfully used on *N*-ethylaniline,[159] and the Doebner–von Miller synthesis, perhaps more surprisingly, with diphenylamine,[160] giving the quaternary salts (**113**) and (**114**) respectively.

Much effort has been expended on attempts to improve the Skraup or Doebner–von Miller synthesis by variation of medium, temperature, acidity, and nature of the oxidant and other additives. The early Skraup reactions, while notoriously violent, could give high yields, notably of quinoline itself. One of the most effective modifications was the addition of moderators, such as ferrous sulphate or boric acid, to keep the reaction under control; by the original Skraup procedure, but using ferrous sulphate, quinoline was obtained in 84–91% yield.[97] An example of the use of both ferrous sulphate and boric acid was the preparation of 8-fluoroquinoline (72% yield).[59] Nitrobenzene and other simple aromatic nitro-compounds have appreciable volatility at the temperature of the Skraup reaction. In one modification a mixture of nitrobenzene and water was allowed to distil out slowly, more nitrobenzene being added; this has the additional advantage that there is a slow rise in the temperature of the reaction mixture.[161–163] More obvious improvement has been achieved by the use of involatile oxidizing agents; involatile nitrocompounds used include *m*-nitrobenzenesulphonic acid (added as its sodium or iron salt)[164–166] and chloropicrin.[167] Inorganic oxidizing agents can be even more satisfactory, as they eliminate the necessity to remove organic nitro-compounds from the final reaction mixture. The most widely used inorganic oxidants have been arsenic acid or arsenic oxides, first suggested by Knueppel,[168] iodine,[169–172] iron oxide or sulphate,[173] stannic chloride (the chlorostannate of the amine was used),[174] and various rare-earth oxides.[175] Metal oxides have also been added to the original Skraup mixture.[176] Variations in the acid have been few; for the Skraup reaction sulphuric acid remains the most popular, for the Doebner–von Miller reaction concentrated hydrochloric acid. The concentration of acid used has been said in some cases to affect the yield in Skraup reactions; many workers have preferred a concentration of around 70%.[78] A notable improvement in the yield of quinoline was claimed when a mixture of sulphuric and acetic acid was used;[177] the acetic acid was thought to give glycerol acetates and to moderate the formation of acrolein. This mixture has, for example, given a high yield of the 8-hydroxyquinoline (**115**).[178] Dilution of the reaction mixture with Cellosolve has



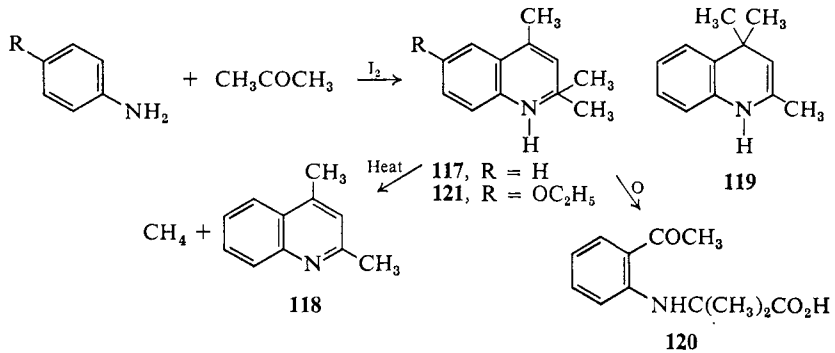
been shown to improve the yield of the 8-nitroquinoline (**116**).[145] Polyphosphoric acid has been reported to give good yields of quinoline in the Skraup reaction[179] and has been used with acrolein;[102] it may have advantages over sulphuric acid if oxidizable groups are present, but it has been reported to give inferior yields in the preparation of methoxy- and (trifluoromethyl)-quinolines.[180] The successful use of polyphosphoric acid in the cyclization of β-arylamino-ketones has ample analogy with other

cyclodehydration reactions.[21-23] Phosphoric acid has found occasional use, notably when acroleins were used in place of glycerol.[104]

In the Doebner–von Miller synthesis no oxidizing agent is necessary, although ferric chloride or arsenic acid have often been used to improve yields. Zinc chloride has also been frequently used, though its function seems obscure.

B. Synthesis of 2,2-*Dialkyl*-1,2-*dihydroquinolines*

An obvious variant of the Doebner–von Miller synthesis was provided by the reaction between an aromatic primary or secondary amine and acetone, a reaction that gives a 2,2-dialkyl-1,2-dihydroquinoline (**117**); the earliest observation of this reaction, although the intermediate (**117**) was not isolated, was by Engler and Riehm in 1885.[181] They heated aniline hydrochloride and acetone in a sealed tube at 180 °C for 3 days; much pressure was produced and the gas which escaped when the tube was opened was correctly identified as methane. The residual base was a dimethylquinoline, later identified as 2,4-dimethylquinoline (**118**). Although Knoevenagel and his co-workers discovered milder conditions (notably the use of iodine as a catalyst), which enabled them to isolate the intermediate (which they called "acetone-anil"), their investigations were hampered by an incorrect molecular formula.[182, 183] Further examination of this intermediate, first by chemical methods, showed that it was not an anil, being resistant to mild hydrolysis, that it was a secondary amine, and that it had one readily reducible double bond. Reddelien and Thurm,[184] in correcting the molecular formula, were able to suggest, correctly, that "acetone-anil" was 1,2-dihydro-2,2,4-trimethylquinoline (**117**), a view shared by other workers.[185-187]

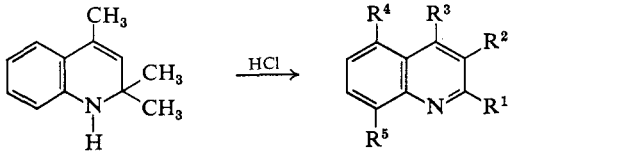


Craig[188] pointed out that the isomeric 1,4-dihydroquinoline structure (**119**) was not ruled out, and a series of inconclusive spectral studies[187, 189-191] led eventually to an oxidative degradation of compound (**117**) to give the acetophenone derivative (**120**),[191] thus finally confirming structure (**117**).

Modification of the reaction conditions has led to very high yields of the dihydroquinolines of type (**117**). The use of iodine has been claimed to give high yields of the 6-ethoxy-1,2-dihydroquinoline (**121**);[192, 193] yields of over 90% have been claimed for the synthesis of the same compound (**121**) using toluene-*p*-sulphonic acid with[194, 195] or without[193] a polymerization inhibitor. Similar high yields have been reported for the synthesis of compound (**117**);[195] in one procedure a quartz tube was used with an iodine catalyst.[196] Particular importance has been attached to the use of polymerization inhibitors,[194, 197] and a continuous system has been described.[197] Aromatic

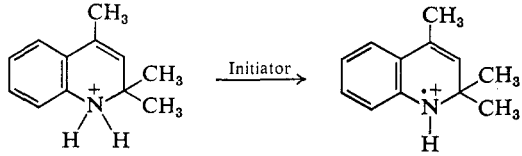
amines other than aniline which have been used include *m*-xylidine[198] which gave a mixture of dihydropentamethylquinolines, *o*-toluidine,[199] chloroanilines,[186] and *p*-ethoxyaniline.[192–195, 200] Other ketones have included butanone[182, 186, 199] where the intermediate was reported[186] to be very unstable and contaminated with 4-ethyl-2-methylquinoline; and acetophenone[181, 201] leading eventually to 2,4-diphenylquinoline[181] or 2-methyl-4-phenylquinoline.[201]

The conversion of the dihydrotrimethylquinolines into quinolines with loss of methane was for long a mysterious reaction, and various products were reported, notably from the dihydroquinolines obtained from ketones other than acetone. Knoevenagel's original reagent (dry hydrogen chloride) for accelerating the process was shown[199] to give mixed products. Sodium amide[188] or sodium anilide[202] gave high yields of the corresponding 2,4-disubstituted quinoline. The mechanism of the formation of the 2,2,4-trialkyl-1,2-dihydroquinolines is still unproved; the conversion into quinolines with "hydrocarbon" loss has been carefully studied:[199] acceleration of the reaction by radical accelerators was dramatic; the use of hydrogen chloride gave, from compound (**117**), nine quinolines, including compounds (**122**)–(**124**), in accord



117

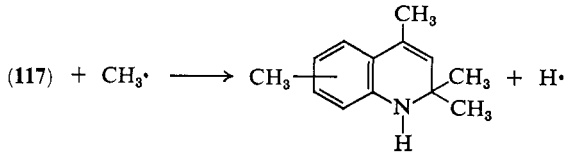
122, $R^1 = R^2 = R^3 = CH_3$; $R^4 = R^5 = H$
123, $R^1 = R^3 = R^5 = CH_3$; $R^2 = R^4 = H$
124, $R^1 = R^3 = R^4 = CH_3$; $R^2 = R^5 = H$



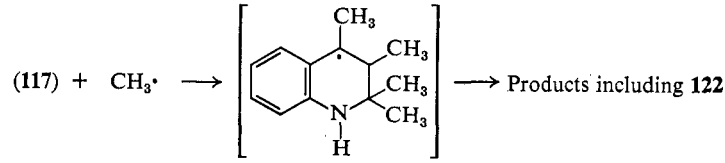
117 (radical ion)

$(117)^{\cdot+} \longrightarrow$ 2,4-Dimethylquinoline + $CH_3\cdot$

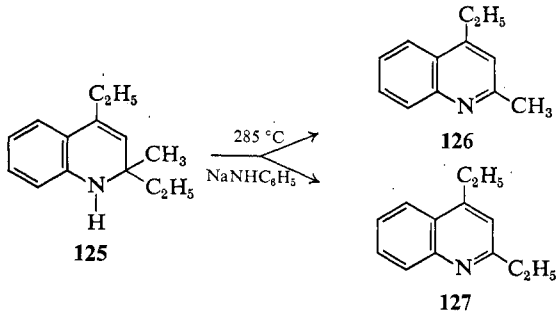
(**117**) HCl + $CH_3\cdot \longrightarrow (117)^{\cdot+} + CH_4$



Products including **123**

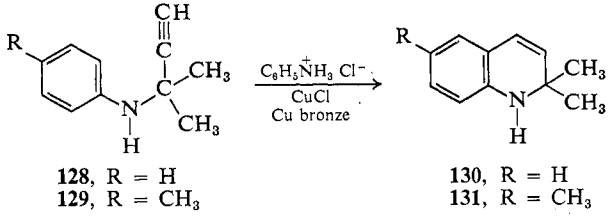


with the suggestion[199] of a methyl radical as participant. The proposed mechanism is shown. The authors indicate the complexities of quinoline formation from mixed alkyl compounds such as **125**, obtaining up to 50% of quinoline (**126**) in the quinolines formed on heating to 285 °C, but entirely 2,4-diethylquinoline (**127**) with sodium anilide.



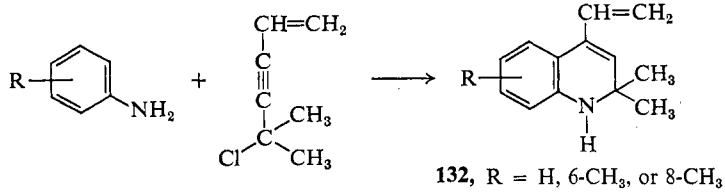
125 **126** **127**

Easton and Hennion[203, 204] have reported an alternative approach to 1,2-dihydro-2,2-dimethylquinolines (**130**) and (**131**) by cyclization of the acetylenes (**128**) and (**129**) and the principle was carried further in the synthesis of compounds (**132**).[205]



128, R = H
129, R = CH_3

130, R = H
131, R = CH_3

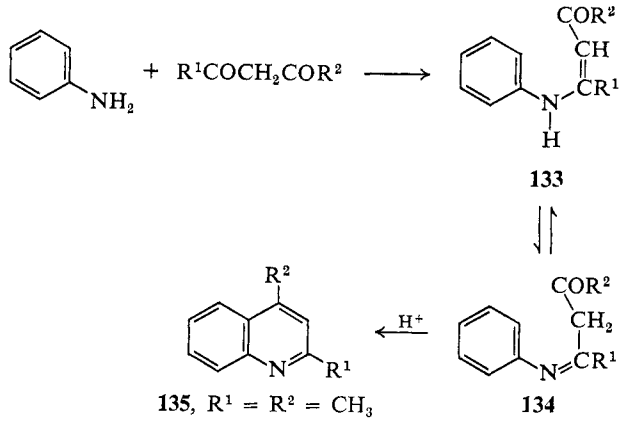


132, R = H, 6-CH_3, or 8-CH_3

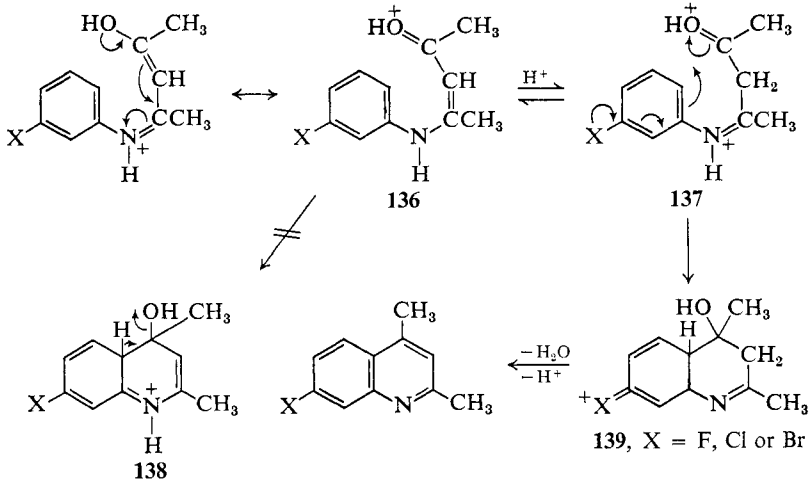
C. Combes' Synthesis of 2,4-*Disubstituted Quinolines*

A reaction related to the Skraup and the Doebner–von Miller syntheses was discovered by Combes[206] in 1888. He condensed an aromatic amine with a 1,3-diketone to give an intermediate which has been variously represented as (**133**) or (**134**); he cyclized this intermediate under acid conditions to give, for example, 2,4-dimethylquinoline (**135**).

a. Mechanism of the Reaction. The nature of the intermediate (anil or enaminoketone) is not of particular importance, since it is the protonated form that undergoes cyclization. Roberts and Turner, in a detailed study[207] of the effect of various substituents on the aromatic amine on the cyclization step, showed a dramatic

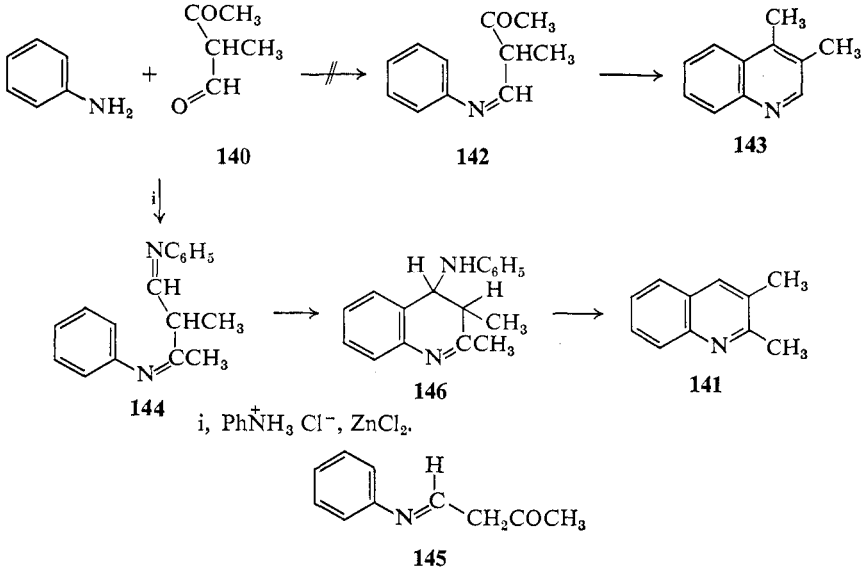


increase in the ease of cyclization when a *m*-substituent with electron-donating properties was present. Thus an electrophilic attack would appear to be involved in the cyclization. Bonner and his co-workers, in a series of papers,[208-212] have reported kinetic and isotopic-labelling experiments designed to elucidate the detailed mechanism of Combes' synthesis. In the first instance[208, 209] a study of rate and acidity functions using aromatic monoanils and the corresponding 2,4,6-trideuterio-derivatives led to a mechanism in which cyclization of the protonated monoanil (**136**) proceeded through the hydroxyl derivative (**138**); formation of (**138**) was



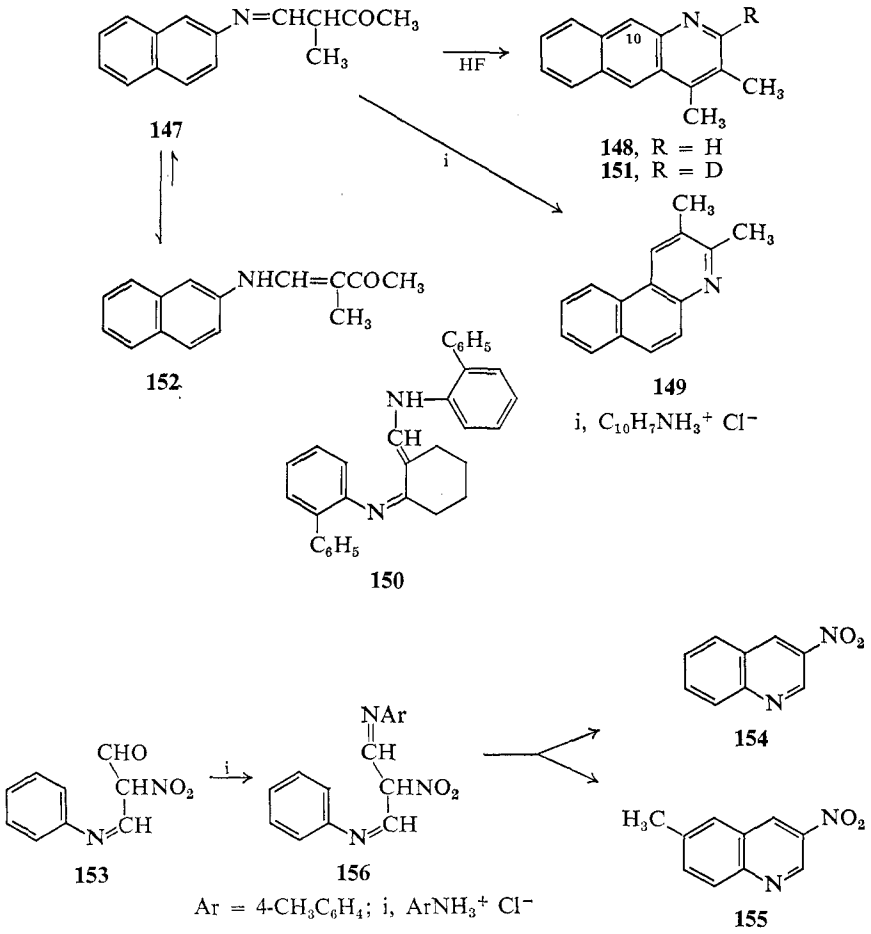
thought to be rate-determining. Criticism of Bonner's use of acidity functions led to a modified mechanism, in which the anil was assumed to be almost entirely mono-protonated [intermediate (**136**)] whereas cyclization proceeded through a small percentage of the diprotonated form (**137**).[210] A further refinement of this mechanism uses the possibility of mesomeric contribution in formation of the ion (**139**) to explain the rate enhancement shown by *m*-substituted halo-anils.[211]

A variant of the Combes procedure, in which a mixture of amine hydrochloride and zinc chloride is added to the usual mixture of aromatic amine and 1,3-dicarbonyl compound, must operate by a different mechanism. The procedure can be used with 3-ketoaldehydes, where the original Combes method is unsatisfactory.[213, 214] More to the point, a substituted 3-ketoaldehyde such as compound (**140**) gives a 2,3-disubstituted quinoline (**141**); the more reactive aldehyde group should first form the anil (**142**) and cyclization of this by Bonner's mechanism would give a 3,4-dialkylquinoline (**143**). The evidence favours an intermediate dianil such as (**144**) for this

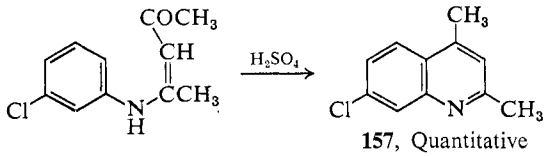


variation, and Petrow[214] discussed the mechanism of the reaction, starting from an observation by Thielepape[215] that the anil (**145**) could not cyclize because of its *trans*-configuration. Filling in details, the cyclization of the dianil (**144**) gives an intermediate (**146**) of the type invoked (p. 103) for the Doebner–von Miller synthesis. Further evidence that a monoanil is not involved in the cyclization comes from a study of the cyclization of the monoanil (**147**) from β-naphthylamine.[214, 216] Under the influence of hydrogen fluoride cyclization occurred to give the linear polycycle (**148**), while treatment with β-naphthylamine hydrochloride gave the angular polycycle (**149**). The conflicting results of cyclizations that give polycyclic systems and are hence outside the scope of this volume are well discussed by Hall and Walker,[217] but Acheson and Bolton's isolation of a bisanil (**150**) which cyclized with loss of 2-aminobiphenyl, while the monoanil did not[218] (see also Tilak[219, 220]), seems to add weight to Petrow's suggested mechanism. Born[221] has discussed the preference for linear acene formation in anils of β-naphthylamine, comparing Johnson's view[222] that position 1 is deactivated with Huisgen's view[223] that the intermediate (**147**) protonates at position 1, thus inhibiting cyclization at this position. Born showed that the product (**151**) had no deuterium at position 10, so that Huisgen's view was incorrect; it was also established that the intermediate was the enamine (**152**) rather than the anil (**147**). Finally, when the monoanil (**153**) of nitromalondialdehyde was treated with *p*-toluidine hydrochloride in acetic acid both 3-nitroquinoline (**154**) and

the 6-methyl-3-nitroquinoline (**155**) were obtained; this seems clear evidence for an intermediate mixed dianil (**156**).[224]



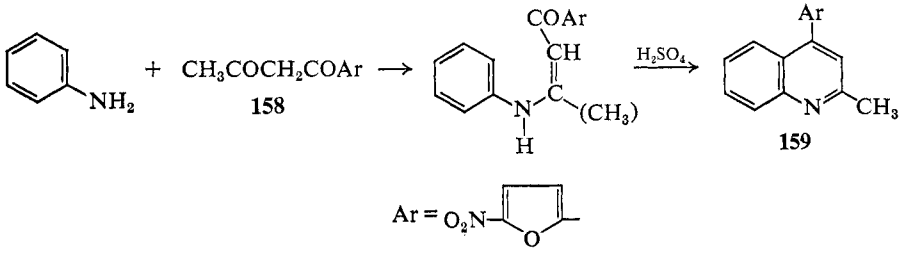
b. Scope of the Combes Reaction. A wide range of aromatic amines has been used successfully (see Table I, p. 247); a comprehensive study of the effect of varying substituents on the aromatic ring was made by Roberts and Turner.[207] In condensation of the aromatic amine with the carbonyl component the basic strength of the amine is crucial, steric hindrance being relatively unimportant; nitroanilines do not normally react, but 2,6-dimethylaniline readily condenses with pentane-2,4-dione. An intermediate case is that of 2,5-dichloroaniline, where reduced basicity with some steric effect leads to partial reaction. In the cyclization stage the effect of substituents on the benzene ring is more complex. An electron-donating substituent in the *meta*-position causes exceptionally easy cyclization, leading almost exclusively to a 7-substituted quinoline, as illustrated with the synthesis of the 7-chloroquinoline (**157**). On the other hand, an electron-donating group in the *para*-position inhibits cyclization. Failure in the cyclization stage was observed with the anils derived from



157, Quantitative

2- and 4-chloroaniline, 2,4-, 2,5-, and 3,5-dichloroaniline, and 2- and 4-methoxyaniline.[207, 157] Tamura and Yabe have reported[225] the synthesis of 6-chloro-2,4-dimethylquinoline from the 4-chloro-anil by using a temperature of 140°, but they were unable to obtain 4-methylquinoline from 4-anilinobut-3-en-2-one. In the latter case higher temperatures merely caused sulphonation of the aromatic ring; the cyclization of 4-(4-chloroanilino)but-3-en-2-one failed at higher temperatures, even though sulphonation was now prevented by the 4-chloro-substituent. Roberts and Turner reported[207] that the intermediate anils were best cyclized crude, inferior yields being obtained if the intermediates were distilled.

For the conventional Combes synthesis aliphatic 1,3-diketones and 3-keto-aldehydes, 1,3-diarylpropane-1,3-diones, and 1-aryl-1,3-diketones have been used. When an unsymmetrical dicarbonyl compound is used the carbonyl groups must differ considerably in reactivity if mixtures are to be avoided. The usual order of reactivity of CHO > CO-Alkyl > CO-Aryl is followed; thus, from the 1-(2-furyl)-butane-1,3-dione (**158**) the 4-furylquinoline (**159**) was exclusively obtained.[226] A



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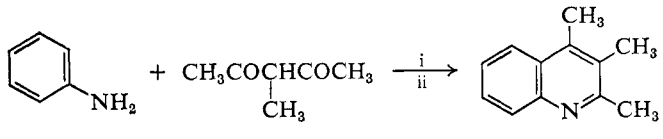

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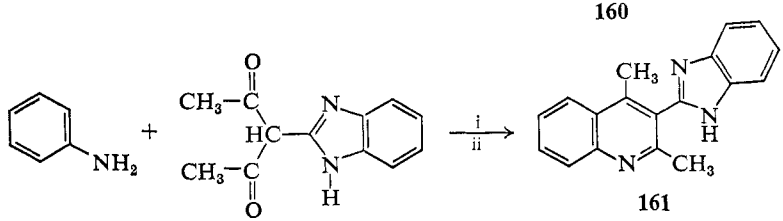
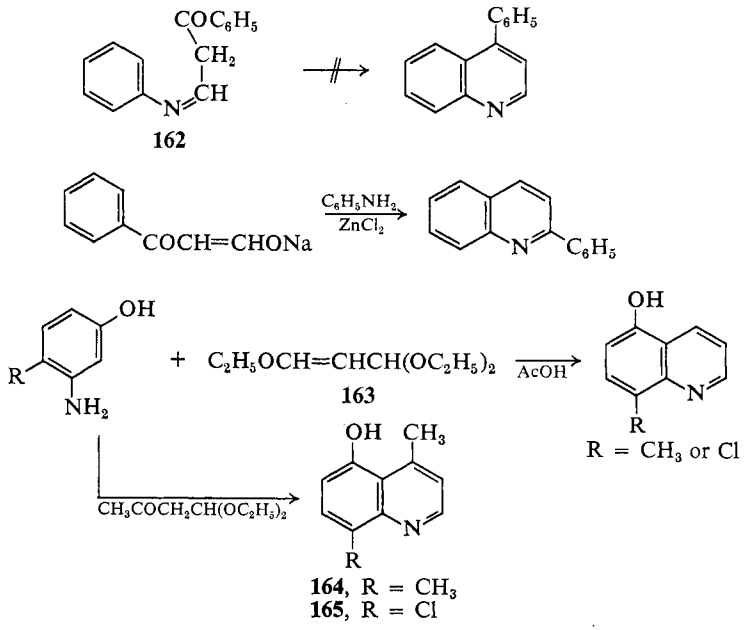


161

i, Condense. ii, Cyclize

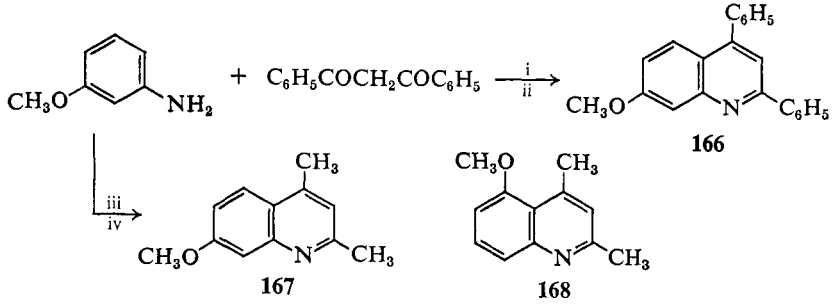
higher degree of substitution in the pyridine ring has been achieved by using 3-substituted pentane-1,3-diones, as illustrated by the synthesis of the quinolines (**160**)[227] and (**161**).[228] Nitromalondialdehyde and cyanomalondialdehyde gave 3-nitro- and 3-cyano-quinoline, respectively.[229]

Difficulties have been reported with the sulphuric acid cyclization of anils derived from 3-keto-aldehydes; for example, Koenigs and Jaeglé were unable to prepare 4-phenylquinoline from the corresponding anil (**162**).[230] Petrow's modification,[214] using amine hydrochloride as cyclizing agent, was particularly successful with these keto-aldehydes; also, when the sodium salt of the keto-aldehyde was heated with zinc chloride and aniline, 2-phenylquinoline was obtained.[231, 232] Malondialdehydes present even more difficulty although the "latent" malondialdehyde (**163**) has been



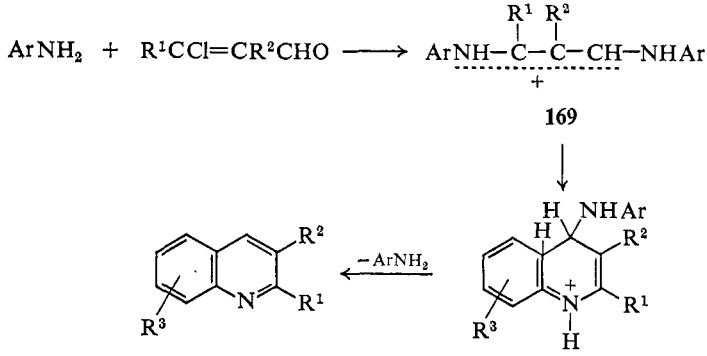
used to prepare quinolines unsubstituted in the pyridine ring.[117] The same workers used the dimethyl acetal of butan-3-on-1-al to prepare 4-methylquinolines (**164**) and (**165**). Nitro- or cyano-malondialdehydes gave poor yields of 3-nitro- or 3-cyano-quinolines when cyclized with zinc chloride,[229] but better yields with the amine hydrochloride in acetic acid.[224]

The acid catalyst most widely used for the cyclization has been sulphuric acid. The only disadvantage reported was in the sulphonation of aromatic rings containing electron-donating substituents.[233–235] In such cases a mixture of acetic and hydrochloric acid has been satisfactorily used, for example to produce the 7-methoxyquinoline (**166**).[233] The temperature of the cyclization reaction has ranged from 0° for quinoline (**166**) to 140° (with sulphuric acid) for 6-chloro-2,4-dimethylquinoline,[225] and 220° with zinc chloride.[229] Other acid cyclizing agents used were phosphoric acid,[223] hydrogen fluoride,[222] and phosphoryl chloride.[233] The use of phosphoryl chloride has provided a rare example of cyclization of a *m*-methoxyaniline to give not only the 7-methoxyquinoline (**167**) but also a trace of the 5-methoxyquinoline (**168**).[233] The use of zinc chloride[229, 231, 232, 235] and of the amine hydrochloride (often in acetic acid or alcohol)[214, 229] has often been successful, but, as discussed above (p. 121), differs in mechanism and in the products obtained.



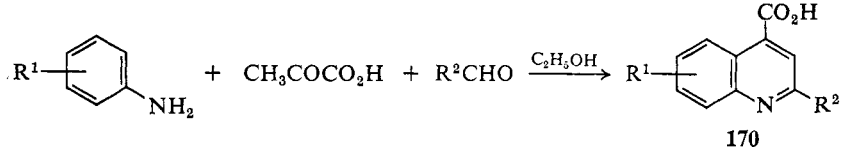
i, Condense. ii, CH_3CO_2H, HCl. iii, $CH_3COCH_2COCH_3$. iv, $POCl_3$

A synthesis that has a clear relation to the Combes reaction makes use of an aromatic amine with a chlorovinylaldehyde. The intermediate dianilinium salts (**169**) were cyclized in boiling acetic acid or butan-1-ol.[236, 237] The mechanism suggested closely resembles that proposed for the dianil cyclization in the modified Combes' synthesis. The use of *N*-alkylarylamines leads to *N*-alkylquinolinium salts.



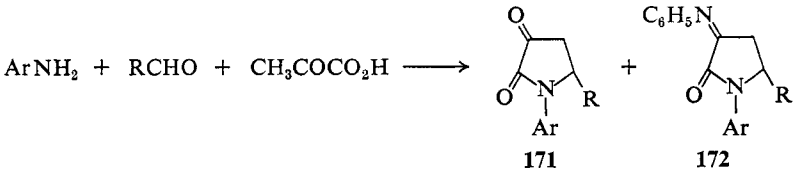
D. Doebner's Cinchoninic Acid Synthesis

The modification of the Doebner–von Miller synthesis in which pyruvic acid is used was actually discovered by Böttinger in 1887.[238] Aniline, heated with pyruvic acid, gave "aniluvitoninsaure" which was a methylquinolinemonocarboxylic acid. Decarboxylation of this acid gave a methylquinoline, but Böttinger observed that he would leave the question of the relation of this methylquinoline to that prepared by Doebner and von Miller "to those gentlemen", since he lacked the time. Doebner duly identified the methylquinoline as quinaldine (2-methylquinoline), and the acid as 2-methylquinoline-4-carboxylic acid.[239] He also deduced that some of the pyruvic acid must be decarboxylated to acetaldehyde and hence that mixtures of pyruvic acid with an aldehyde should react with aromatic amines to give 2-substituted quinoline-4-carboxylic acids (**170**) ("cinchoninic" acids); the general scheme is



shown. As the acids (**170**) are decarboxylated when heated, this provides a synthesis of 2-substituted quinolines. In his first paper, Doebner reported the preparation of 2-ethyl-, 2-isopropyl-, and 2-phenyl-cinchoninic acids (**170**; $R^1 = H$, $R^2 = C_2H_5$, C_3H_7, C_6H_5); the conditions were very mild (a boiling solution in ethanol) and particularly high yields of 2-phenylquinoline-4-carboxylic acid ("cinchophen") were obtained.

a. MECHANISM OF THE REACTION. In his early papers[240, 241] Doebner noted that a neutral by-product was formed and became the major product if cold ether was used as solvent. The neutral materials were dioxopyrrolidines (**171**), and careful examination of the reaction mixture sometimes revealed a third product, the anil (**172**). Once



171 **172**

the structures of the three possible products were known, mechanisms for the reaction could be advanced. An early discussion by Garzarolli-Thurnlackh contains most of the essential points:[242] from benzaldehyde anil and pyruvic acid an intermediate, formulated as (**173**) or (**174**), could be formed by the routes shown; of these, intermediate (**174**) would give the 2-carboxylic acid after cyclization, whereas (**173**)

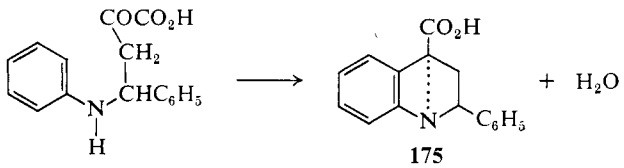
$$C_6H_5CH{=}NC_6H_5 + CH_3COCO_2H \longrightarrow C_6H_5CH(NHC_6H_5)CH_2COCO_2H$$

173

$$C_6H_5CH{=}NC_6H_5 + CH_3COCO_2H \longrightarrow C_6H_5CHO + C_6H_5N{=}C(CH_3)CO_2H$$

$$C_6H_5N{=}C(CH_3)CO_2H + C_6H_5CHO \longrightarrow C_6H_5N{=}C(CO_2H)CH_2CH(OH)C_6H_5$$

174



175

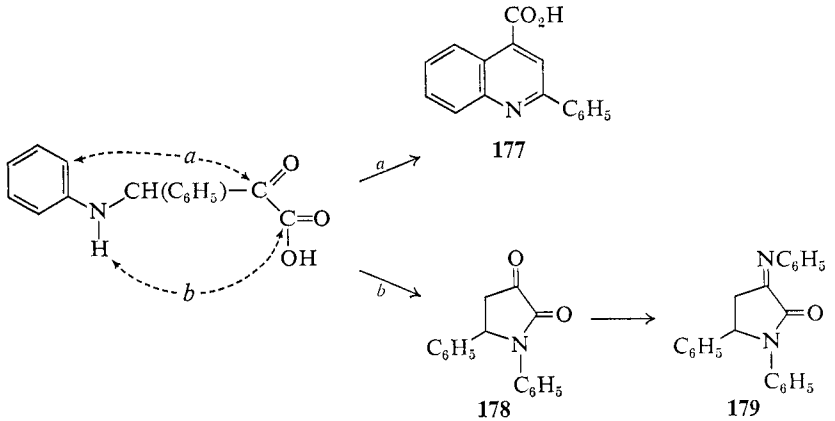
$$RCHO + CH_3COCO_2H \longrightarrow RCH{=}CHCOCO_2H$$

176

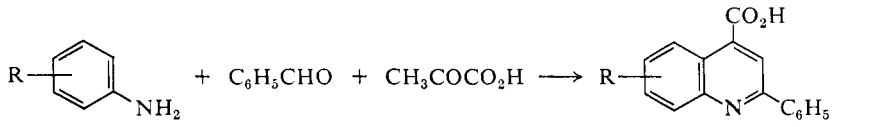
$$\xrightarrow{C_6H_5NH_2} RCH(NHC_6H_5)CH_2COCO_2H$$

would give the dihydrocinchoninic acid, formulated as (**175**). Intermediate (**173**) has been generally accepted and its mode of formation via the anil also appears firmly established. The Schiff base is a less likely intermediate when aliphatic aldehydes are used, and an alternative mechanism via the unsaturated keto-acid (**176**) gives the same type of intermediate as (**173**).

Bodforss confirmed that neither the anil nor the anilide of pyruvic acid was an intermediate in the reaction and that cinnamic acid was very unlikely to be formed under the conditions of the reaction.[243] The intermediate (**173**) has the additional advantage that it can be readily seen to cyclize either to the dihydrocinchoninic acid (route *a*) or to the dioxopyrrolidine (route *b*). The balance between routes *a* and *b* has been examined by a number of workers. Bucherer and Russischwili[244] were able to maximize the production of any one of the three possible products from benzaldehyde, pyruvic acid, and aniline. By using boiling ethanol as solvent the yield of cinchoninic acid (**177**) is maximized; in ether the main products were the dioxopyrrolidine (**178**) and the anil (**179**). In the presence of mineral acid the anil (**179**) became



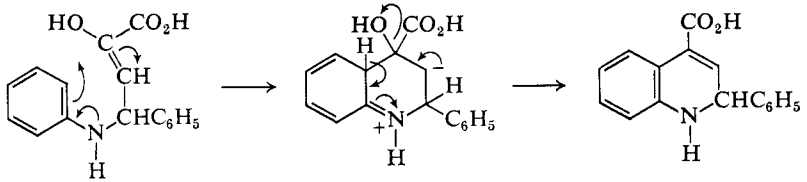
predominant. It is not surprising that aromatic amines carrying electron-withdrawing substituents tend to give poor yields of cinchoninic acids, since the cyclization stage must depend on the nucleophilicity of the *ortho*-position in the amine. The acids (**180**) and (**181**) were obtained in better yields from the *m*-aminophenol and *m*-toluidine than were the isomeric acids from *p*-aminophenol and from *p*-toluidine;[245]



Compound	**180**	**181**	**182**
R	7-OH	7-CH_3	6-CH_3CO
%	57	38	20

conversely, *m*-aminoacetophenone gave no cinchoninic acid while a 20% yield of cinchoninic acid (**182**) was obtained from the *p*-isomer. When very reactive amines were used, only cinchoninic acids were obtained, even in cold, non-polar solvents;[246] Weil could not obtain cinchoninic acids under any normal conditions from nitroanilines or from aromatic amines bearing arsonic or sulphonic acid substituents.[247]

There is no clear proof of the exact mechanism of cyclization, although the enol may be involved, giving, for example, intermediates (**183**) and (**175**). The other point of doubt in the mechanism is the nature of the dehydrogenation step which is essential

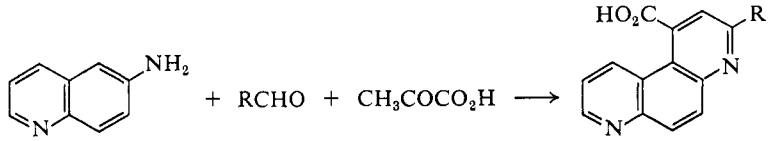


183 175

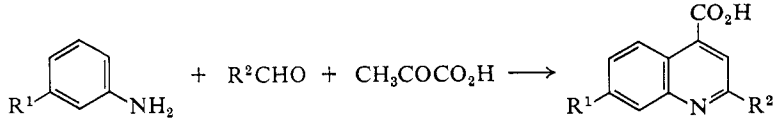
to convert intermediate (**175**) into the cinchoninic acid. Addition of oxidizing agents (nitrobenzene, arsonic acids, etc.) has been reported to have no effect on the yield.[248] Most workers favour a Schiff base as an internal oxidizing agent, a suggestion advanced by Simon and Mauguin after a careful examination of the products from reaction between a benzylidenenaphthylamine and pyruvic acid.[249] There are, however, reports of the isolation of tetrahydrocinchoninic acids, which may imply disproportionation of the intermediate (**175**).[249, 250]

b. Scope and Limitations. Variations in the aromatic amine have been largely covered in the previous section. Briefly, deactivating substituents in the amine lead to poor or even negligible yields of cinchoninic acids. Good examples of this rule are provided by the use of aminoquinolines to prepare polycyclic compounds; 2- and 4-aminoquinoline failed to react in the Doebner synthesis, but 5-, 6-, 7-, and 8-aminoquinoline do, giving, for example, the polycycles (**184**) and (**185**).[251–253]

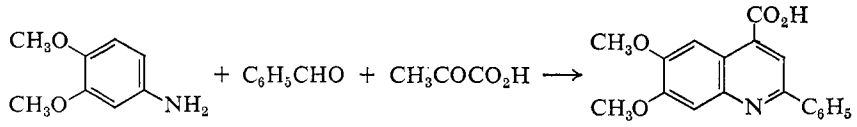
One of the most satisfactory features of the pyruvic acid synthesis is the predominance of 7-substituted cinchoninic acids when a *meta*-substituted aniline is used. Two examples are provided by the synthesis of the 7-substituted quinolines (**186**),[254]



184, R = CH_3
185, R = C_6H_5



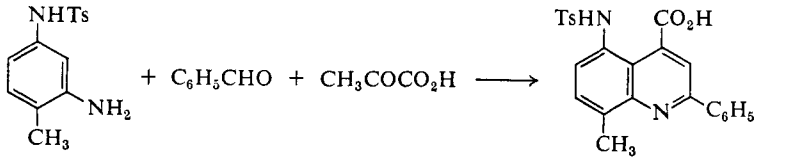
186, R^1 = CH_3; R^2 = *p*-ClC_6H_4
187, R^1 = OH; R^2 = 3,4-$(CH_3O)_2C_6H_3$
188, R^1 = $N(CH_3)_2$; R^2 = 3,4-$(CH_3O)_2C_6H_3$



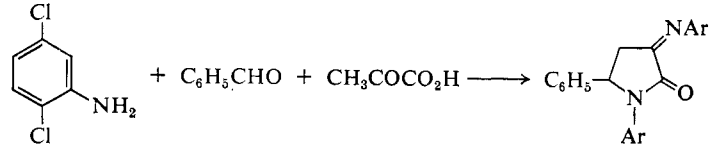
189

(**187**), and (**188**).[255] Similarly, 3,4-disubstituted anilines give only 6,7-disubstituted quinolines such as (**189**),[256] Lutz and his co-workers give a particularly good experimental procedure.[254] In cases where 2,5-disubstituted anilines were used the yields of

5,8-disubstituted quinolines were poor, as in the synthesis of compound (**190**),[244] or negligible, as in the case of the reaction from 2,5-dichloroaniline (**191**).[254] In the latter



190, Ts = *p*-$CH_3C_6H_4SO_2$

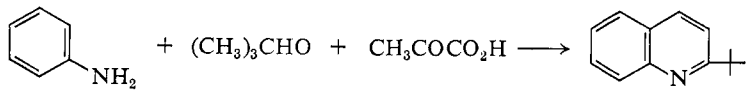


191

Ar = 2,5-$Cl_2C_6H_3$

case it must be remembered that *m*-chlorine substituents always have a depressing effect on the yield. However, in this context, it is notable that 8-chloro-2-phenylcinchoninic acid[257] and even 8-nitro-2-phenylcinchoninic acid[258] have been obtained, the latter in 34% yield, when concentrated sulphuric acid was used as a cyclizing agent. Fortunately, many of the cinchoninic acids that are difficult to prepare by Doebner's procedure are readily obtained by the Pfitzinger synthesis (p. 197).

All types of aldehyde have been used in the Doebner synthesis: aromatic aldehydes give the best yields, and α,β-unsaturated aldehydes are among the least satisfactory. The successful use of isobutyraldehyde,[239] of pivalaldehyde to give the 2-*tert*-butylquinoline (**192**),[259] and of *ortho*-substituted benzaldehydes,[260] indicates that steric hindrance is not an important factor with pyruvic acid itself, although it may be



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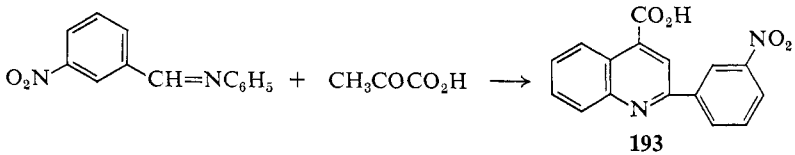

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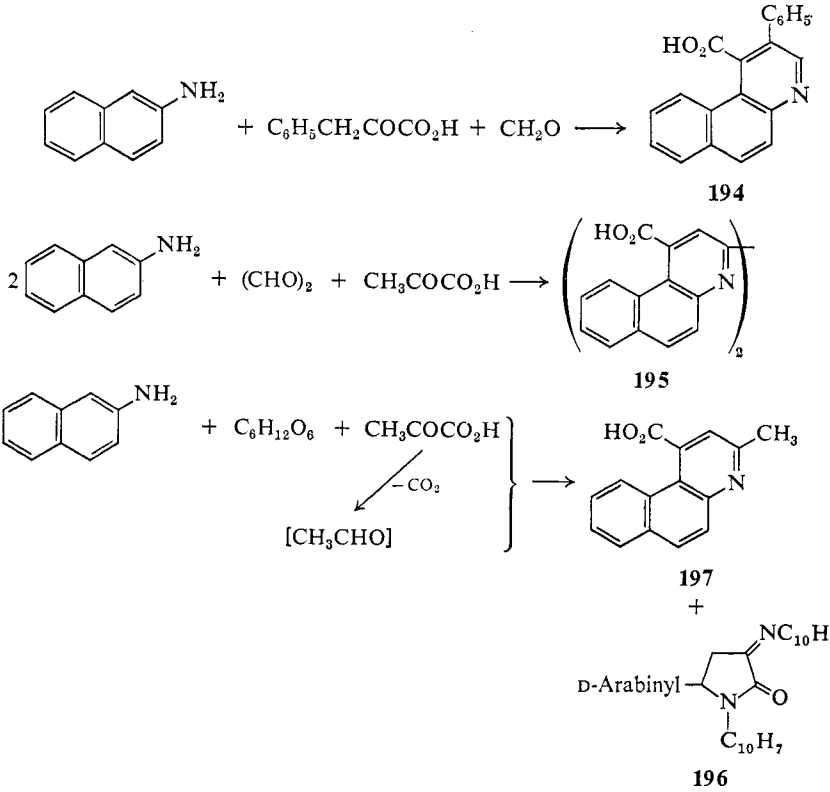
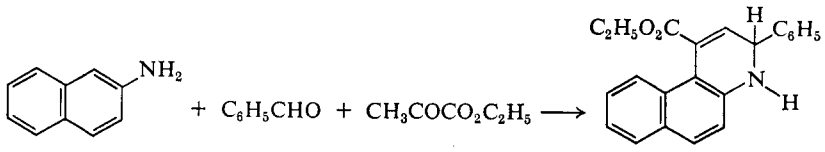
when substituted pyruvic acids are used (p. 130). Decreased activity in the carbonyl group of the aldehyde might be expected to inhibit the reaction; nitrobenzaldehydes have been reported to give poor yields of cinchoninic acids with increased amounts of dioxopyrrolidine.[244, 261] Shivers and Hauser obtained 2-(*m*-nitrophenyl)cinchoninic acid (**193**) in 47% yield, using the anil as starting material.[262]

Formaldehyde has been used in the Doebner synthesis to give cinchoninic acids without 2-substituents, as in (**194**),[252, 263] and glyoxal to give 2,2′-biquinolines such as (**195**).[264] D-Glucose failed to form a cinchoninic acid even with the very reactive β-naphthylamine; the products were the D-arabinyldioxopyrrolidine (**196**), and some



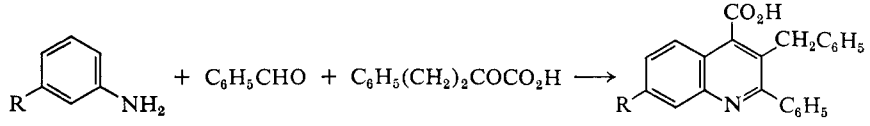
3-methylbenzo[*f*]quinoline-1-carboxylic acid (**197**).[265] The benzoquinoline was formed from acetaldehyde, in turn formed by decarboxylation of pyruvic acid, as in Böttinger's original synthesis. It is worth emphasizing that the isolation of 2-methylcinchoninic acids from decarboxylated pyruvic acid is uncommon, even when unreactive aldehydes are used. Aldol has been used as an aldehyde source, but α-hydroxyaldehydes did not give cinchoninic acids.[266]

The pyruvic acid component can also be varied; with pyruvic acid itself it has been reported that better yields were obtained when distilled pyruvic acid was used.[254] Ethyl pyruvate has been reported to react with β-naphthylamine to give a low yield of the dihydrocinchoninate intermediate (**198**).[249] A mixture of sodium pyruvate and concentrated hydrochloric acid has also been used.[267]

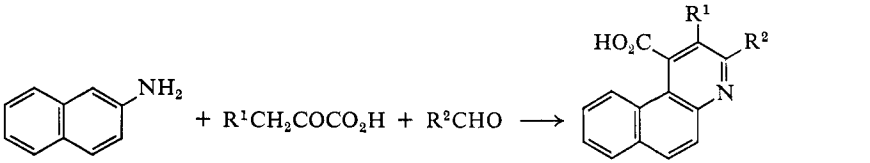


Borsche studied the variations possible in the pyruvic acid component; with unreactive amines pyruvic acid and, in a few cases, benzylpyruvic acid [as, for

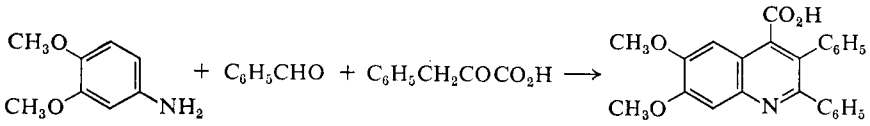
example, in the synthesis of compounds (**199**) and (**200**)] could be used.[263] With more reactive amines such as β-naphthylamine,[263] *m*-hydroxy- or *m*-methoxy-aniline,[253] or 3,4-dimethoxyaniline,[256] other substituted pyruvic acids could be used, as in the synthesis of compounds (**201**)–(**204**).



199, R = H; 13%
200, R = CH_3; 18%



201, $R^1 = R^2 = C_6H_5$; 48%
202, R^1 = 2-$O_2NC_6H_4$, $R^2 = C_6H_5$; 33%
203, $R^1 = C_6H_5CO$, $R^2 = C_6H_5$; 25%



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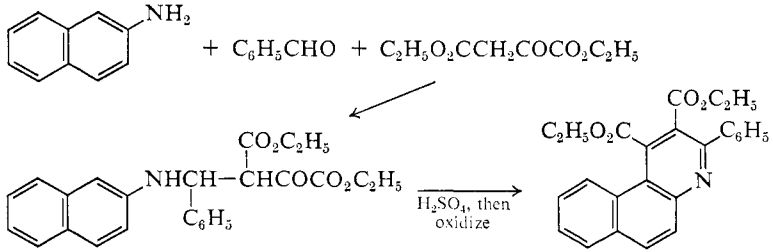
Oxalacetic ester has been used with β-naphthylamine to give benzo[*f*]quinoline diesters, such as (**205**), in a two-stage procedure.[268] Yields were not recorded.



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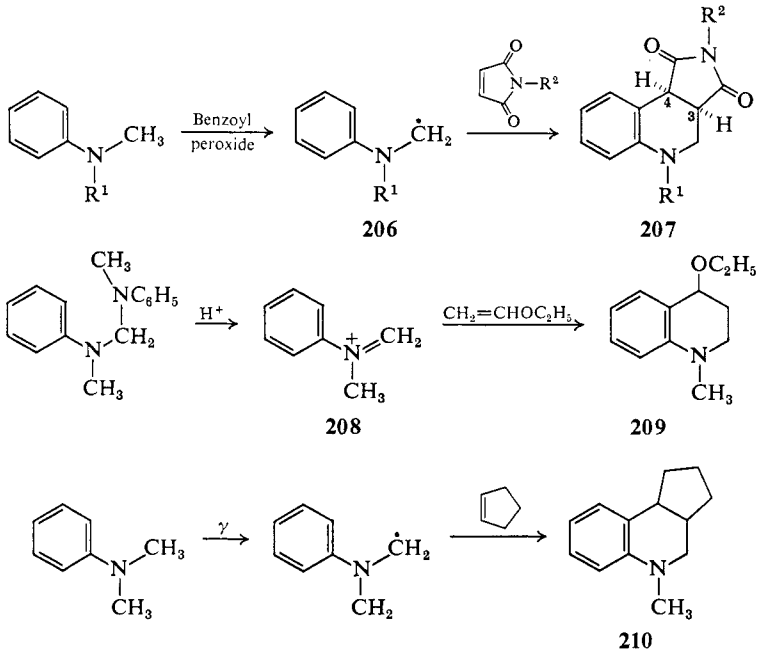
E. Miscellaneous Syntheses from Substituted Anilines or Schiff Bases

In most of the syntheses described in this section, an aniline or a Schiff base was treated with an acetylene or an enol ether. In one exceptional synthesis Swan and Roy reported that generation of the radical (**206**) in the presence of *N*-substituted maleimides led to *N*-alkyltetrahydroquinolines of type (**207**).[269-272] In the summarizing paper, [271] it was established that the reaction was not due to the iminium ion (**208**), which did, however, react with ethyl vinyl ether to give a product (**209**) analogous to

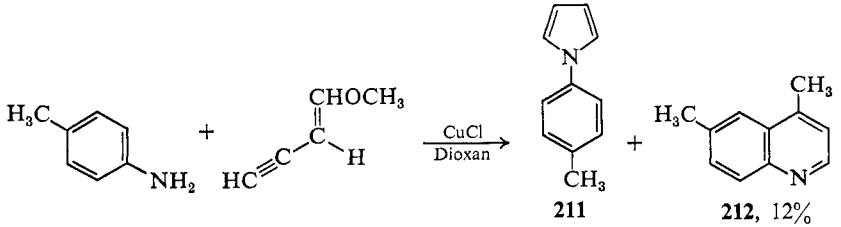
those discussed below (p. 134). The stereochemistry about the 3,4-position was tentatively assigned. In a later paper,[272] products of the same type were described, obtained by γ-radiation; some simpler compounds, such as (**210**), were obtained from cycloalkenes.

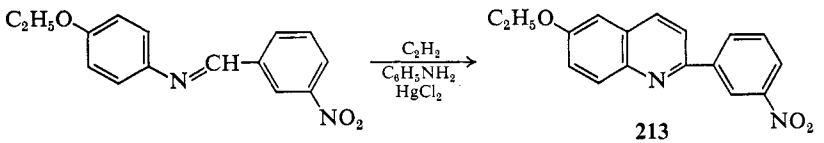


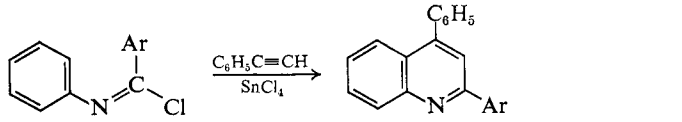
a. Syntheses from Amines or Schiff Bases and Alkenes or Alkynes. It has been reported that aniline and acetylene at high temperatures and over a catalyst can give quinoline.[273, 274-276] The same workers[274-276] reported the isolation of quinoline from mixtures of aniline, acetaldehyde, and methanol or formaldehyde. The reaction between 1-methoxybut-1-en-3-yne with *p*-toluidine in the presence of cuprous chloride gave mainly the pyrrole (**211**), with only 12% of the quinoline (**212**).[277] Much better yields of quinolines were obtained when Schiff bases in toluene with aniline were treated with mercuric chloride and acetylene. This reaction has been exhaustively studied by Kozlov and his co-workers; a few references from many describe the mechanism,[278] the effect of various catalysts,[279] and the effects of working in the liquid phase as against the vapour phase.[280] The yields varied from 27% to 76%; the preparation of a 6-ethoxyquinoline (**213**) is illustrated.[281] The chloro-imines of general type (**214**) gave with phenylacetylene and stannic chloride good yields of 2-aryl-4-phenylquinolines such as (**215**).[282] In an abnormal reaction for an aromatic amine, 3,4-dimethoxyaniline reacted with ethyl propargylate to give the 1,4-dihydroquinoline (**216**).[283] Over five years the dihydroquinoline (**216**) gave the quinoline (**217**); for less leisurely chemists, heating of compound (**216**) in Dowtherm led to elimination of the ethyl acetate residue, giving quinoline (**218**).

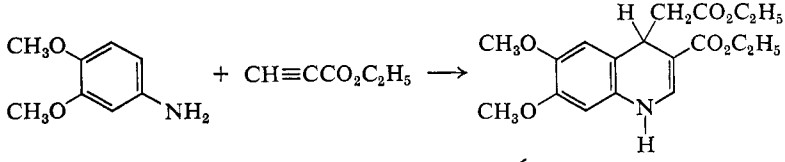
A synthesis that may involve an intermediate Schiff base or carbinol amine is that using an aromatic amine, an aldehyde, and an alkene, in the presence of an acetic–sulphuric acid mixture.[284, 285] The range of products is indicated on the general

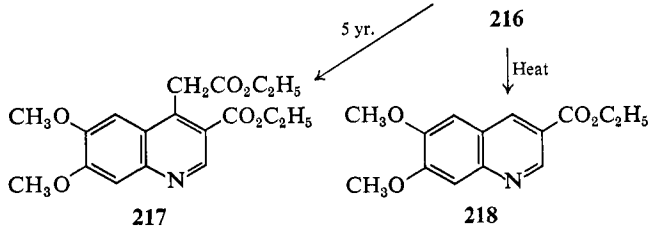
formula (**219**); formaldehyde with primary amines was reported to give benzoquinolines by secondary condensation, but even formaldehyde gave good yields with *N*-alkyl- or with *ortho*-substituted anilines.

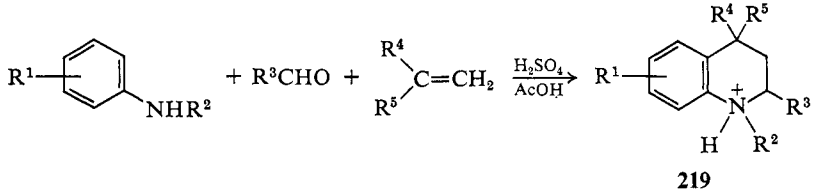






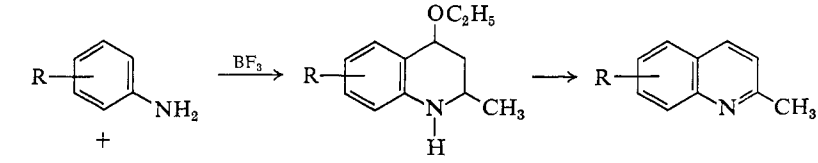


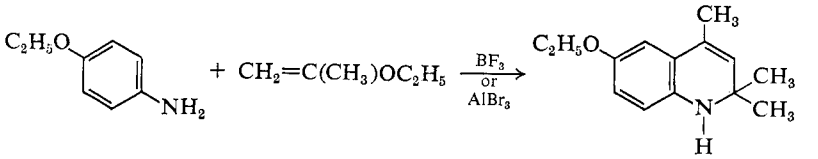




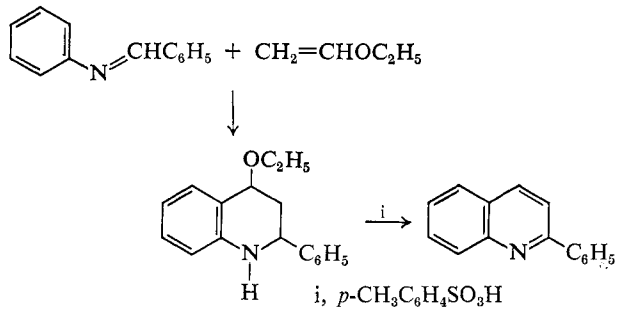
R^1 = H, *m*-CH_3, *p*-CH_3, *o*-CH_3, *p*-CH_3O, *p*-Cl, *o*-NO_2, or *p*-NO_2
R^3 = CH_3, iso-C_3H_7, C_5H_{11}, C_6H_5
R^4 = C_6H_5 C_6H_5
R^5 = H CH_3

b. Syntheses from Aromatic Amines or Schiff Bases and Enol Ethers. Two major groups have studied the synthesis of dihydro- and tetrahydro-quinolines by the reaction between aromatic amines (or more commonly Schiff bases) and enol ethers. Povarov and his co-workers have reported the reaction between aromatic amines and enol ethers under mild conditions, using boron trifluoride[286-288] or aluminium bromide[287] as catalyst. With ethyl vinyl ether the products were the 4-ethoxy-1,2,3,4-tetrahydro-2-methylquinolines (**220**),[286] converted by acid treatment into the corresponding quinolines. With isopropenyl ethers, the dihydroquinolines



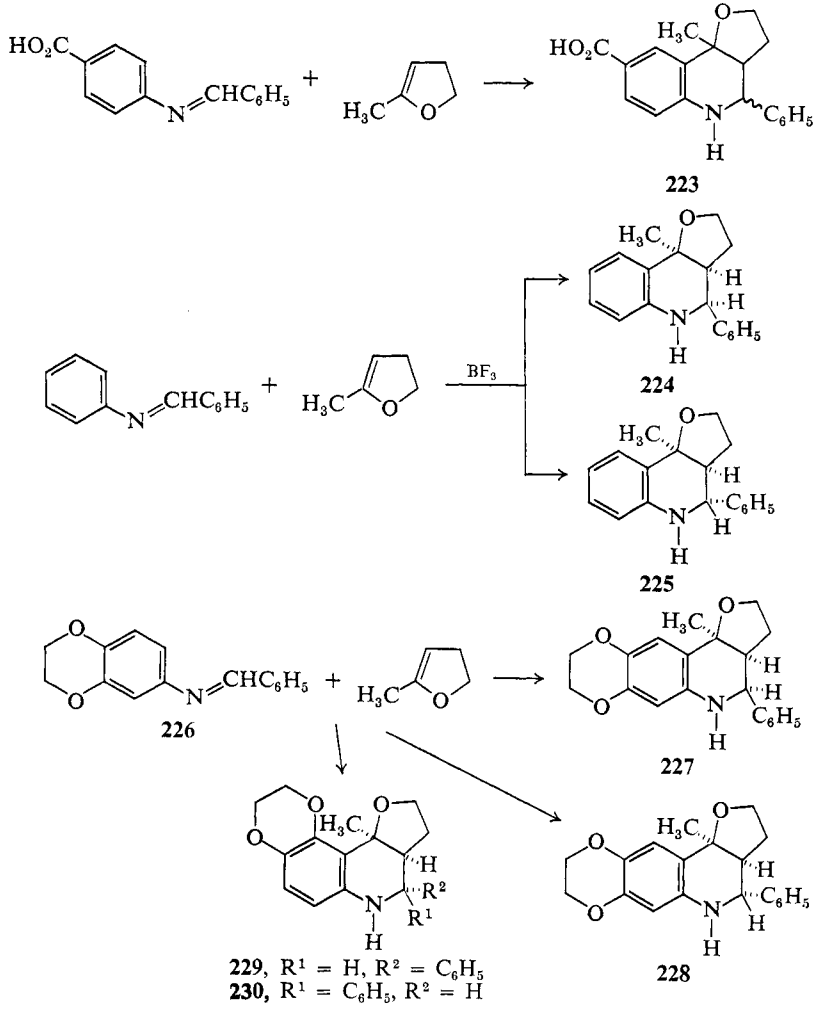


[e.g. (**221**)] were obtained similar to those prepared by condensation of amines with acetone (p. 117).[287, 288] Similar reactions between the Schiff base and an unsaturated ether, under the influence of boron trifluoride, gave 2-aryl-4-ethoxytetrahydroquinolines such as (**222**), again reported to be converted into the corresponding



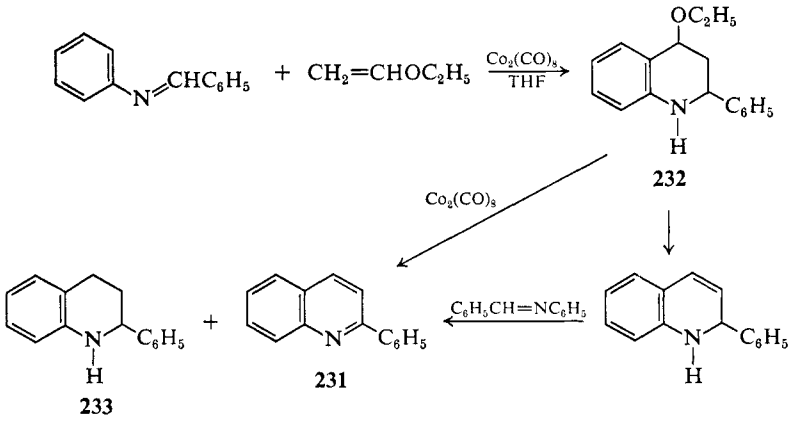
quinolines on treatment with toluene-*p*-sulphonic acid[289] or permanganate.[290] In this case, isopropyl or butyl vinyl ethers gave inferior yields to ethyl vinyl ether, and ethyl isopropenyl ether gave poor yields,[289] but 3,4-dihydro-2-methylfuran gave good yields, as in the preparation of compound (**223**).[290] No stereochemistry was at first assigned to the tricyclic compounds of type (**223**), but subsequently a detailed stereochemical examination of the reaction was reported[291] and the presence of isomers (**224**) and (**225**) was shown. A similar reaction between the dihydrofuran and a 3,4-disubstituted aniline derivative (**226**) showed the presence of other isomers due

to cyclization in both possible modes, (**227–230**);[292] other examples were also reported.[293]

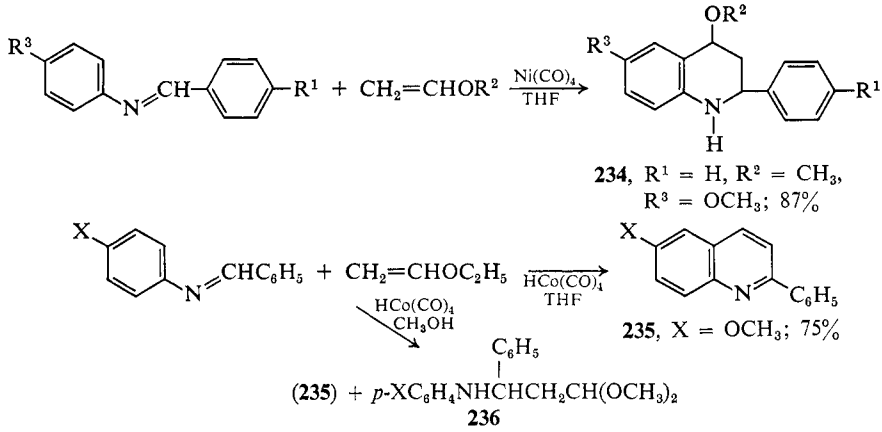


Joh and Hagihara have studied the reaction between unsaturated ethers and Schiff bases in the presence of metal carbonyls.[294–298] In the earlier experiments[294, 295] octacarbonyldicobalt was used, and the products were *N*-phenylbenzylamine, 2-phenylquinoline (**231**), and 4-ethoxy-1,2,3,4-tetrahydro-2-phenylquinoline (**232**); in the suggested mechanism, the tetrahydroquinoline (**232**) was an intermediate, giving 1,2-dihydroquinoline, oxidized by the Schiff base, which thereby was converted into the benzylamine. Treatment of the intermediate (**232**) with octacarbonyldicobalt gave a mixture of the quinoline (**231**) and the tetrahydroquinoline (**233**), suggesting a disproportionation of the intermediate 1,2-dihydroquinoline. In a subsequent paper[296] the effect of variation in the unsaturated ether (little effect) and of various substituents

on the aromatic amine were reported. Electron-withdrawing substituents in the *para*-position completely inhibited quinoline formation; the anil of acetophenone and the β-naphthylamine Schiff base of benzaldehyde also failed to give quinolines. Nickel

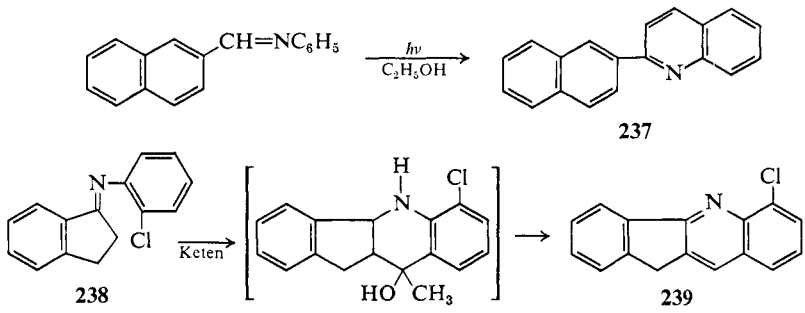


carbonyl gave successful reactions, producing compounds of general type (**234**) even with electron-withdrawing substituents on the aromatic amine; yields were in some cases very high. [298] An infrared study of the reaction using octacarbonyldicobalt suggested[297] the intermediacy of tetracarbonylcobalt hydride, and the use of the



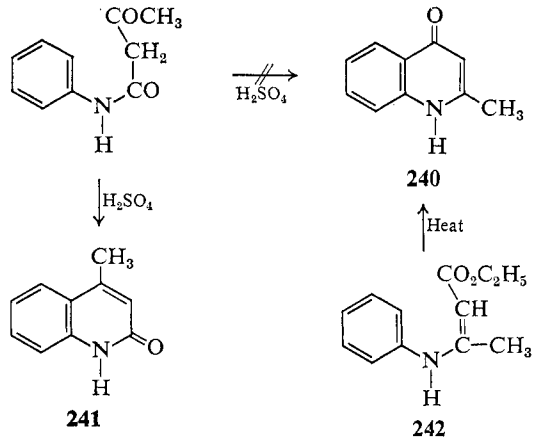
hydride in place of octacarbonyldicobalt gave, for example, a 75% yield of the compound (**235**). The use of methanol in place of the more usual tetrahydrofuran was not advantageous; some acetal (**236**) was obtained.[297]

c. Miscellaneous Syntheses Using Schiff Bases. Photolysis of Schiff bases in ethanol has been reported[299] to give some substituted quinolines such as (**237**), the two-carbon fragment coming from acetaldehyde. The Schiff base (**238**) in the molten state, treated with keten, gave the quinoline (**239**).[300]



3. Cyclization of Substituted Anilines to give 2-Quinolones or 4-Quinolones

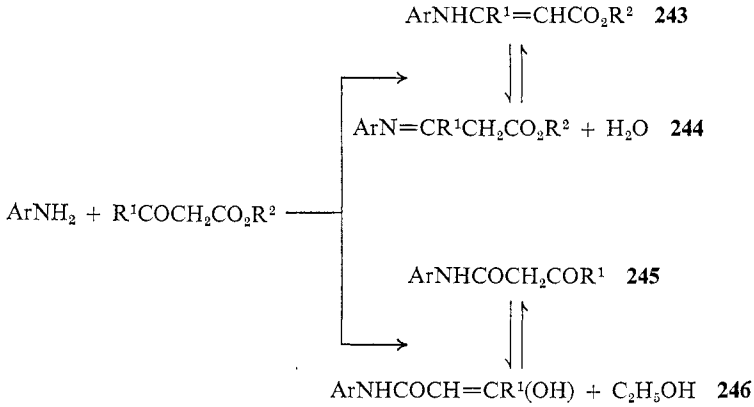
A number of cyclization reactions closely related to the Skraup and the Doebner–von Miller syntheses lead to 2-quinolones or 4-quinolones. Knorr discovered[301] that acetoacetanilide cyclized when treated with sulphuric acid to give a methylquinolone which he incorrectly formulated as 2-methyl-4-quinolone (**240**). Conrad and Limpach prepared an alternative condensation product from aniline and ethyl acetoacetate,



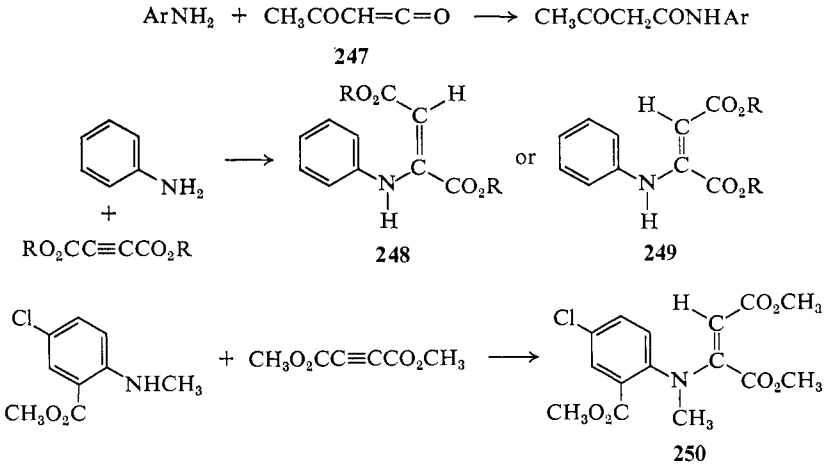
ethyl 3-anilinocrotonate (**242**), and showed that this cyclized when heated, giving 2-methyl-4-quinolone (**240**);[302] as their product differed from that obtained by Knorr, he corrected the structure for the cyclization product from acetoacetanilide to that of 4-methyl-2-quinolone (**241**).[303]

Since two condensation products are possible from β-keto-esters and aromatic amines, and either can be cyclized, it is necessary to discuss the condensation reaction before the Knorr or the Conrad–Limpach syntheses are separately considered. The general equations for the condensation reactions lead to the intermediates (**243**) or (**244**), and (**245**) or (**246**). The conditions for the production of either condensation product have been well summarized by Hauser and Reynolds.[304] To obtain the crotonates (**243**) the two components are best heated with an acid catalyst, the reaction then proceeding at the temperature of boiling methylene chloride or benzene. Higher temperatures without an acid catalyst (even on occasion a basic catalyst)

gives the anilide (**245**) in good yield. Much of the confusion in the early literature has arisen because the crotonates and anilides are interconvertible. Heating the crotonate (**243**) with water and acid gives the anilide (**245**); heating the anilide (**245**) with



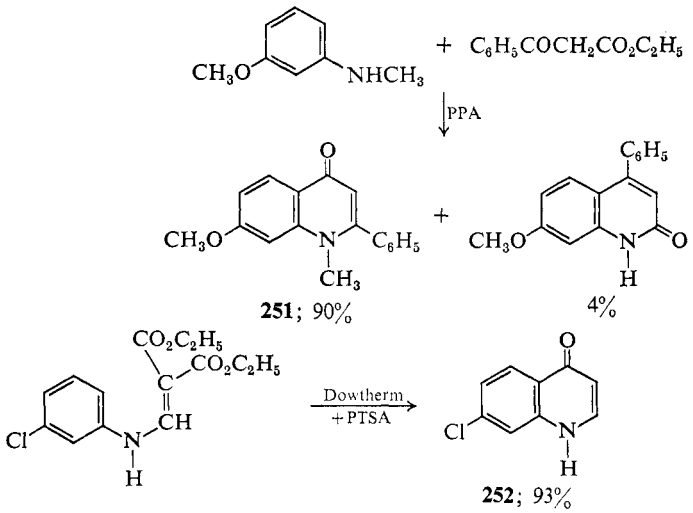
Drierite and alcohol gives the crotonate (**243**). Acetoacetanilides have been prepared unambiguously from aromatic amines and diketen (**247**).[305, 306] The structure of the intermediate (**243**) in the Conrad–Limpach reaction presents another point of difficulty. If the β-aminoacrylates are made at low temperature, as for example in the reaction between anilines and acetylenedicarboxylates,[307–309] the products can be



either fumarates (**248**) or maleates (**249**). Of these, only the fumarates (**248**) can cyclize to quinolones. In one case, that of the *N*-alkyl derivative (**250**), the ester was recovered unchanged after treatment with boiling diphenyl ether. In this case tautomerism was impossible and *cis–trans*-isomerism was hence impossible. With an unalkylated amine tautomeric equilibrium allows *cis–trans*-mixtures to be used.

A. The Conrad–Limpach Cyclization of Arylamino-acrylates

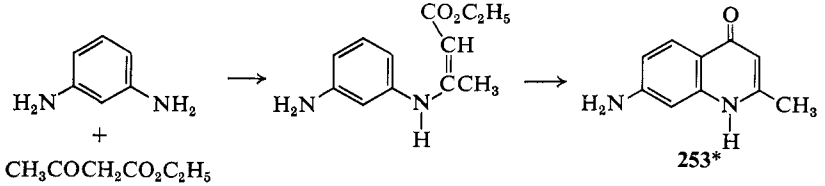
The original Conrad and Limpach synthesis,[302] with one major modification, has been used more widely than any other route to 4-quinolones. Limpach reported[310] the use of paraffin oil as the cyclization medium, and subsequently boiling diphenyl ether or a mixture of diphenyl ether with diphenyl (Dowtherm) have been reported as superior. A minimum time at high temperature (260–280 °C) is desirable, and the common practice has been to add a solution of the amino-acrylate to preheated cyclization medium, preferably maintaining high dilution, whereupon cyclization is complete in a few minutes. Older procedures using acid catalysts (or heating without solvents) gave much poorer yields, but more recently a number of 4-quinolones have been prepared by cyclization of various amino-acrylic acids using polyphosphoric acid.[311-313] A direct condensation and cyclization has been reported[314] in polyphosphoric acid, giving compound (**251**) related to the alkaloid edulein. Acid catalysts



have also been reported to accelerate the cyclization of (arylamino)methylenemalonates (p. 147) and to give increased yields of 4-quinolones such as (**252**), hydrolysis and decarboxylation occurring during the same reaction.[315-319]

a. Scope and Limitations. A very large number of amines have been used in the Conrad–Limpach synthesis. The most notable exceptions are the nitroanilines; Coffey, Thomson, and Wilson pointed out that crotonates could not be obtained from nitroanilines, and also that *o*- and *m*-chloroanilines failed to react with ethyl acetoacetate without a catalyst.[317] The range of possibilities is best illustrated by consultation of the Tables on pp. 263 to 273 which show 4-quinolones thus prepared. As with most syntheses that involve the cyclization of an aniline derivative, a *meta*-substituted aniline can give both 5- and 7-substituted quinolones. Most workers report mixtures from such anilines, usually with a preponderance of the 7-substituted 4-quinolone. There are a number of examples in the older literature that lack structure proof, and the products reported from *meta*-substituted anilines should not be assumed to have established structures. Diamines gave satisfactory yields only when the monocrotonate was cyclized, as in the production of the aminoquinolone

(**253**);[318] it is often better to use the monoacetyldiamine, as shown in examples (**254**)–(**256**).[319–321] A second amino-group in the *ortho*-position can give alternative cyclization possibilities; thus *o*-phenylenediamine has been reported to give either of



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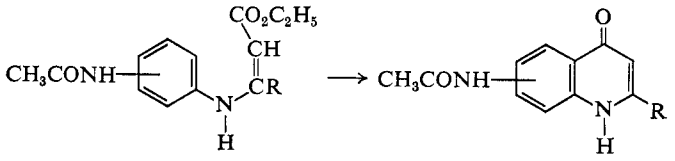
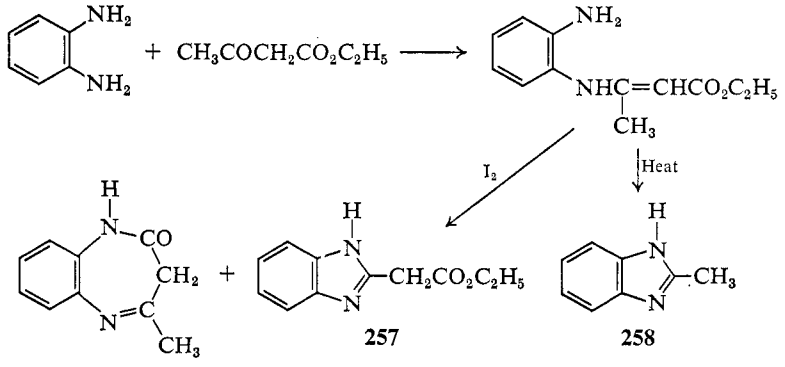


254, R = CH_3, 6-CH_3CONH
255, R = *p*-$CH_3OC_6H_4$, 6-CH_3CONH; 92%
256, R = CH_3, 8-CH_3CONH

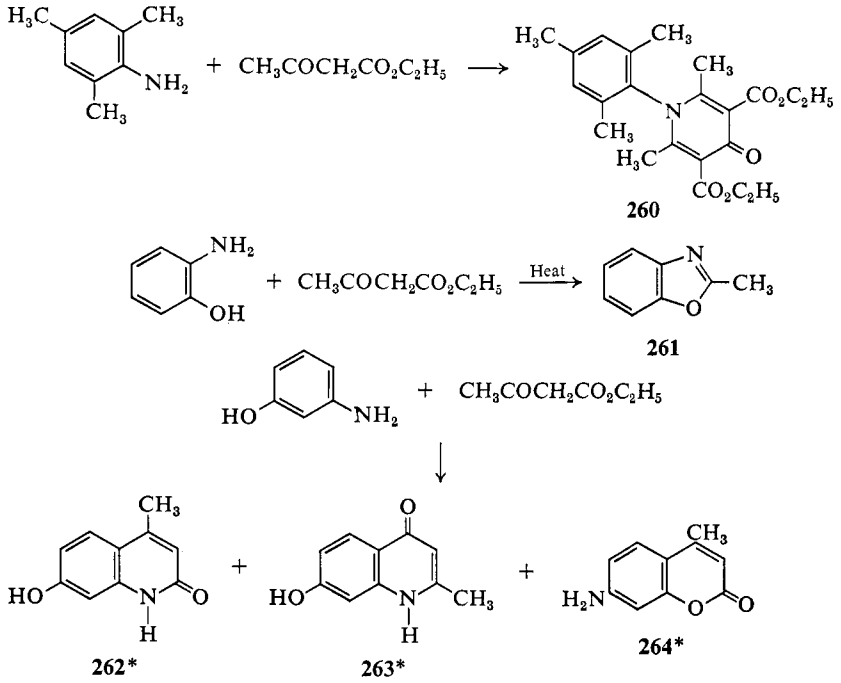


259 **257** **258**

the benzimidazole (**257**)[322] or (**258**)[323] when the monocondensation product with ethyl acetoacetate was cyclized; a further product was the diazepinone (**259**).[322] The observation that the 2,6-disubstituted anilines can give with ethyl acetoacetate a pyridone such as (**260**) has led to the suggestion that such pyridones may be normal by-products even when Conrad–Limpach cyclization is possible.[324] Heating together *o*-aminophenol and ethyl acetoacetate gave 2-methylbenzoxazole (**261**).[325] Von Pechmann and Schwarz have examined the reaction between *m*-aminophenol and ethyl acetoacetate;[326] while the reaction was unnecessarily complicated by the *meta*-pattern of cyclization, three reaction types were clearly established; the products were the 2-quinolone (Knorr product) (**262**), the 4-quinolone (Conrad–Limpach product) (**263**), or the benzopyrone (**264**). Additional products of the benzopyrone or benzoxazole type are avoided by the use of the appropriate methyl ether.

A great deal of variation is possible with the three-carbon fragment which makes up the pyridine ring in the 4-quinolone. The simplest variation in the original β-keto-ester component is in the use of keto-esters other than ethyl acetoacetate. It has been

* Structure assumed, not rigorously proved.

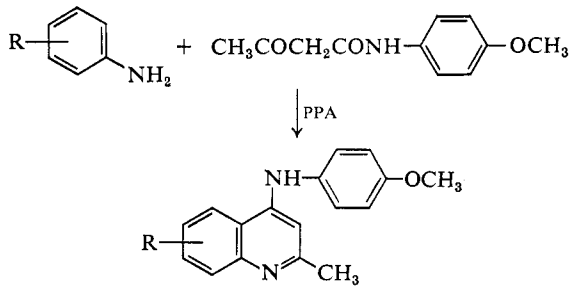


reported[327] that methyl esters were more readily cyclized than the corresponding ethyl esters, but that in the initial condensation crotonates were obtained (rather than anilides) if pentyl or 2-ethylbutyl esters were used.[304] For reaction of an amide of acetoacetic acid, 4-aminoquinolines (**265**) and (**266**) were reported by one group[313] but 4-quinolones such as (**267**) by another group.[328, 329]

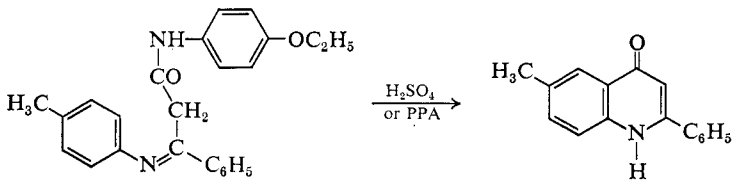
By variation of the β-keto-ester, 4-quinolones with substituents other than the methyl group at the 2-position have been obtained; examples are provided by the synthesis of compound (**267**)[328, 329] and of the mixed 2-(trifluoromethyl)-4-quinolones (**268**) and (**269**) obtained from *m*-methoxyaniline[330] with polyphosphoric acid. The 7-isomer (**269**) only was obtained when diphenyl ether was used as the cyclization medium. Cyclic β-keto-esters give 4-quinolones with additional fused rings, as in the example (**270**) reported by Huggill and Plant.[331]

From β-arylaminoacrylates, 4-quinolones unsubstituted in either the 2- or the 3-position have been obtained. The arylaminoacrylates have been prepared from formyl acetates[332] or from propargylates,[309] the latter method permitting the preparation of a *p*-nitroaniline derivative, and hence 6-nitro-4-quinolone (**271**). The possible problem of *cis*- and *trans*-forms in the intermediate has been mentioned (p. 138) but mixed isomers can be used in the cyclization. An abnormal reaction between an aromatic amine and ethyl propargylate which failed to give a 4-quinolone has already been mentioned (p. 132).[283] The hydroxymethylene-lactone (**272**) has been used to prepare the dihydrofuroquinoline (**273**), a masked 4-quinolone;[333] this is an unusual example of the more common use of 2-formyl esters to produce 2-unsubstituted 3-substituted 4-quinolones. Two further examples, due to Wislicenus[334] (**274**) and to Price, Leonard, and Reitsema[332] (**275**), are formulated.

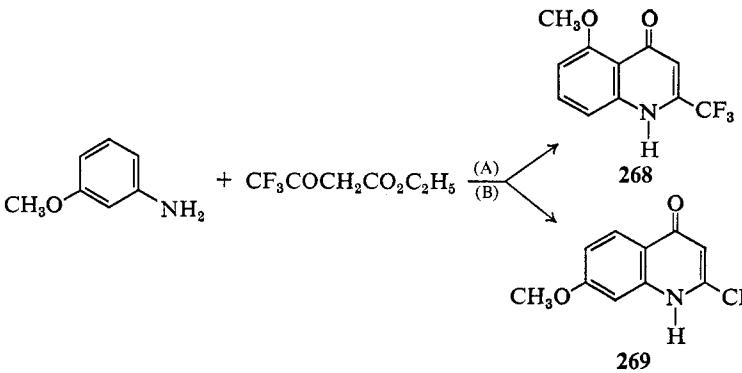
* Position of benzene-ring substituent assumed.



265, R = H
266, R = CH_3



267; 96% (PPA)



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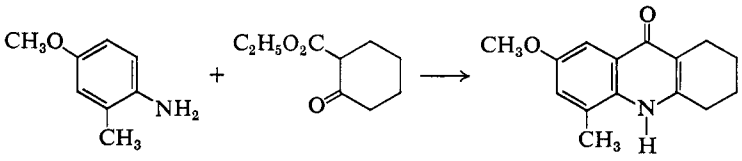
269

(A) HCl, then $(C_6H_5)_2O$; 45% (**269**) only
(B) PPA; 31% (**268**) and 43% (**269**)



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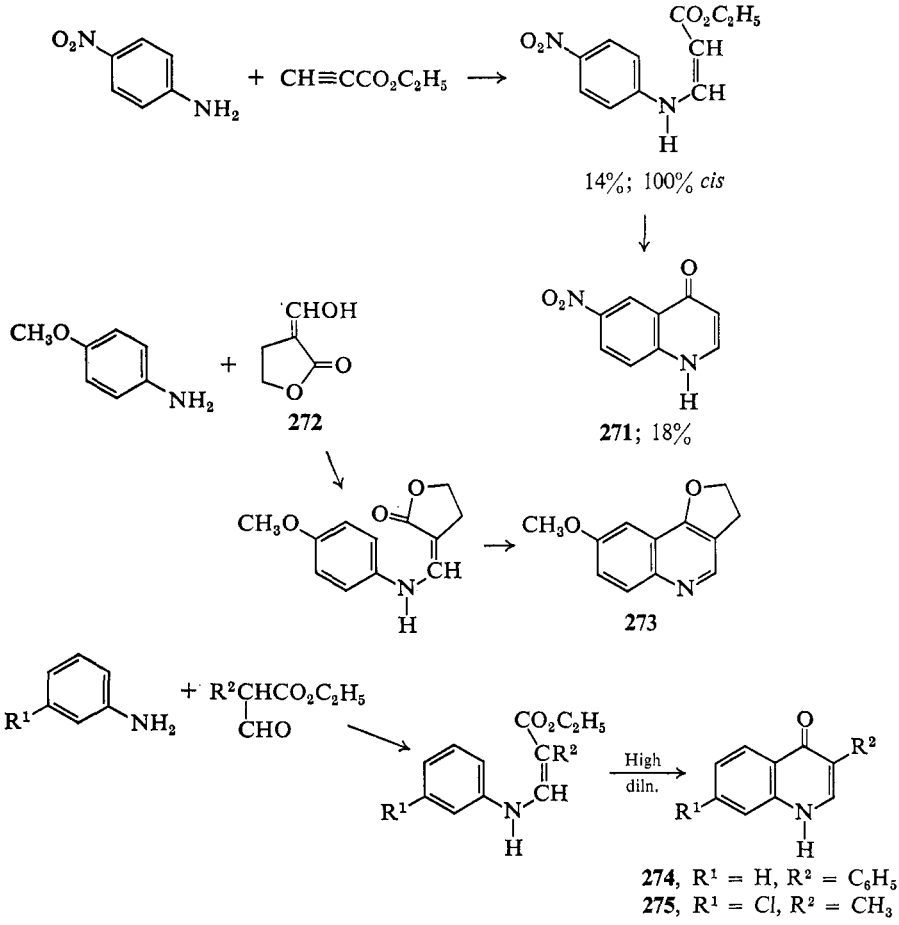
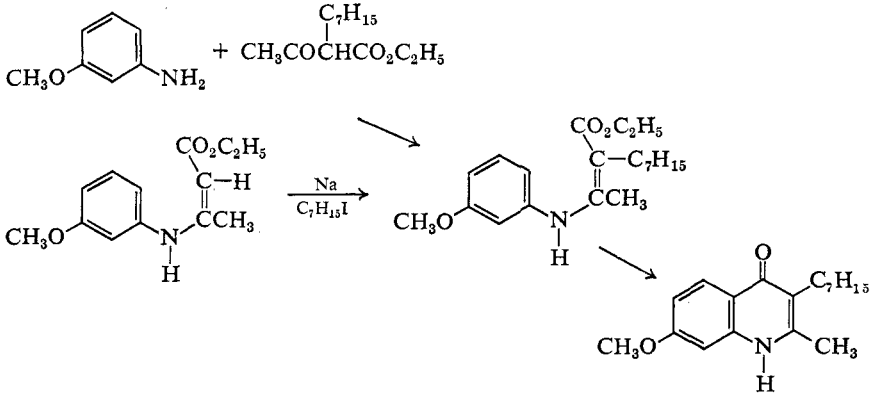


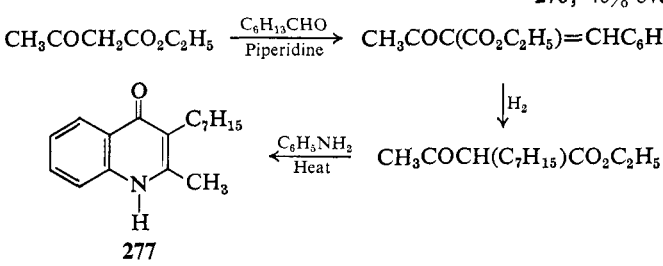
A 2,3-disubstituted 4-quinolone would be expected from an α-substituted β-keto-ester, but in practice the condensation of such hindered esters with aromatic amines gives poor yields. It may be preferable to alkylate the intermediate crotonates;[331] both routes to compound (**276**) have been used.[335] Yet another route makes use of the fact that aldehydes condense with β-keto-esters under Knoevenagel conditions (although there is a danger of bis-condensation, due to a secondary Michael addition); the unsaturated derivatives so formed have been reduced to the α-alkyl-β-keto-esters, which gave 4-quinolones such as compound (**277**).[336]

A synthesis of 2,3-disubstituted 4-quinolones starts from the heterocycle (**277A**).[1365] Thermolysis gives carbon oxysulphide, and thence the suggested mechanism involves an azetidinone and a ketene.

The most valuable variations of the Conrad–Limpach synthesis are those originally reported by Wislicenus and Spiro[337] and by Just.[338] In the former variant aniline was heated with ethyl oxaloacetate; Wislicenus and Spiro could not propose a structure for the product, but Musajo[339] showed that it was ethyl kynurenate [ethyl 4-quinolone-2-carboxylate (**278**)]. The route was thus open to a number of 4-quinolones without



276; 40% overall



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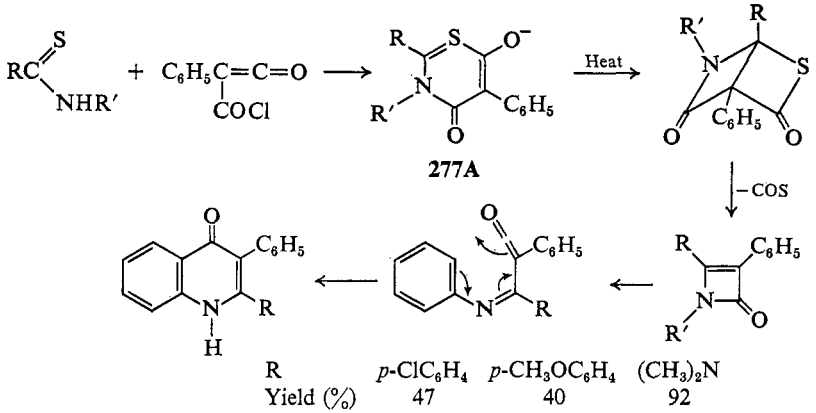
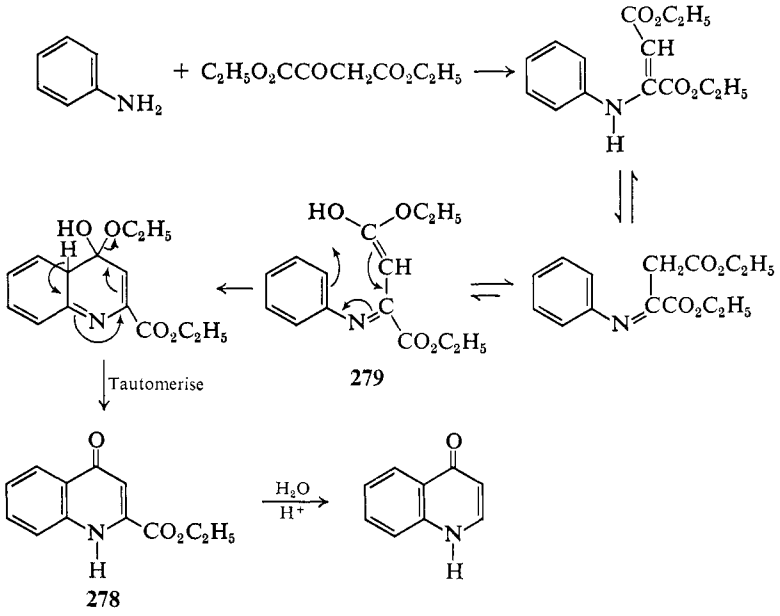


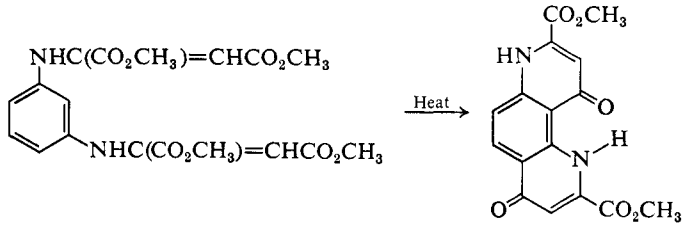
R	*p*-ClC_6H_4	*p*-$CH_3OC_6H_4$	$(CH_3)_2N$
Yield (%)	47	40	92

2- or 3-substituents, since the free 2-carboxylic acids are readily decarboxylated. The mechanism has been elaborated in the sequence shown to indicate that the intermediate (**279**) could be assumed to undergo a 6π-electrocyclic reaction, a suggestion advanced by Jutz and Wagner for the general Conrad–Limpach synthesis.[340]

The range of substituted amines is best illustrated by reference to Table 2c on p. 264. Once more the *meta*-substituted amines gave mixtures of 5- and 7-substituted quinolines, the latter predominating. It has, however, been shown[1292] that in the Gould and Jacobs variation (p. 146) the 5-substituted quinolines can predominate: good yields of mixed quinolines were obtained by the use of ethyl polyphosphate, and



steric hindrance to ring closure was thought to be the main factor that usually favours the production of 7-substituted quinolines. The best yields of the intermediate fumarates (or iminosuccinates; in most cases the structure has not been established) seem to be obtained when ethyl oxaloacetate is freshly released from the sodium salt and then heated in an acid medium, often glacial acetic acid. A phenylenediamine derivative can give a diazaphenanthrene directly, as in the example (**280**) reported by Khetan and George.[341]



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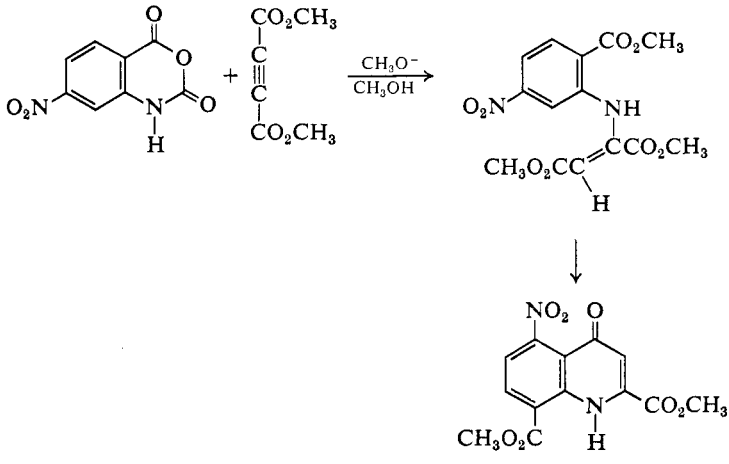
Variation in the four-carbon fragment which provides the pyridine ring and the alkoxycarbonyl substituent is possible in two ways. In the first a compound other than oxaloacetate is used but the result is still a 3-unsubstituted 4-quinolone-2-carboxylate. The use of acetylenedicarboxylates has been quoted (p. 138); base-initiated reaction between isatoic anhydride and acetylenedicarboxylate leads eventually to 4-quinolone-2,8-dicarboxylates such as compound (**281**).[342] The sulphur ylide (**282**) provides all four carbon atoms in a reaction with an aryl azide; the intermediate aminoazo-compound (**283**) cyclized with elimination of nitrogen when heated in diphenyl ether. Both these routes can provide access to nitro-4-quinolones.[343]



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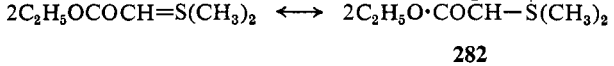

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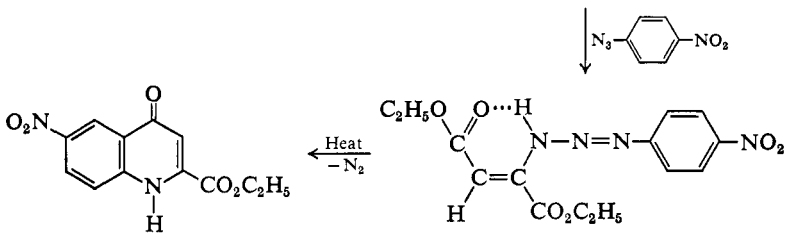

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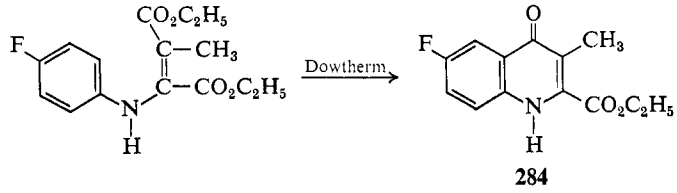
The use of substituted oxaloacetates is not common.[344-347] An excellent yield of the 6-fluoro-4-quinolone (**284**) was obtained from methyloxaloacetate,[345] but in the cyclization of the intermediate (**285**) the iodine atom was lost.[344] Poor yields of 4-quinolones were obtained from *n*-propyloxaloacetates[345] but the 3-substituted 4-quinolone (**286**) was obtained in 49% yield from (4-cyclohexylbutyl)oxaloacetate.[346]

An ingenious variation has been reported by Schmidt and Winterfeldt;[348] *N*-substituted intermediates (**287**) undergo Cope rearrangement and cyclization when heated, giving the 3-substituted 4-quinolones (**288**). In any reaction involving intermediate maleates or fumarates it is very important to remove any excess of aromatic amine before cyclization, since the diesters and the excess amine very readily yield maleimides such as (**289**).[307, 337, 349, 350]

The second important variation of the Conrad–Limpach synthesis was discovered by Just[338] although commonly known by the names of its developers, Gould and Jacobs,[351] and subsequently much used in 1946.[352] Just had caused sodio diethyl malonate to react with the chlorimidate (**290**), and cyclized the resulting substituted malonate thermally, giving a 4-quinolone-3-carboxylate (**291**). Gould and Jacobs simplified the reaction by heating aromatic amines with ethoxymethylene malonates[351] to produce 4-quinolone-3-carboxylates with no 2-substituent. Ethoxymethylene-malonates are expensive, and Snyder and Jones recommended the reaction between



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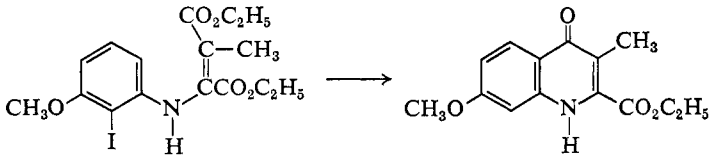

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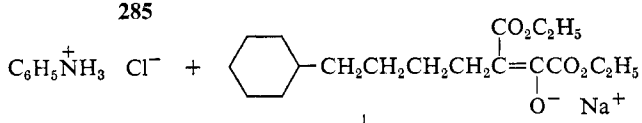

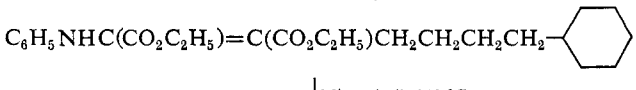

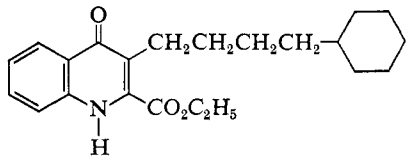

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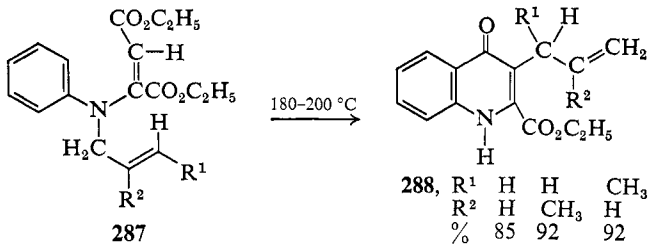
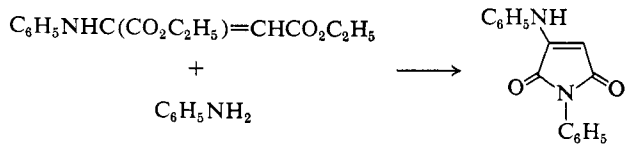


287

288,

R^1	H	H		CH_3
R^2	H	CH_3		H
%	85	92		92



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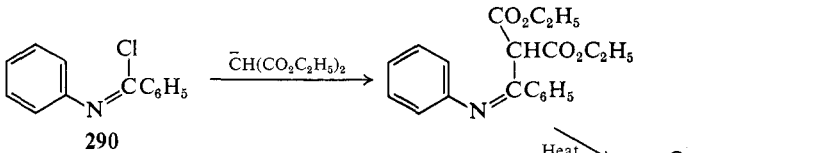
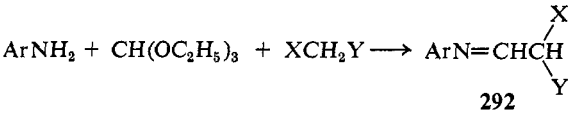


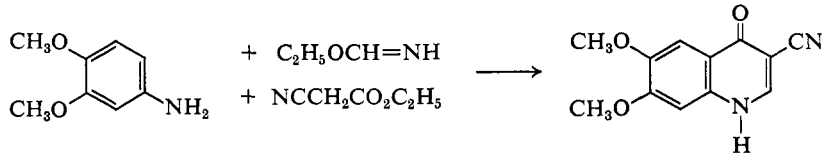
290 291



292

X	CN	$COCH_3$	CONHAr	$COCH_3$	C_6H_5
Y	$CO_2C_2H_5$	$CO_2C_2H_5$	$CO_2C_2H_5$	$COCH_3$	$CO_2C_2H_5$

an aromatic amine, ethyl orthoformate, and an active methylene compound, to give compounds of general formula (**292**).[353] The use of formimidates in place of ethyl orthoformate gives compounds such as (**293**) with no 2-substituent; other imidates give 2-substituted 4-quinolones such as (**294**).[354] Other workers have used a formamidine to react with malonate;[355-357] a disadvantage of this method is that the excess of aromatic amine may react with the malonate to produce a monoanilide, as in the



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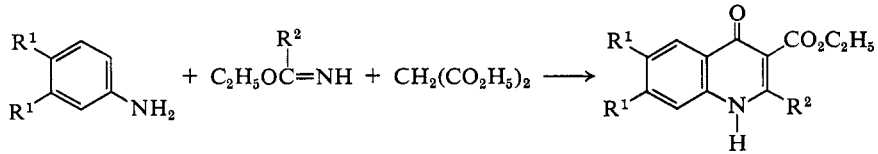
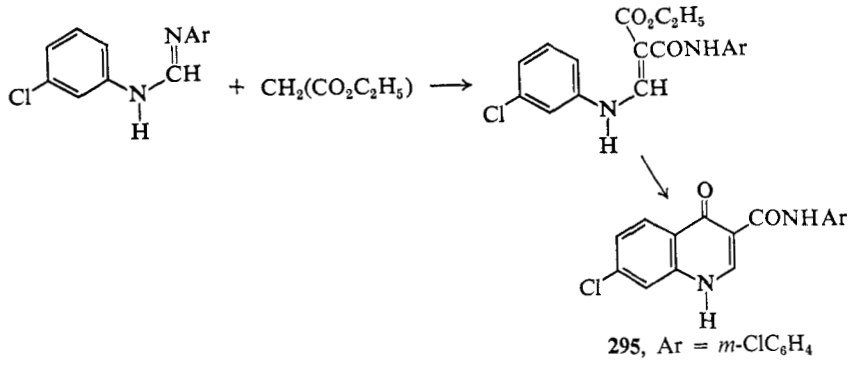


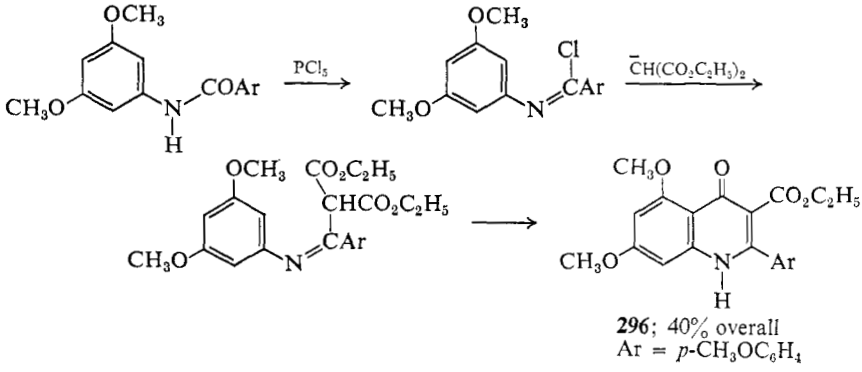
294, R^1 = iso-C_4H_9O

formation of compound (**295**).[352] The original Just procedure has been used mainly to prepare 2-aryl-4-quinolone-3-carboxylates such as compound (**296**).[358]

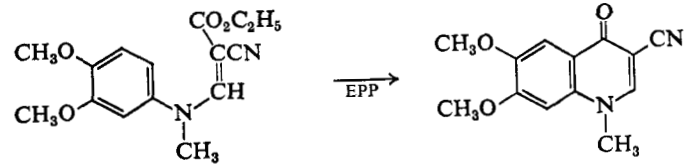
If the original active methylene component has two different activating groups, two modes of cyclization are possible. The order of reactivity need not be obvious, and there are many examples where the mode of cyclization was unpredictable. Thus, the closely similar derivatives (**297**) and (**298**) cyclized in opposite senses under similar conditions;[359, 360] these cyclizations illustrate the use of secondary aromatic amines to give *N*-alkyl-4-quinolone derivatives. Carboxylic acid derivatives other than esters can cyclize, as is shown by the example of compound (**298**), of the malononitrile (**299**),[361] of the thioamide (**300**),[362] and of the 3(2*H*)-furanone ester (**301**).[363] In the case of compounds (**297**)–(**300**) a further point illustrated is the use of



295, Ar = *m*-ClC_6H_4



296; 40% overall
Ar = *p*-$CH_3OC_6H_4$



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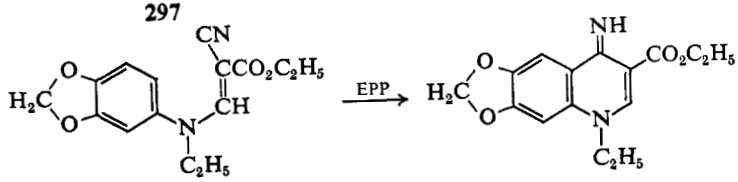
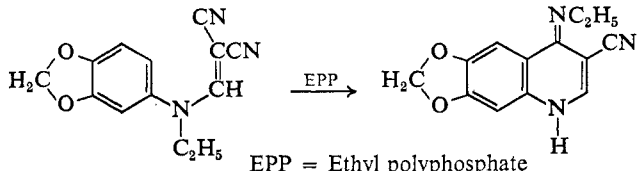


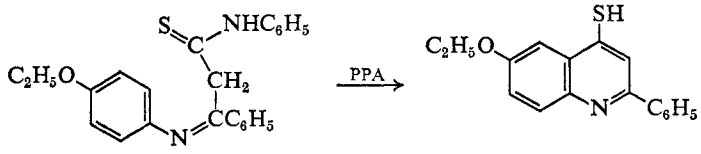
298

cyclizing media other than Dowtherm, diphenyl ether, or mineral oil. The use of ethyl polyphosphate can give 4-ethylimine derivatives.[361] Other cyclizing agents are zinc chloride,[316] phosphorus pentoxide in nitrobenzene [as in the synthesis of the *N*-alkyl-4-quinolone-3-carboxylic acid (**302**)],[364] and phosphoryl chloride[365, 366] [which gave 4-chloroquinolines such a compound (**303**)];[365] it has been reported[367] that high yields in a cyclization using phosphoryl chloride were obtained only when impure phosphoryl chloride was used. In the case of an (*N*-alkylanilino)methylenemalonate, phosphoryl chloride gave a quaternary salt (**304**).[366]



EPP = Ethyl polyphosphate

299



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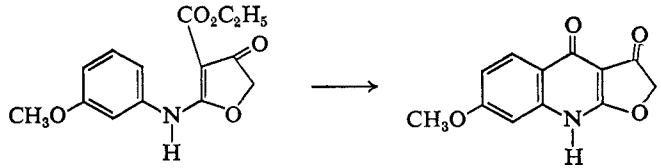

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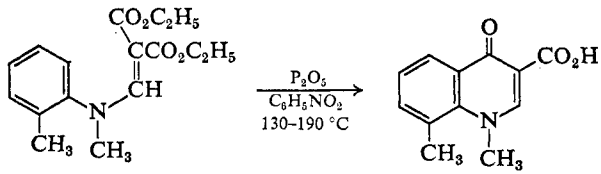

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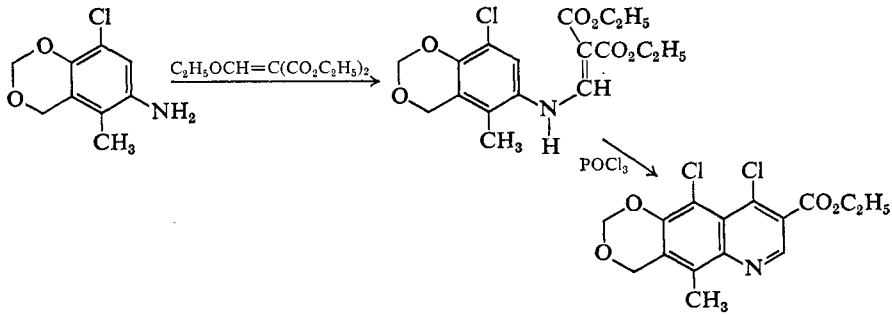

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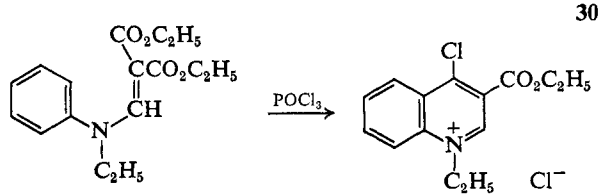
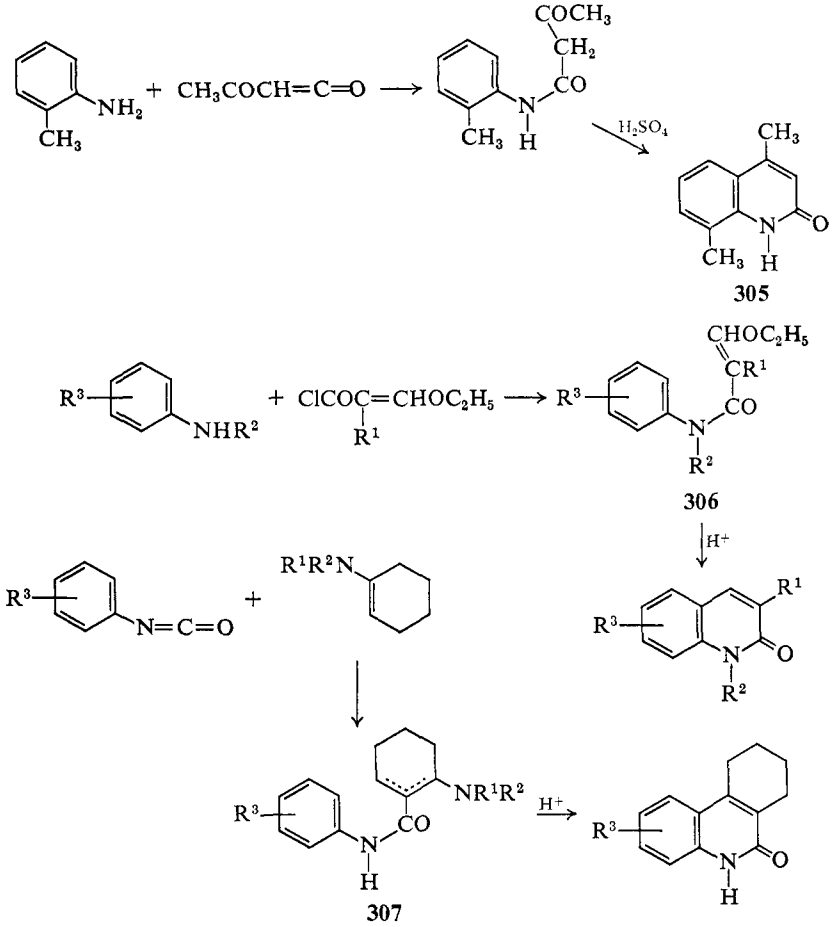


304

B. The Knorr Synthesis of 2-Quinolones from β-Keto-anilides

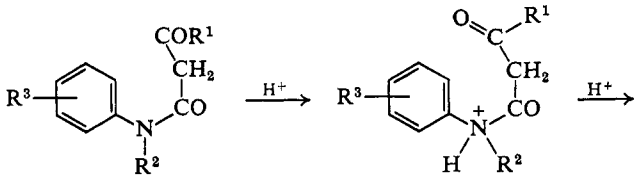
The conditions required to convert β-keto-esters into β-keto-anilides have been defined on p. 137. In principle therefore, as great a range of 2-quinolones is available by the acid-catalysed cyclization of these β-keto-anilides as were 4-quinolones by the Conrad–Limpach procedures. There is a limited number of alternatives to the direct formation of the anilides by heating together amine and β-keto-ester. By far the most versatile is the reaction between aromatic amines and diketen, as illustrated by the synthesis of 4,8-dimethyl-2-quinolone (**305**).[306] Ethoxyacryloyl chlorides reacted



with aromatic amines to give the ethoxyacrylamides (**306**) which are masked β-formanilides.[368] Aryl isocyanates reacted with enamines to give amides of type (**307**), which cyclized to give annulated 2-quinolones;[369] this reaction has not been applied to the enamines of acyclic ketones.

a. Mechanism of the Knorr Cyclization. The mechanism of this acid-catalysed cyclization has been studied by Staskun.[311] Insufficient acid was found to lead to

hydrolysis of the β-keto-anilide, and the diprotonated species (**308**) was implicated, in the mechanism shown. The high acid concentration was thought to be necessary



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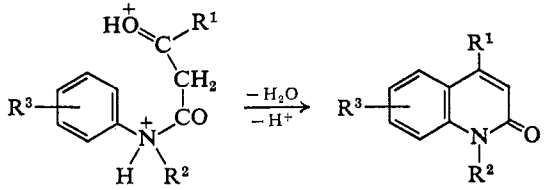
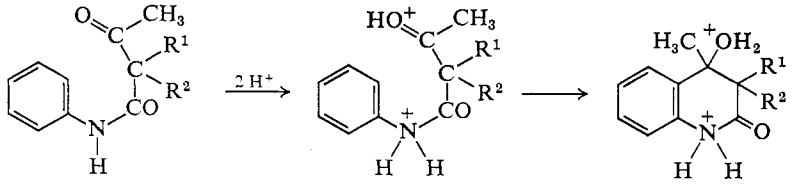


308

for diprotonation; too little acid gives the monoprotonated form (**309**), which can hydrolyse, and the free aniline thus produced is responsible for the 4-quinolones sometimes found as contaminants.[370] Support for the intermediacy of a protonated species comes from the failure in cyclizations sometimes encountered when the amine bears electron-withdrawing groups (p. 153) and also from the interesting work of Searles and his co-workers on cyclization of α,α-disubstituted β-keto-anilides.[371, 372] Here the intermediate (**310**) (given as the monoprotonated form in the original



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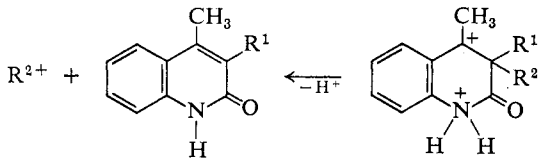
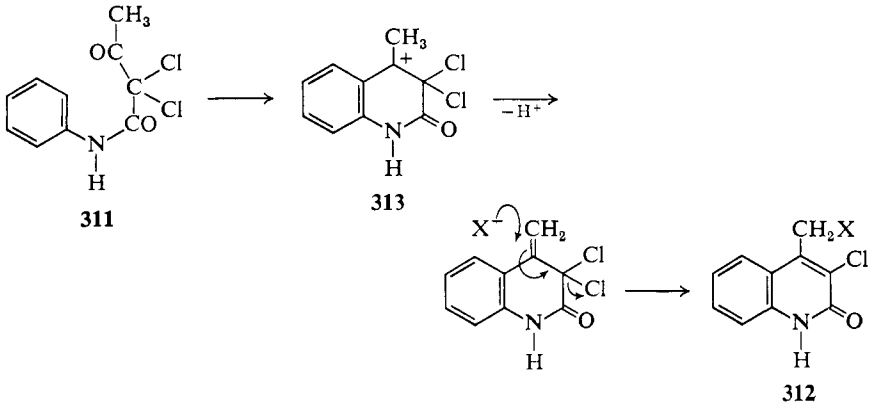


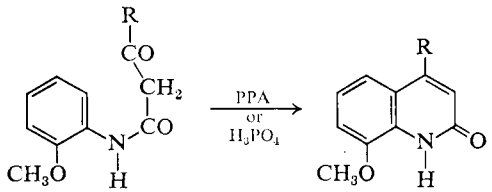
paper) can form a 2-quinolone only by loss of a carbonium ion. Of the two possibilities the group lost was always that forming the more stable carbonium ion.

The mechanism also accounts well for the observation by Hodgkinson and Staskun that cyclization of the dichloro-keto-anilide (**311**) gave 4-hydroxymethyl- or in some cases 4-chloromethyl-2-quinolones (**312**, X = OH or Cl); the intermediate carbonium ion (**313**) can undergo proton loss and then nucleophilic allylic displacement to provide the observed products.[373]



311 313 312

b. Scope and Limitations. The usual wide variety of aromatic amines has been used in the Knorr reaction, as shown in Table IIA (p. 259). Difficulty in forming the anilides from the esters has been observed when very weakly basic amines were used, as for example with nitroanilines.[374] Such difficulties can be overcome by using diketen or, in the case of diphenylamine, acetoacetyl chloride.[375] Some β-keto-anilides are unstable, especially towards hydrolysing agents. Failure to obtain anilides has been reported with *p*-aminophenylacetic acid, and with 2,5-dibromo-*p*-toluidine,[376] and failure in the cyclization with *o*-methoxy- and with *o*-ethoxy-aniline,[374, 377, 378] with *m*- and *p*-nitroaniline,[374, 376] and with *m*- and *p*-acetyl-aniline.[374, 379] Many of these early reports of failure in cyclization may reflect the use of the wrong medium; Nakano[380, 381] has prepared 8-methoxy-4-phenyl- (**314**)



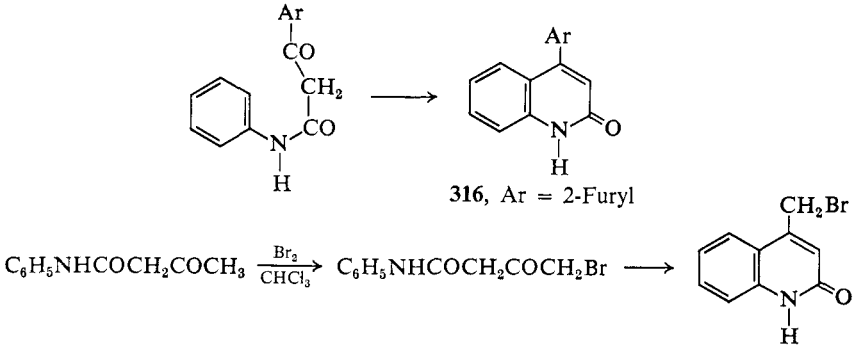
314, R = C_6H_5
315, R = CH_3

and 8-methoxy-4-methyl-2-quinolone (**315**) by cyclization in polyphosphoric acid and phosphoric acid, respectively.

Although no study of product ratios has been made when *meta*-substituted anilides are cyclized, most reports mention only one major product, and when this has been characterized it has been the 7-substituted 2-quinolone. Most side-products arise from the cyclization medium and are mentioned below (p. 156); a failure to obtain a 2-quinolone from *o*-phenylenediamine arose from preferential formation of a benzimidazole (see p. 140).[382]

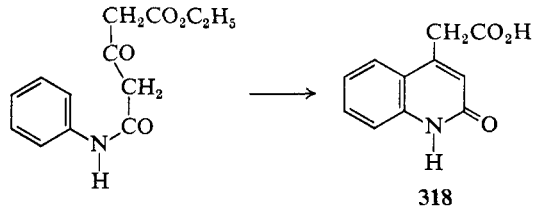
The substituent in the 4-position of the 2-quinolone has, in the majority of cases, been an alkyl group, but aryl β-keto-esters have been cyclized to give a 4-aryl substituent which can be phenyl or a heterocyclic system as in example (**316**).[383] Bromination of acetoacetanilide gave the γ-bromo-anilide which was cyclized to 4-(bromomethyl)-2-quinolone (**317**).[384–386] Alkyl groups other than methyl in the

4-position of the 2-quinolone have been obtained up to fifteen carbon atoms[387] and carrying substituents, as in the example (**318**).[388] A Claisen condensation between ethyl oxalate and *N*-methylacetanilide gave the β-keto-ester (**319**) which on cyclization gave a 2-quinolone-4-carboxylate.[389]



316, Ar = 2-Furyl

317



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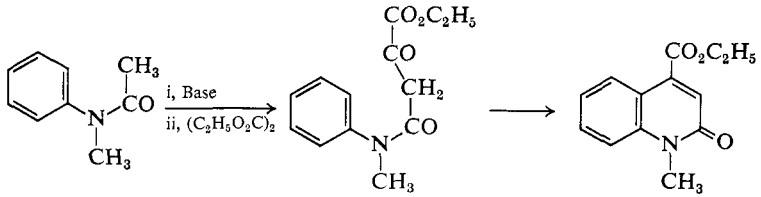
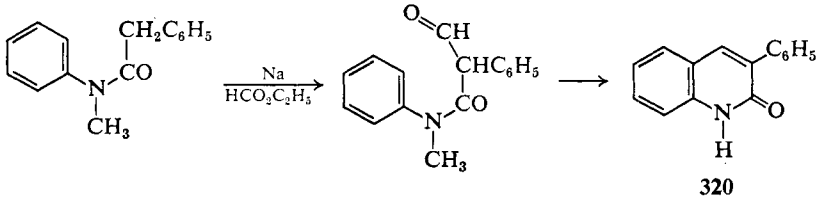


319

A 2-quinolone with a substituent in the 3-position but not in the 4-position can be obtained by using an α-formylacetate. The direct formation of anilides from α-formylacetates requires very forcing conditions; a solution to this problem for the production of 3-aryl-2-quinolones was to formylate phenylacetanilide, subsequent cyclization producing 3-phenyl-2-quinolone (**320**).[390] A more limited approach used the ethoxyacryloyl chloride (**321**) to form the masked formyl derivative (**322**) which cyclized when ground with mineral acid, to give 3-substituted 2-quinolones.[368, 391] A masked formyl group was also used in the production of compound (**323**).[392]

By cyclization of an α-substituted β-keto-anilide a 3,4-disubstituted 2-quinolone is obtained. Because of the greater difficulty of formation of the anilides of such branched acids it has been common practice to form the enolate of a simple β-keto-anilide and to alkylate this with an alkyl halide or by a Michael procedure. Searles and Ressler reported that sodium ethoxide was preferred for the preparation of monoalkyl derivatives, as in the preparation of compound (**324**), and sodium hydride in dimethylformamide for dialkylation;[372] sodium in benzene has also been



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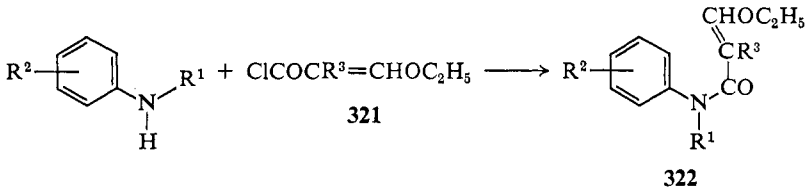

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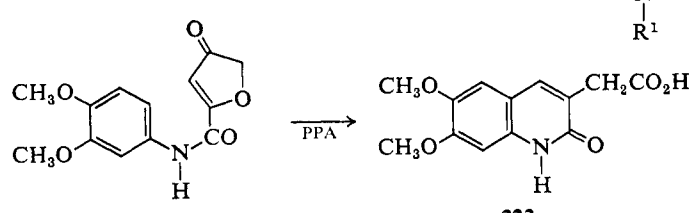
322

R	R^1	R^2	%
CH_3	H	H	82
CH_3	H	8-CH_3	98



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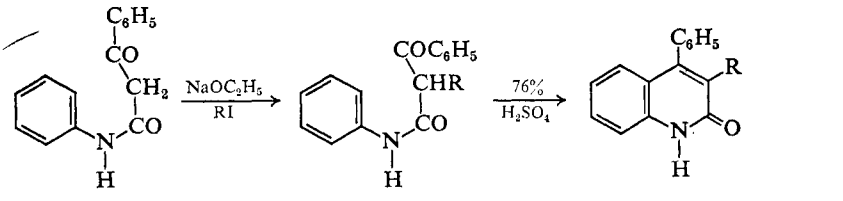
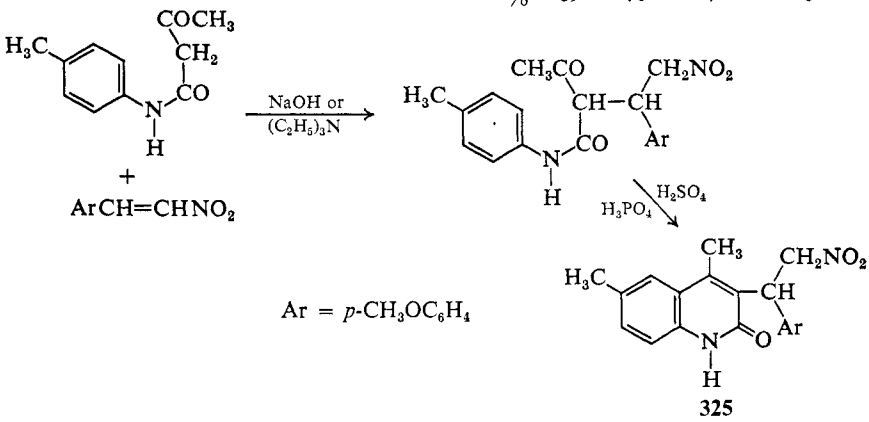


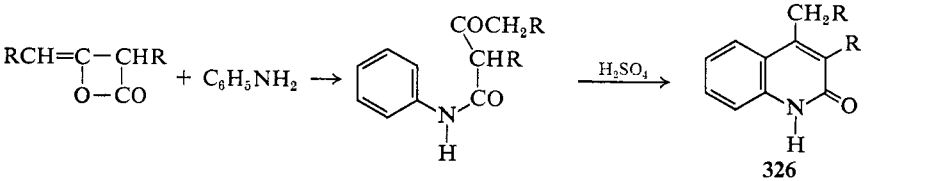
324

R	CH_3	C_2H_5	i-C_3H_7	$CH_2C_6H_5$
%	89	70	7	0



325

used for the preparation of the enolates.[393] An example of the use of Michael addition to produce a 3,4-disubstituted 2-quinolone was the production of the 3-(2-nitroethyl) derivative (**325**); the Michael addition can be done under milder conditions, using an amine catalyst.[394] Another, more limited, approach to 3,4-dialkyl-2-quinolones (**326**) was the use of homologues of diketene.[395] Cyclization of such α-alkylated β-keto-anilides can be hindered as the bulk of either the potential 3- or the potential 4-substituent is increased. The decreasing yields of compounds of type (**324**) is illustrated; α-benzyl-β-keto-anilides could not be cyclized.[372, 396] By the cyclization of α-chloroacetoacetanilide 3-chloro-4-methyl-2-quinolone has been obtained in 87% yield.[373, 397]



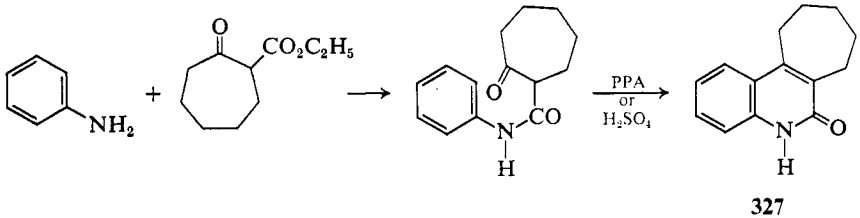
326

R	CH_3	C_2H_5	C_3H_7	C_4H_9
%	80	88	31	56

The anilides of cyclic β-keto-esters give annulated quinolines such as compound (**327**);[398] the 3-(diethylaminoethyl)-2-quinolone (**328**) has been obtained,[399] but it is reported that an allyl group was hydrated during cyclization, giving the 3-(2-hydroxypropyl) derivative (**329**).[397]

Routes depending on an S_N2 attack on allyl halides to produce 3-substituted 2-quinolones are obviously not applicable in general to the preparation of 3-aryl-2-quinolones. Already mentioned (p. 155) is the use of phenylacetanilides to provide a 3-aryl substituent; a dianion, e.g. (**330**), reacted with aroyl chlorides to give β-keto-anilides such as (**331**) which could be cyclized to 3,4-diaryl-2-quinolones.[400] The success in cyclization of compound (**331**) contrasts with the failure to produce a 3-benzyl-4-phenyl-2-quinolone (p. 156); further examples of steric inhibition were provided by the cyclization of the cyclopentyl derivatives (**332**) and (**333**).[401]

The usual cyclization medium has been sulphuric acid (usually concentrated) at temperatures between 0 and 100 °C, and if the substituent groups on the aromatic amine are unaffected by sulphuric acid this remains the medium of choice. It has sometimes been reported that the use of 76% sulphuric acid reduces the possibility of sulphonation, either of an activated aromatic amine (anisidines, dimethoxyanilines) or of a phenyl substituent.[372, 402] Cyclization of the anilide (**334**) using hot concentrated sulphuric acid was reported to give water-soluble products, possibly sulphonic acids; the use of cold concentrated sulphuric acid gave the 2-quinolone (**335**), but more of the demethylated product (**336**).[403] Demethylation of ethers is uncommon; hydrolysis of ester groups is more often observed, as in the preparation of the 3-substituted 2-quinolone (**337**)[404] (see also p. 154).[388] Other commonly used cyclization media are phosphoric or polyphosphoric acid. The hydration of side-chain double bonds has been mentioned (p. 155); polyphosphoric acid being used in a similar case, but when there was no *N*-methyl group the tricyclic product (**338**) was obtained.[405] Direct condensation of aromatic amines with β-keto-esters in polyphosphoric acid has been reported to give a 2-quinolone in one case although such a procedure would normally give 4-quinolones.[406] Less common acid cyclizing



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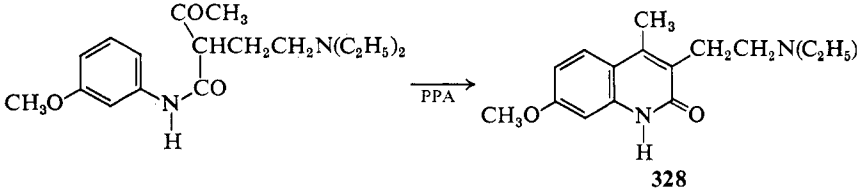

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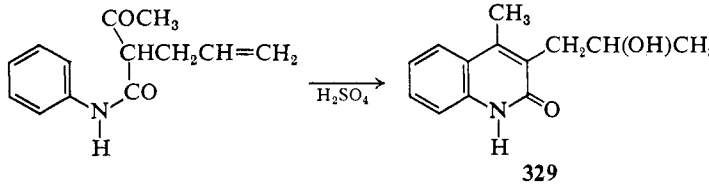

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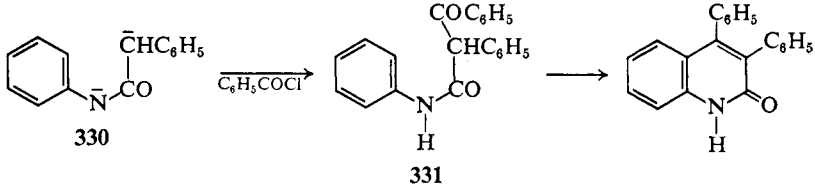

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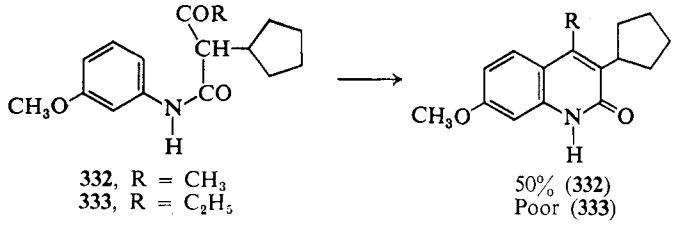
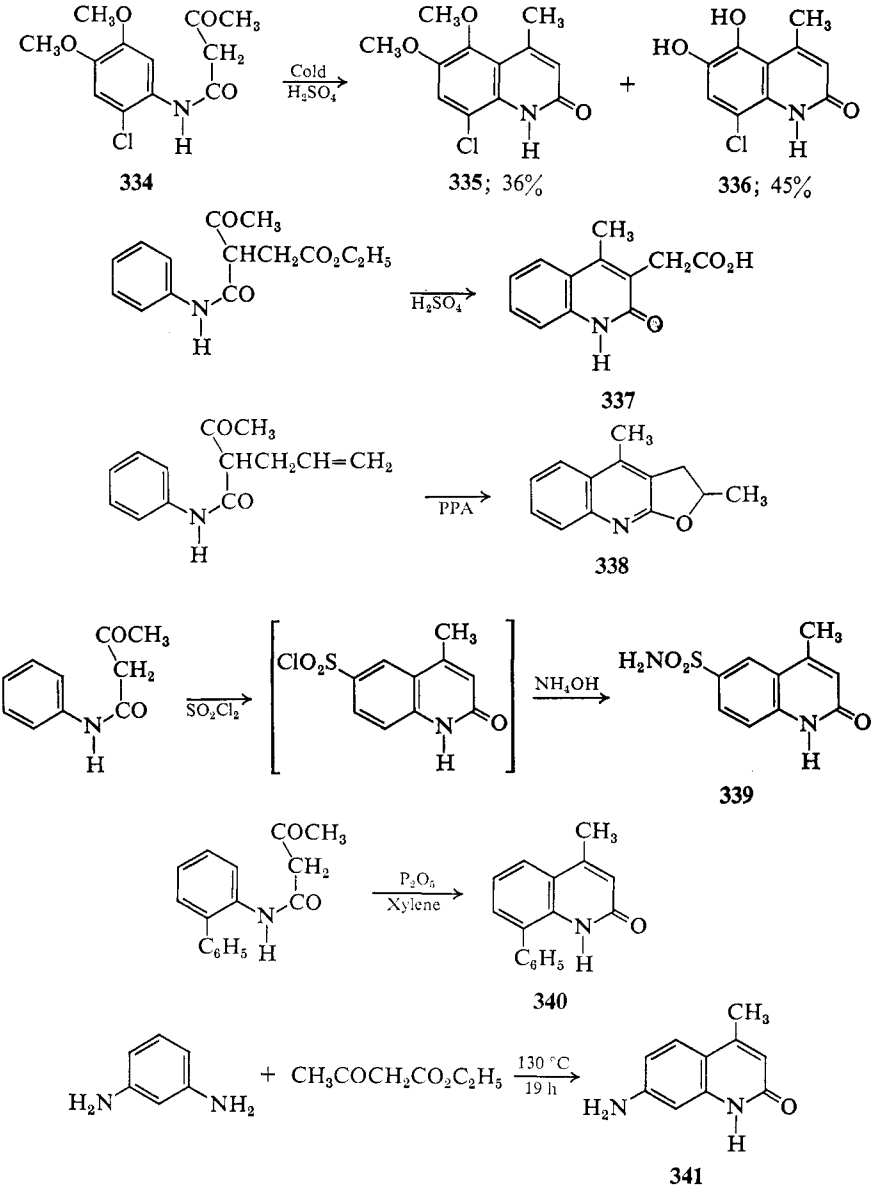


332, R = CH_3
333, R = C_2H_5

50% (332)
Poor (333)

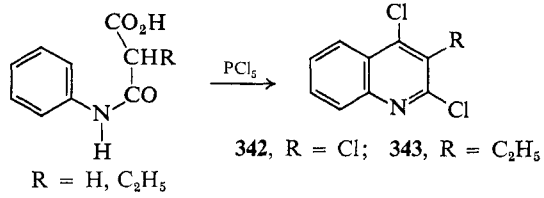
agents include hydrochloric acid used for a series of *m*-phenylenediamines;[407] sulphuryl chloride was reported to cyclize the anilide and subsequently to chlorosulphonate the carbostyril to give the 6-substituted derviative (**339**)[408] (this observation was not confirmed by subsequent workers,[373] who could isolate only 2,2,4′-trichloroacetoacetanilide from the reaction); phosphorus pentoxide in xylene gave an 8.5% yield of 2-quinolone (**340**) when sulphuric acid had failed.[371] Neutral[409–412] or even basic[413] conditions have been used for some electron-rich amides, as shown for *m*-phenylenediamine giving the 7-amino-2-quinolone (**341**).[409] There is no report of the formation of tricyclic derivatives from *m*-phenylenediamines, although this is commonly observed in Conrad–Limpach syntheses.



C. Preparation of 4-Hydroxy-2-quinolones by Cyclization of Malonanilides

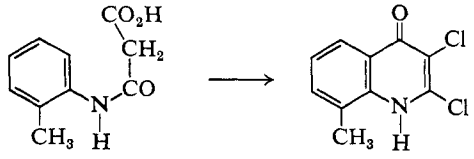
Rügheimer, in 1884, first performed the logical extension of the Conrad–Limpach and the Knorr syntheses, by cyclizing malonic acid derivatives to give 2,4-dihydroxyquinolines, or 4-hydroxy-2-quinolones in the usually preferred tautomeric form.[414-418] The monoanilide of malonic acid was cyclized by phosphorus pentachloride in boiling benzene, producing a trichloroquinoline. Subsequently this was proved to be

2,3,4-trichloroquinoline (**342**), since the monoanilide of ethylmalonic acid gave 2,4-dichloro-3-ethylquinoline (**343**).[418] When an *ortho*-substituted anilide was used the product was a dichloro-4-quinolone, such as compound (**344**).[417] As would be expected from consideration of the Conrad–Limpach cyclization the malonanilic acid esters can by cyclized at high temperatures, although Rügheimer and Hoffman reported only decomposition.[415] The 4-hydroxy-2-quinolones have been prepared either by heating together the aromatic amine and a malonic ester, or from the preformed malonanilates. The amine and ester can be heated without diluent or in an excess of the malonate;[419–421] an example of the use of an *N*-alkylaniline is provided by the synthesis of compound (**345**).[421]



R = H, C_2H_5

342, R = Cl; **343**, R = C_2H_5



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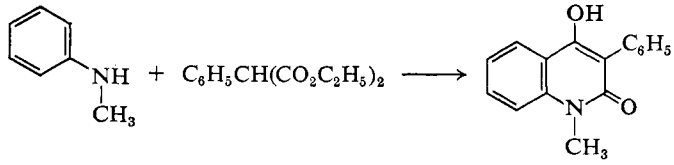
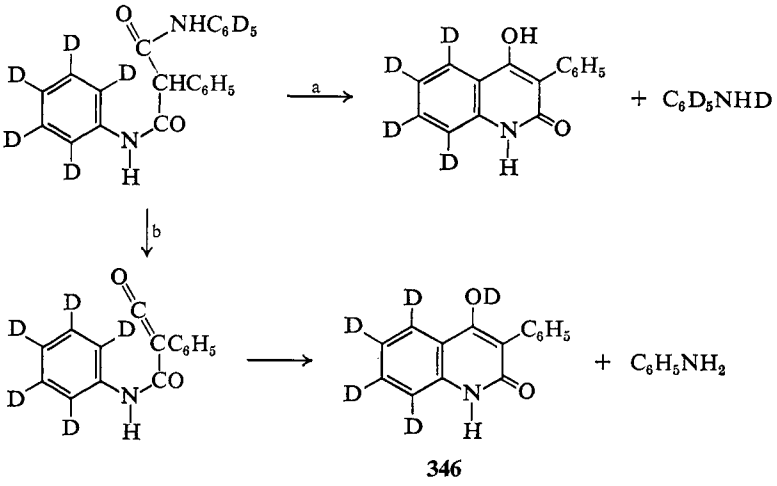


345

a. MECHANISM. The 6π-cyclization advanced for the Conrad–Limpach synthesis by Jutz and Wagner[340] could be applied also to the cyclization of malonanilates. Ziegler, Sterk, and Steiger have proposed a keten intermediate for the cyclization of malondianilides, and have established by deuterium-labelling experiments that 93% of the 4-hydroxy-2-quinolone (**346**) obtained is formed by this route b rather than by the alternative route a.[422]

b. SCOPE AND LIMITATIONS. The basicity of the aromatic amine has a smaller effect than in the Knorr procedure; diphenylamine gave satisfactory yields of 4-hydroxy-1-phenyl-2-quinolone when substituted malonates were used.[421] With diethyl malonate itself, diphenylamine gave the tricyclic derivative (**347**), not as earlier reported[423] 4-hydroxy-1-phenyl-2-quinolone (**348**); other similar reactions are known.[424] However, heating a mixture of *o*-nitroaniline and malonate was reported[425] to give no cyclized product; *m*-chloroaniline gave the expected mixture of 5- (**349**) and of 7-chloroquinolone (**350**) in the proportions shown.[426]

The reaction with *m*-chloroaniline illustrates two further points: the use of nitrobenzene as solvent (diphenyl ether has also been used[425]), and the introduction of a



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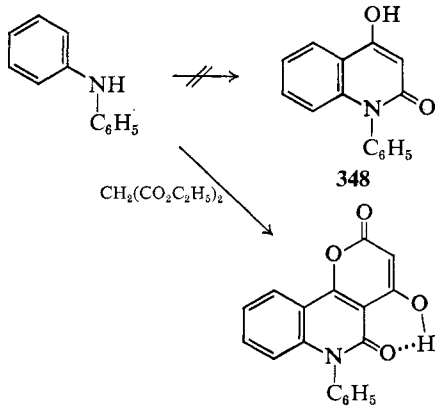

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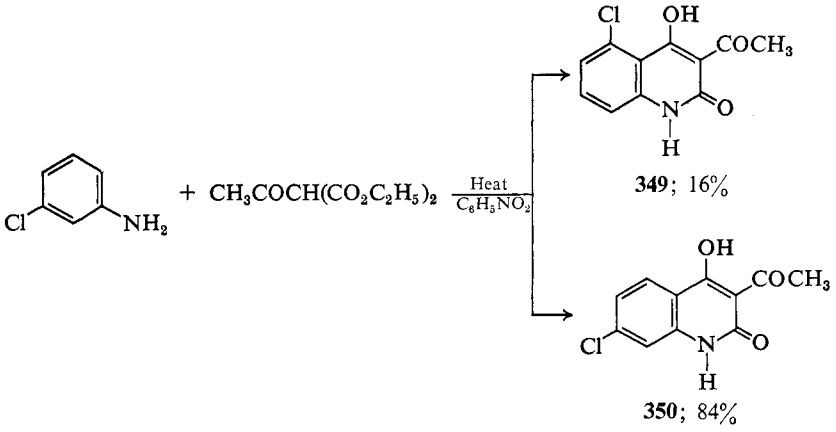
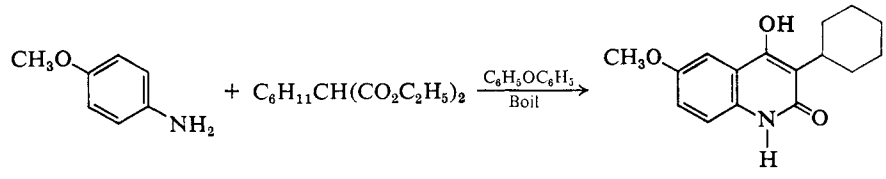


349; 16%

350; 84%

substituent in the 3-position by the use of a substituted malonate. Substituents thus introduced into the 3-position have included various alkyl groups,[420, 421, 426] including the benzyl group,[420, 427] aryl,[420] alkenyl,[428] and dialkylamino-groups,[429] as shown in the examples (351)–(354).



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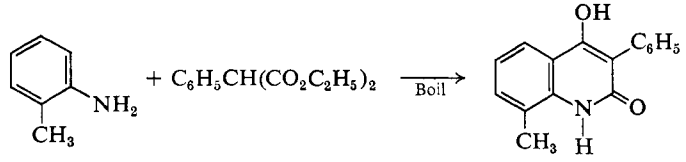

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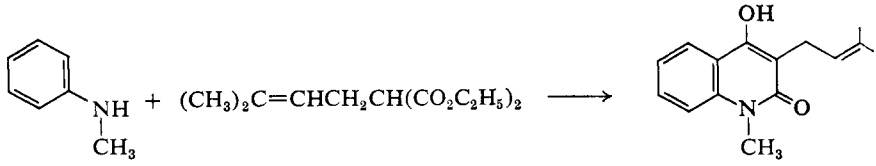

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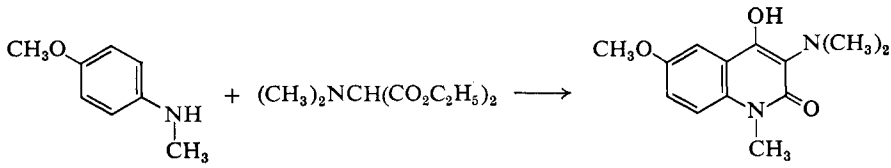

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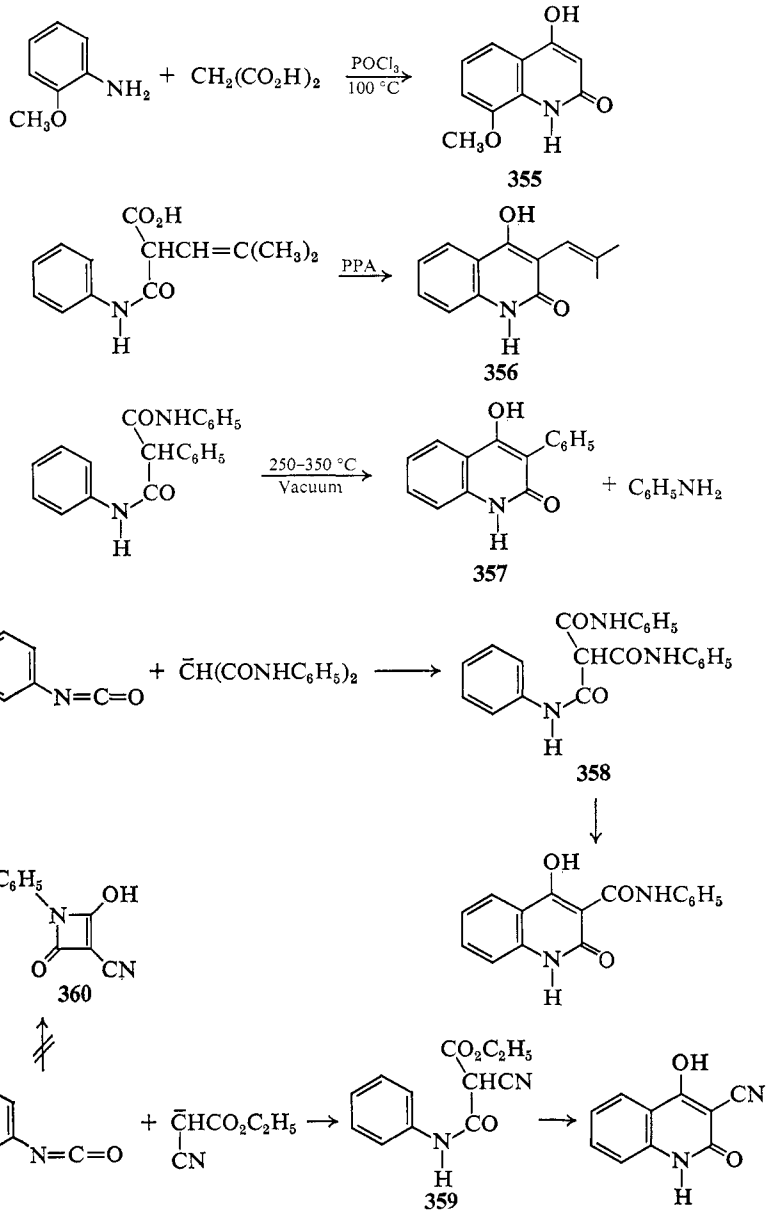
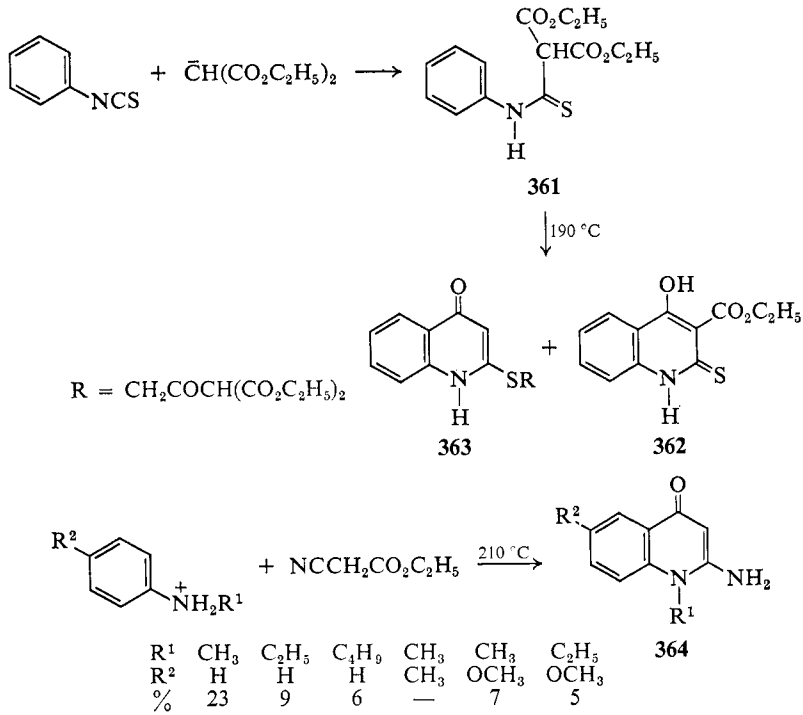
Derivatives of malonic acid other than the esters have been used, and approaches to the malonanilides other than direct synthesis from amine and malonic acid or esters. It has been reported that the aromatic amine and malonic acid can be directly converted into the 4-hydroxy-2-quinolone by phosphoryl chloride, as in the synthesis of compound (355);[430, 431] polyphosphoric acid has been used to cyclize preformed malonalides including one with an unsaturated side chain which gave the 3-substituted quinolone (356).[432–434] Direct reaction between malonamide and aromatic amines at 220 °C was reported to give good yields of 4-hydroxy-2-quinolones.[435] Cyclization of bisanilides of malonic acid such as (357) was reported to be almost quantitative under vacuum.[420] The mechanism of cyclization of such bisanilides has been studied in detail (see p. 160).

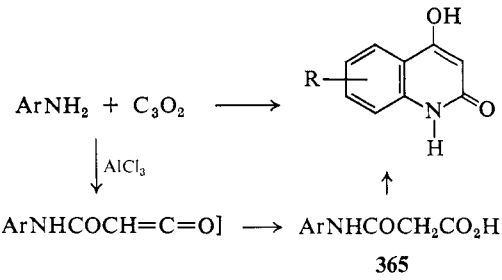
Other routes to the malonanilides widen the range of 3-substituted 4-hydroxy-2-quinolones available. The most general route is provided by the reaction between phenyl isocyanate (or phenyl isothiocyanate) and the anion derived from any active methylene derivative. Examples of the use of phenyl isocyanate are provided by the synthesis of the trisanilide (358)[436] and of the substituted cyanoacetate (359),[437]



wrongly reported to be an azetinone (**360**).[438] Phenyl isothiocyanate with diethyl malonate gave the thioanilide (**361**), which cyclized when heated to the 4-hydroxy-2-thione (**362**) and a smaller amount of the thioether (**363**).[439] The cyclization of the cyanoacetate (**359**) to give a 3-cyanoquinoline provides an interesting contrast with the direct reaction between aromatic amine salts and ethyl cyanoacetate, which gave small yields of 2-amino-4-quinolones (**364**).[440]

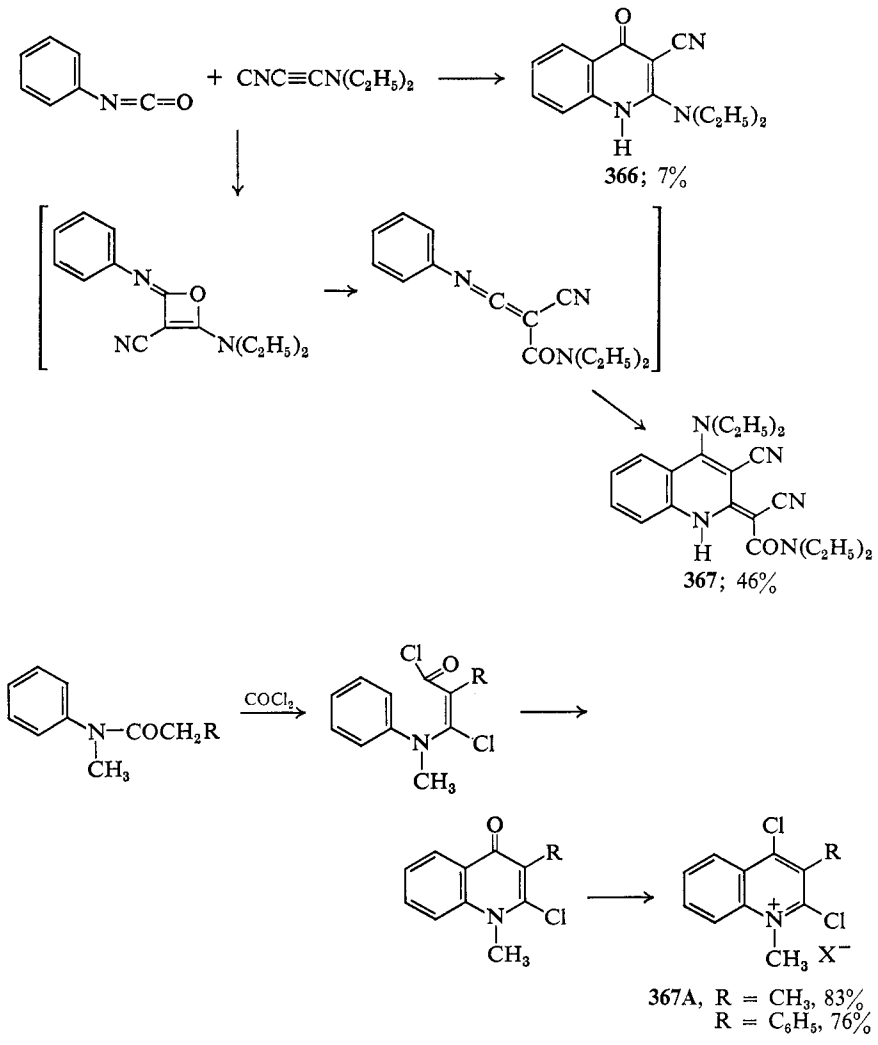


Related reactions of less synthetic interest were those reported between carbon suboxide and aromatic amines,[441] and between phenyl isocyanate and cyanoynamines.[442] In the former reaction yields of 28–67% were reported when anisidines were used; with aluminium chloride present the intermediate anilic acid (**365**) could



be isolated. In the latter reaction the minor products were the 2-diethylamino-4-quinolones (**366**), the major products were the more complex compounds (**367**), formed by the route shown.

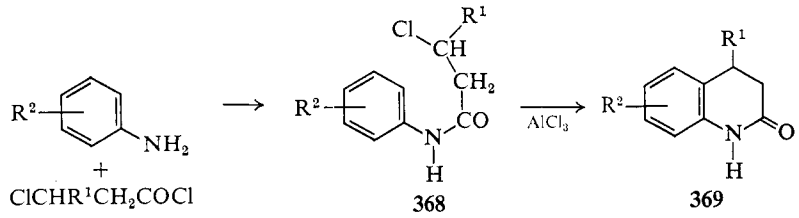
An interesting synthesis involves the reaction of an acyl-*N*-methylanilide with phosgene.[1143] The mechanism is shown; the products are 2,4-dichloro-1-methylquinolinium salts (**367A**).



D. Production of 3,4-*Dihydro-2-quinolones by Cyclization of N-Acylanilines*

The anilides of alkanoic acids can be cyclized intramolecularly if a suitable active site can be generated in the β-position of the alkane or alkene chain. Satisfactory syntheses of 3,4-dihydro-2-quinolones have been devised based on a Friedel–Crafts procedure and on a photochemical approach.

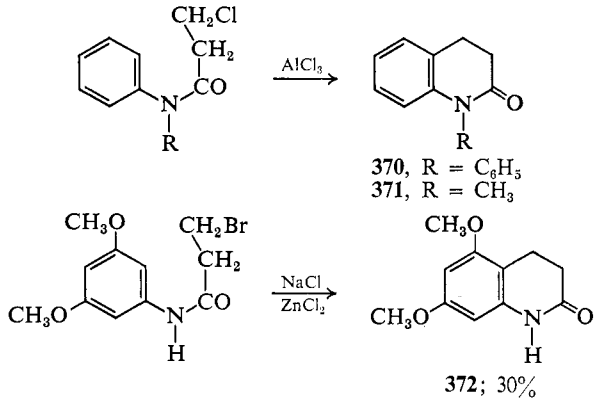
The precursors for the Friedel–Crafts synthesis (or, more generally, the electrophilic cyclizations) have been either β-halopropionanilides or cinnamanilides. Mayer, van Zütphen, and Philips illustrated the range of the Friedel–Crafts approach by preparing the anilides (**368**) in excellent yield, and cyclizing these in an aluminium chloride melt to give dihydro-2-quinolones (**369**) in the yields shown.[443]



R^1 = H; R^2 = H	8-CH_3	6-CH_3	6-Cl	6,8-Cl_2	8-HO	6-HO*
Yield of (**369**) 95	90	Quant.	85–90	Quant.	60	80

R^1 = CH_3; R^2 = H	6-CH_3	8-Cl	6-Cl	6,8-Cl_2
Yield of (**369**) 55	57	79	92	84

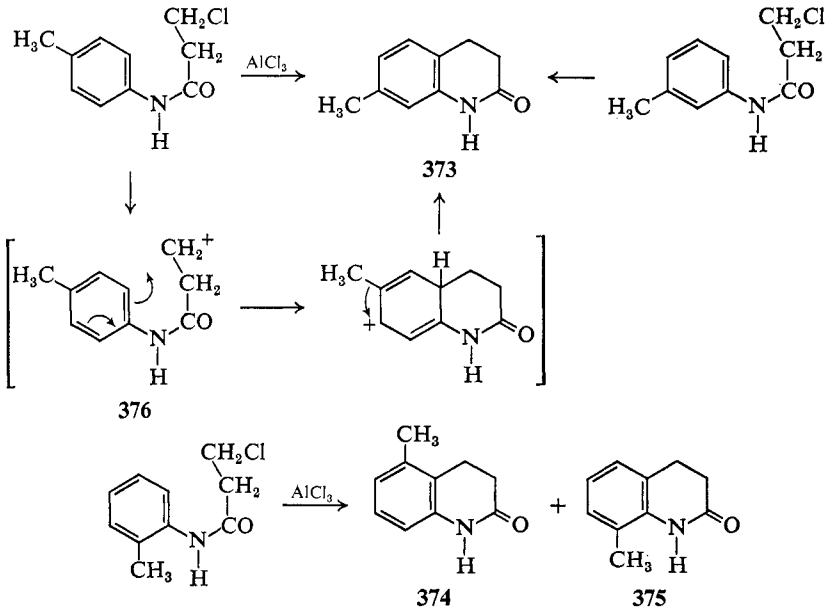
In this series for (**369**) the limit of deactivation in the benzene ring is probably reached with 6,8-dichloroaniline. From diphenylamine and *N*-methylaniline the dihydroquinolones (**370**) and (**371**) were respectively obtained, but *N*-ethylanilides would not cyclize. A sodium chloride–zinc chloride mixture was used to cyclize the dimethoxyanilide (**372**) without demethylation;[444] cyclization of *m*-chloroanilides



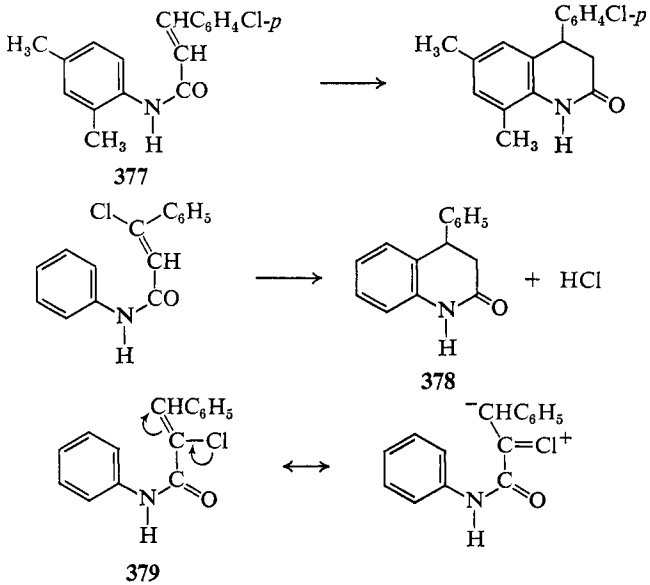
gave mixtures of 5- and 7-chlorodihydro-2-quinolones.[445] Some doubt about the assignment of structure to the products of apparently straightforward Friedel–Crafts cyclizations must be noted after the reports by Kametani and his co-workers on the cyclization of some β-chloropropionyltoluidines.[446, 447] Both the *m*-toluidide and the *p*-toluidide gave 3,4-dihydro-7-methyl-2-quinolone (**373**), while the *o*-toluidide gave the dihydro-5-methyl- and the dihydro-8-methyl-quinolones (**374**) and (**375**). The suggested mechanism involved a primary carbonium ion (**376**).

Cinnamanilides have been cyclized to give 4-aryl-3,4-dihydro-2-quinolones both by acid treatment and photochemically. Conley and Knopka reported a number of successful cyclizations of cinnamanilides using polyphosphoric acid; all the examples quoted were unsubstituted in the aromatic ring of the cinnamoyl residue.[448] Yields in

* From *p*-hydroxy- or *p*-ethoxy-aniline.

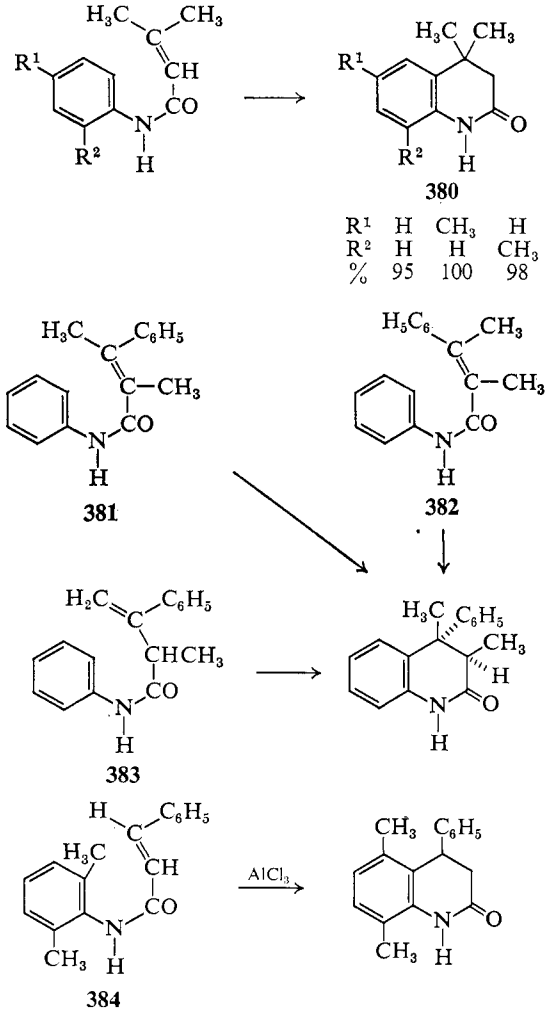


this cyclization are normally high, but no cyclization was achieved with *N*-cinnamoyl-*p*-nitroaniline or with crotonanilide. Johnston extended the range of substituents used and also improved the yields by using much shorter reaction times.[449, 450] As might be expected, substituents on the cinnamic acid residue also affect the ease of cyclization; (*p*-chlorocinnamoyl)anilines, such as (**377**) required long reaction times and higher temperatures for cyclization, while (*p*-nitrocinnamoyl)aniline failed to cyclize. A



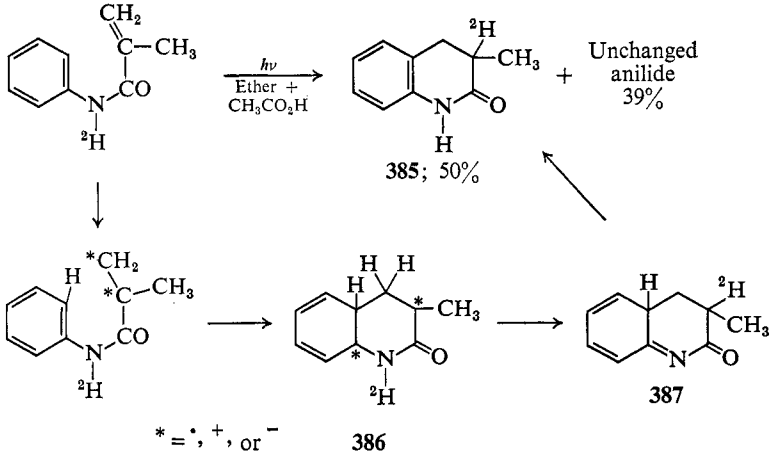
number of workers have noted the possiblity of loss of a phenyl group during the cyclization, notably when the phenyl carbonium ion was stabilized (for example by a 4-methoxyl substituent[449, 450]). The loss of a phenyl group was more of a problem when the aluminium chloride procedure was applied to cinnamanilides.[451] Johnston, Luker, and Williams noted that cyclization and elimination of phenyl groups was almost simultaneous.[452] When cinnamanilides with chlorine substituents were used, it was discovered that 4-phenyl-2-quinolone (**378**) could be obtained if a β-chlorocinnamanilide was used; α-chlorocinnamanilide, and 2′- and 4′- chloro-, and 2′,4′-dichloro-α-chlorocinnamanilide failed to cyclize because of the negative polarization of the β-carbon atom, as shown in compound (**379**).

Although crotonanilides have not been cyclized, β-branched crotonanilides have (providing a potential tertiary carbonium ion site), giving high yields of dihydro-2-quinolones (**380**).[451, 453, 454] In the similar, more branched cinnamanilides (**381**) and



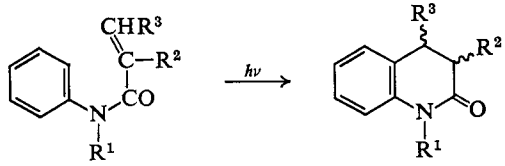
(**382**), very poor yields of cyclized material were obtained; inexplicably, a good yield of cyclized material was obtained from the non-conjugated amide (**383**).[455] Following Kametani's report (p. 165) of methyl migration in aluminium chloride-initiated cyclizations, Johnston, Luker, and Williams examined carefully the cyclization products from the various methyl- and dimethyl-cinnamanilides; they found evidence of migration only with the 2,6-dimethylaniline derivative (**384**) where methyl migration was essential if cyclization was to occur.[452]

Photochemical cyclization of unsaturated anilides has been studied by a number of groups. Cleveland and Chapman obtained an 82% yield of 3,4-dihydro-3-methyl-2-quinolone (**385**) under the most favourable circumstances.[456] Using 2,4,6-trideuterioaniline to label the anilide they showed the presence of deuterium at position 3 of the quinolone. When *N*-deuteriated anilide was used, position 3 in the product was again



labelled, indicating a mechanism proceeding through the intermediates (**386**) and (**387**); the sequence is illustrated here for the *N*-deuterioanilide but a similar shift of the *ortho*-hydrogen can occur.

Ogata, Takagi, and Ishino examined similar cyclizations under irradiation, through quartz, of solutions in a wide range of solvents.[457] Optimum yields were obtained in non-polar solvents such as hexane and benzene, no cyclization being achieved in polar solvents (acetonitrile, methanol, acetone, propan-2-ol). Finding no apparent sensitization, or quenching, they concluded that the cyclization was of an



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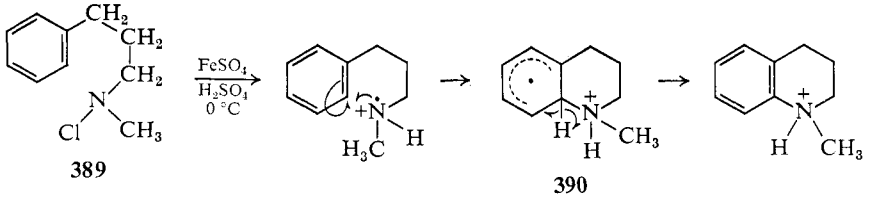
excited singlet, not an excited triplet. In the general case (**388**), no cyclization was achieved when R^3 was a phenyl group, or when R^1 was a methyl group, and the yield was poor also in the case of the parent ($R^1 = R^2 = R^3 = H$).

4. Cyclization of 3-Phenylpropylamines and Related Systems

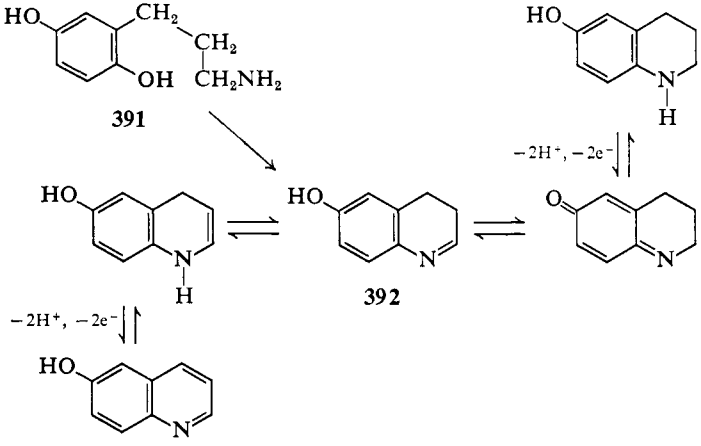
If an electrophilic or free-radical centre could be established on the nitrogen atom of a 3-phenylpropylamine, intramolecular attack on the benzene ring would lead to a tetrahydroquinoline. With a 3-phenylallylamine the corresponding dihydroquinoline would be formed. Examples of the free-radical approach are uncommon but Minisci and Galli have established a simple route.[458] Reduction of the *N*-chloro-amine (**389**)



389 **390**

with ferrous sulphate in concentrated sulphuric acid gave an 81% yield of 1,2,3,4-tetrahydro-1-methylquinoline; the suggested mechanism involved the intermediate radical cation (**390**).

Oxidation of the *o*-hydroxyphenylpropylamine (**391**) with limited reagents and reaction times gave a mixture of 6-hydroxyquinoline and its tetrahydro-derivative.[459]

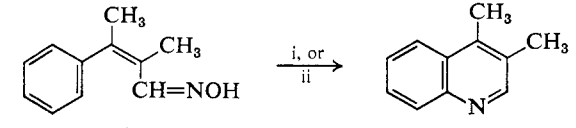


391 **392**

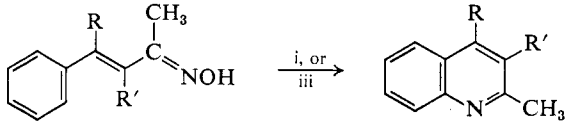
Moore and Capaldi pointed out that the 3,4-dihydroquinoline (**392**) was the probable intermediate in the mechanism (as shown), and found that the use of two equivalents of ferricyanide gave only 6-hydroxyquinoline.[459]

The electrophilic cyclizations have centred largely, and at first surprisingly, on cinnamaldoximes. The earlier reports of acid treatment of cinnamaldoximes (using phosphorus pentoxide and, later, alumina) cited isoquinolines as the products, presumably via Beckmann rearrangement. In 1962 Troszkiewicz and Glinka reported that treatment of the cinnamaldoxime (**393**) with acetic anhydride or with phosphoryl chloride gave 3,4-dimethylquinoline.[460] The cinnamaldoximes normally have the *trans*-configuration and *trans–cis*-isomerization is important. Cyclization with irradiation during[461, 462] or after[463] the acid treatment was shown to be essential for

other than minimal yields. By this method the quinolines shown in the general formula (**394**) were prepared.[464] The yields shown are those obtained without



393



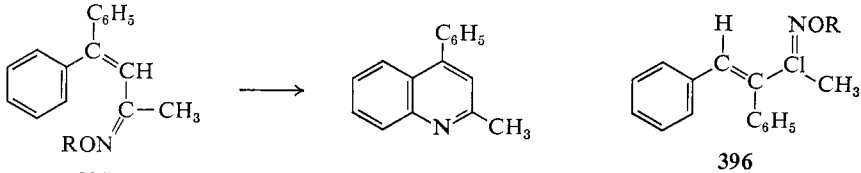
i, $(CH_3CO)_2O$
ii, $POCl_3$
iii, *hν*, then i

394

R	H	H	CH_3	H	C_6H_5
R′	H	CH_3	H	C_6H_5	H
%, reagent i	0.2	0.6	1.4	20	90
%, reagent iii	10	21	23	38	—

irradiation and with irradiation; it is noteworthy that a yield of 90% was obtained without irradiation when the diphenylacraldoxime was used.

The function of the Lewis acid in the cyclization is obviously to develop the electrophilic centre at the nitrogen atom.[465] The cyclization was achieved without Lewis acids when the oxime esters (**395**) were used.[466] Solvents of different polarity



395 **396**

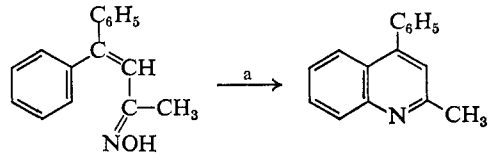
Relative rates:

Ester	C_6H_5CO	CH_3CO	C_6H_5CO	C_6H_5CO	CH_3CO	CH_3CO
Solvent	$HCONH_2$	$HCONH_2$	Decalin	$C_6H_5NO_2$	Decalin	$C_6H_5NO_2$

were used, and rates measured. The rates are valid, however, only for the example given; using the isomeric series (**396**) only the acetate, in decalin as solvent, gave 2-methyl-3-phenylquinoline over the whole range from 160 to 240 °C, all other combinations giving less quinoline with increasing temperature. A study of the effect of variation of the Lewis acid catalyst on the cyclization of oxime (**397**) showed yields varying from 5–60%.[467] The same oxime, with phosphorus pentoxide or alumina, gave the isoquinoline (**398**) in 43–58% yield.

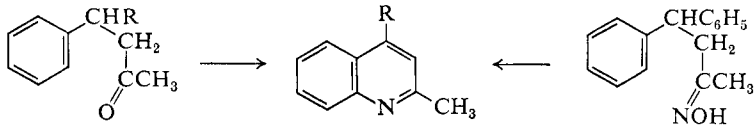
The saturated ketones (**399**) and (**400**) were cyclized on treatment with hydroxylamine hydrochloride in boiling mixtures of propionic and succinic acids, to give the expected quinolines (see also the "pyridine" synthesis, p. 172).[468] The oxime (**401**) gave the same quinoline when boiled with acetic anhydride.

An attempt to cyclize the *N*-hydroxy-amide (**402**) gave the oxazepine (**403**) and not, as hoped, the dihydro-2-quinolone (**404**);[469] the *N*-hydroxypyrrolidine (**405**) did give the 2-quinolone (**406**) when treated with polyphosphoric acid.



397 398

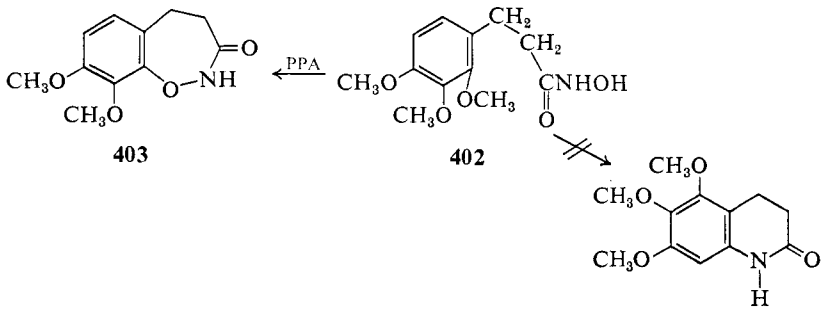
a: $SnCl_4$, BF_3, $SbCl_3$, $SbCl_5$, $ZnCl_2$, $CdCl_2$, PCl_3, $C_6H_5SO_2Cl$, p-$CH_3C_6H_4SO_3H$, p-$CH_3C_6H_4SO_2Cl$
b: Al_2O_3, P_2O_5



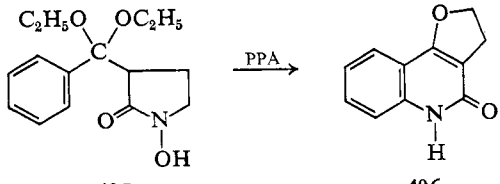
399, R = H
400, R = C_6H_5

R = H or C_6H_5

401

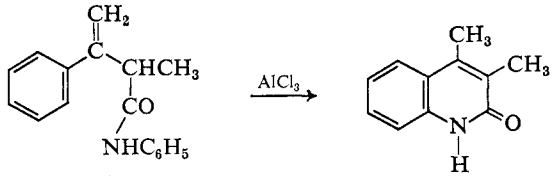


403 402 404



405 406

It should be possible to generate an electrophilic nitrogen centre from an amide, although normally cyclizations proceed through the electrophilic carbon (as in the Bischler–Napieralski synthesis of isoquinolines). Schmutz and Künzle have achieved such a synthesis with elimination of a phenyl group in the reaction between amide



407

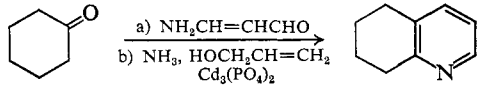
(**407**) and aluminium chloride.[455] As reported on p. 168, cyclization by polyphosphoric acid gave a dihydro-2-quinolone.

5. Syntheses of Reduced Quinolines from Cyclohexane Derivatives ("Pyridine" Syntheses)

In principle, any of the syntheses used to prepare pyridines, if applied to a suitable cyclohexane as precursor, could yield quinolines reduced in the "benzene" ring. As all these suffer from the necessity of a dehydrogenation step before a quinoline is obtained, they are not of general synthetic importance. In this section a selection of such procedures will be given; more may be found in the later section on "reduced quinolines". Most of the syntheses start from cyclohexanones or cyclohexanediones, and these two major categories are subdivided into those that start from the ketone, those from an α-substituted ketone, and those from enamines.

A. Cyclohexanones as Precursors

a. Syntheses from Cyclohexanones Having No α-Substituent that Takes Part in Ring Formation. The simplest reaction of this type is that between cyclohexanone and 3-aminoacrolein, to give 5,6,7,8-tetrahydroquinoline (**408**);[470, 471]



408

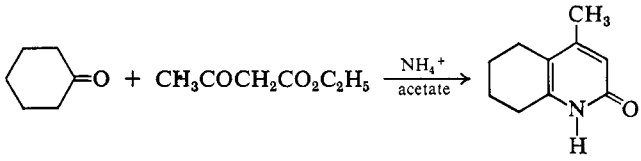
Route a, 40%
Route b, 38–43%

closely related is the reaction between cyclohexanone, ammonia, and allyl alcohol over cadmium phosphate at 400 °C.[472] The latter route was also used with methylcyclohexanones.[473]

Cyclohexanones reacted with β-keto-esters[474] and β-keto-nitriles[475] under Knoevenagel condensation conditions to give the reduced carbostyril (**409**) and the 1,4,5,6,7,8-hexahydroquinoline (**410**) (see p. 174).

Cyclohexanones also reacted with *p*-anisylidenecyanoacetic acid, but under basic catalysis, to give octahydrocarbostyrils such as (**411**), or hexahydrocarbostyrils such as (**412**), the former interconvertible with the latter on acid treatment.[476]

A reaction starting with cyclohexanone but obviously proceeding through the enamine (**413**) was reported to give 1-benzyl-2,3,5,6,7,8-hexahydro-4(1*H*)-quinolone (**414**) in 52% yield.[477]



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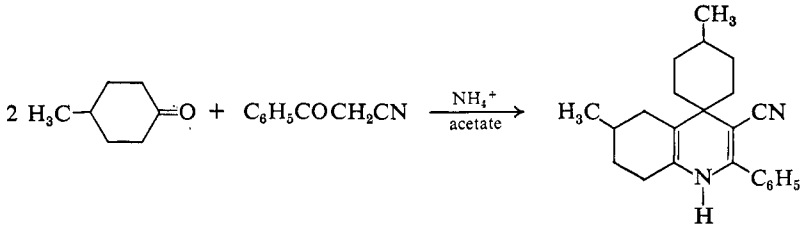

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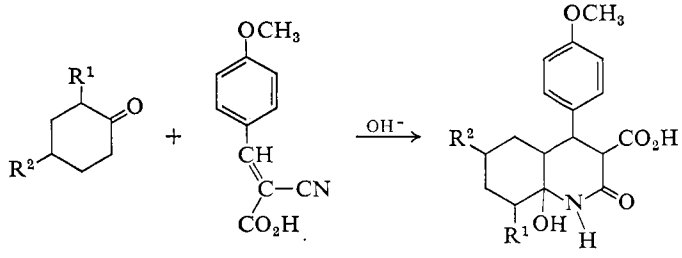
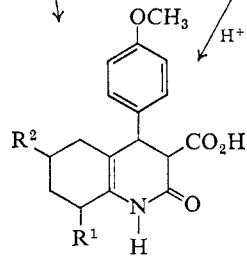
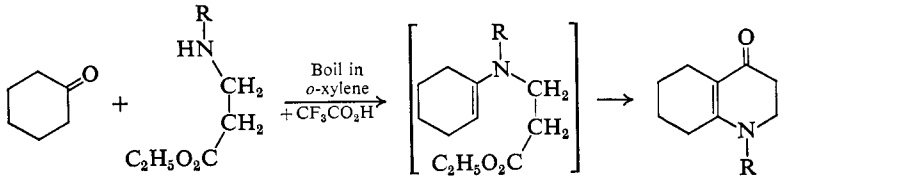


411, $R^1 = R^2 = H$



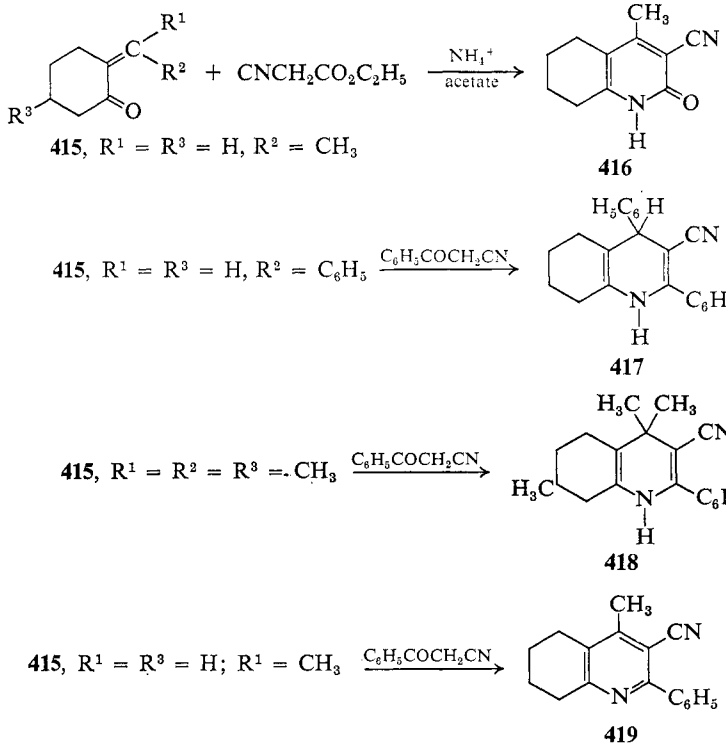
412, $R^1 = R^2 = H$



413

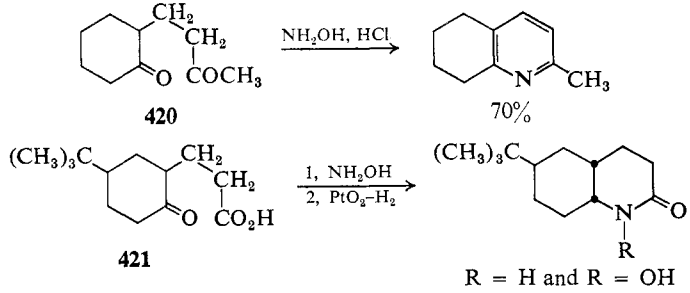
414, R = $CH_2C_6H_5$ or $CH(CH_3)C_6H_5$

b. CYCLOHEXANONES IN WHICH AN α-SUBSTITUENT TAKES PART IN RING FORMATION. When 2-alkylidenecyclohexanones (**415**) were treated with ethyl cyanoacetate[474] or benzoylacetonitrile[475] they gave the cyclized Michael adducts (**416**), (**417**), anp



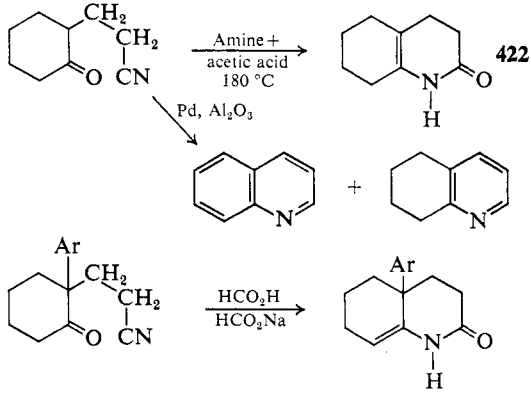
(**418**). Rather surprisingly, ethylidenecyclohexanone and benzoylacetonitrile gave the tetrahydroquinoline (**419**), with loss of two atoms of hydrogen.[475]

Two processes involving intermediate oxime formation started from the diketone (**420**)[478] and the keto-acid (**421**);[479] in the latter process the oxime was used as an



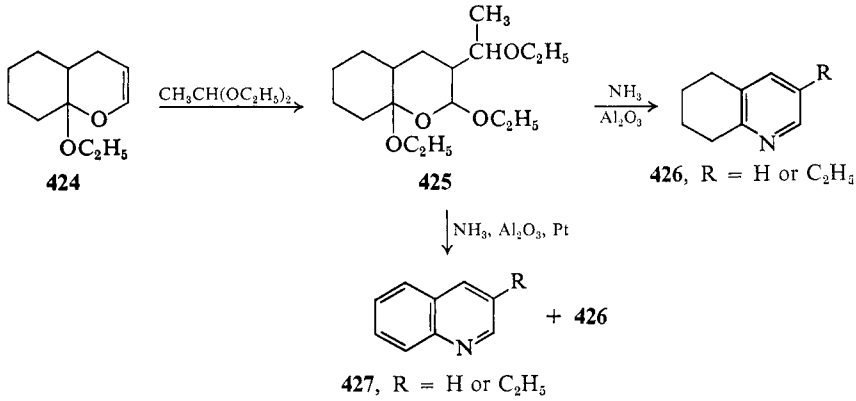
intermediate for amine production, which was followed by lactamization. Other examples of cyclization by hydroxylamine of diketones are in the patent literature.[480]

The readily available 2-(2-cyanoethyl)cyclohexanones have been cyclized by the action of amine salts[481] of amino-acids,[481] of sodium formate and formic acid,[482] and of palladium on alumina.[483] In the first three cases hexahydrocarbostyrils [examples (**422**) and (**423**)] were formed; in the last case quinoline itself or, at lower temperatures, a mixture of quinoline and 5,6,7,8-tetrahydroquinoline.



423, Ar = C_6H_5 or *p*-$CH_3OC_6H_4$

The latent keto-aldehyde (**424**), after addition of acetal, gave compound (**425**) which could be converted into a 5,6,7,8-tetrahydroquinoline (**426**) by ammonia and alumina, or into a quinoline (**427**) by ammonia, alumina, and platinum.[484]

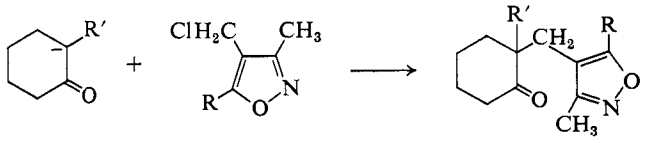


424 **425** **426**, R = H or C_2H_5

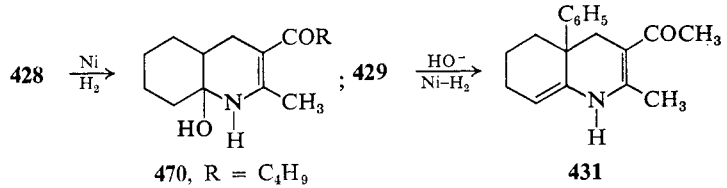
427, R = H or C_2H_5

Stork[485–487] has used isoxazoles ingeniously as masked aminoethyl substituents, and thus from the substituted cyclohexanones (**428**) and (**429**) obtained the quinoline derivatives (**430**) and (**431**).

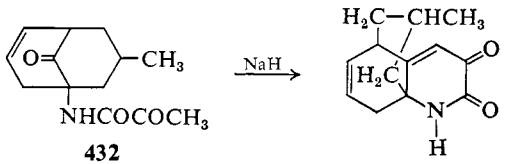
In a rather complex example of the cyclization of an α-aminocyclohexanone, the bicylic compound (**432**) gave with sodium hydride the tricyclic compound (**433**).[488]



428, R′ = H, R = C_4H_9
429, R′ = C_6H_5, R = CH_3

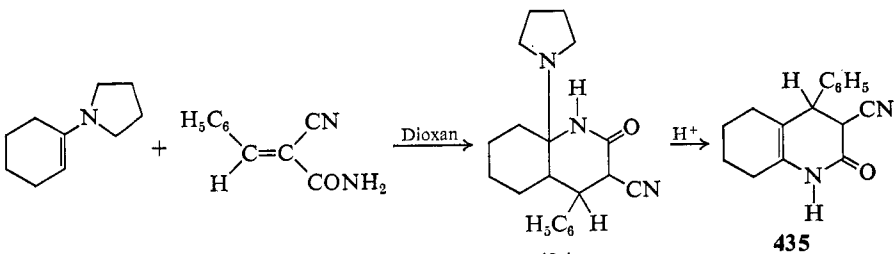


470, R = C_4H_9 431



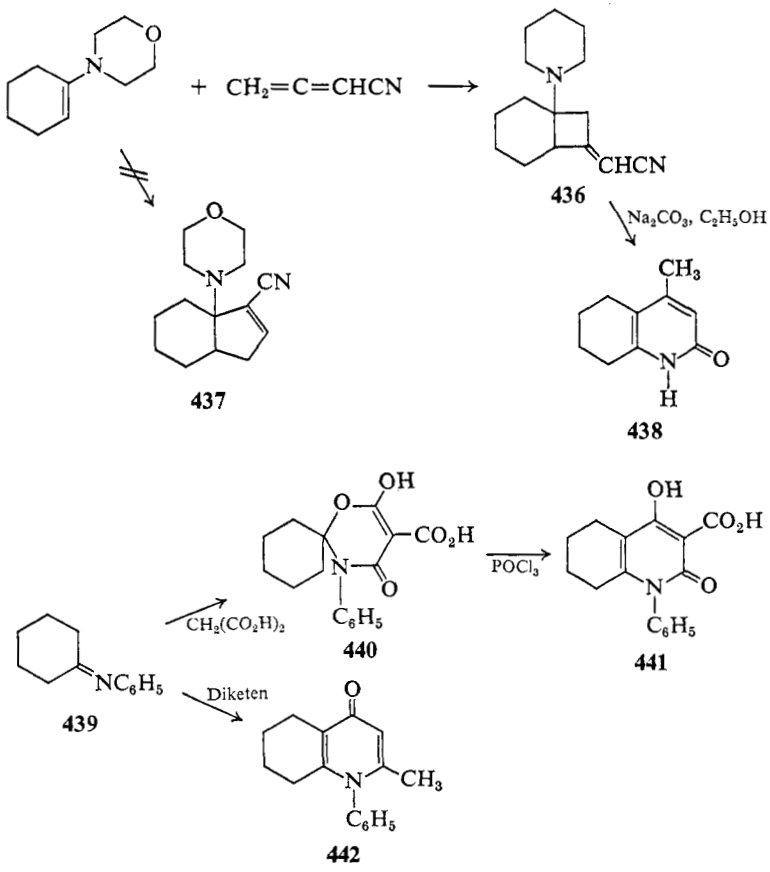
432 433

c. Syntheses from Enamines Derived from Cyclohexanones. Simple enamines derived from cyclohexanone can react with suitable activated alkenes; if the alkenes also bear a group that can complete the cyclization, a reduced quinoline results. Examples are more common with enamino-ketones derived from cyclohexane-1,3-dione (p. 178), but a few are available using simple enamines. Benzylidenecyanoacetamide reacted with the pyrrolidine enamine from cyclohexanone to give the octahydrocarbostyril (**434**), losing pyrrolidine on acid treatment to give compound (**435**).[489]

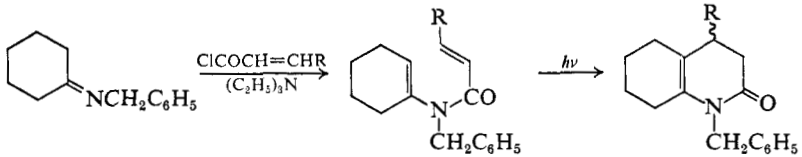


434 435

The structure of the adduct of cyanoallene to the morpholine enamine from cyclohexanone has been finally established as a bicyclo[4.2.0]octane (**436**)[490] rather than as originally suggested[491] a bicyclo[4.3.0]nonene (**437**). Treatment of the adduct (**436**) with bicarbonate in ethanol gave the tetrahydrocarbostyril (**438**). The mechanism of the last stage has been discussed.[490] The tautomeric ketimines have also been used as quinoline precursors. Thus the phenylketimine (**439**) gave with malonic acid a spiro-compound (**440**) converted by phosphoryl chloride into the compound (**441**);[492] the same ketimine with diketen gave the tetrahydro-4-quinolone (**442**).[493]



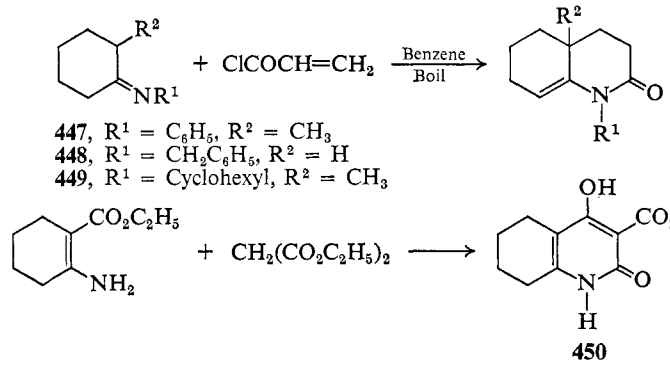
Acylation of *N*-benzylcyclohexanimine gave the enamides (**443**) and (**444**). Amide (**443**) cyclized on irradiation to give, in 61% yield, the hexahydrocarbostyril (**445**). Use of the phenyl-substituted amide (**444**) gave only moderate yields of cyclized



443, R = H
444, R = C_6H_5
445, R = H
446, R = C_6H_5

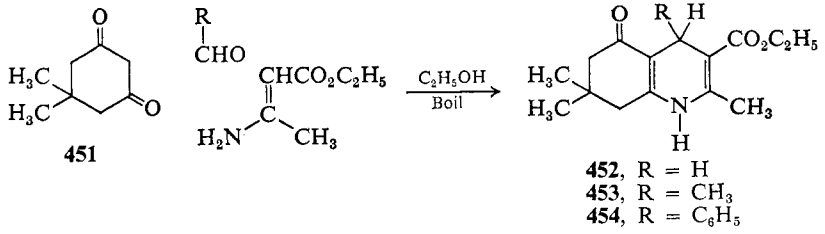
material (**446**).[494] A similar cyclization, without irradiation, was achieved when the 2-substituted cyclohexanimines (**447**)–(**449**) were heated in benzene with acryloyl chloride.[495] No cyclization was achieved with crotonoyl or cinnamoyl chloride.

Ethyl 2-aminocyclohex-1-enecarboxylate reacted with diethyl malonate to give the compound (**450**)[471, 496] which was converted[496] in three stages into 5,6,7,8-tetrahydroquinoline.

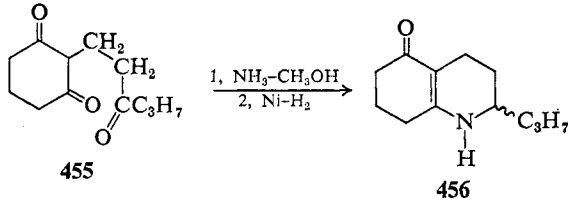


B. Cyclohexane-1,3-diones as Precursors

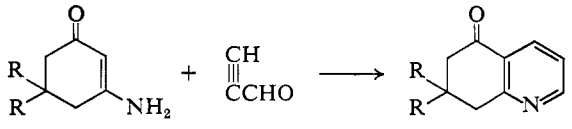
a. Syntheses from Cyclohexane-1,3-diones Having No 2-Substituent. Dimedone (**451**) reacted with formaldehyde and 3-aminocrotonate to give the tetrahydro-quinolin-5-one (**452**).[497] Similar reactions with acetaldehyde or benzaldehyde in place of formaldehyde gave compounds (**453**) and (**454**).



b. Synthesis from Cyclohexane-1,3-diones Having a 2-Substituent. The triketone (**455**), treated with ammonia and then with nickel and hydrogen, gave the unsaturated ketone (**456**).[498]

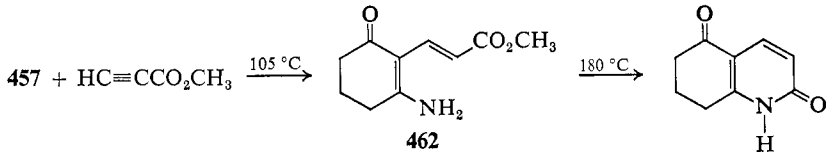


c. Syntheses from Monoenamines of Cyclohexane-1,3-diones. Reaction between cyclohexane-1,3-dione and ammonia gives the enamino-ketone (**457**). This reactive enamine, with propargylaldehyde, gave the quinolin-5-one (**458**);[499] the dimethyl derivative (**459**) from dimedone similarly gave the ketone (**460**). With methyl propargylate the enamino-ketone (**457**) gave the quinoline-2,5-dione (**461**);[500, 501] Pettit, Fleming, and Paull[500] showed the unsaturated ester (**462**) to be an intermediate in the reaction. Active methylene compounds such as ethyl acetoacetate and benzoylacetone reacted in the presence of toluene-*p*-sulphonic acid with



457, R = H
459, R = CH_3

458, R = H
460, R = CH_3



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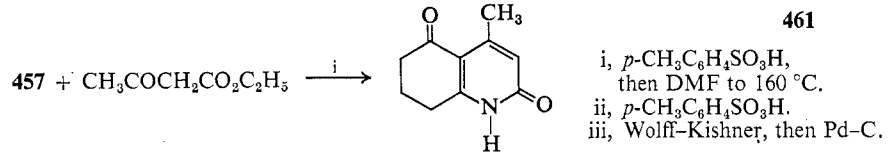
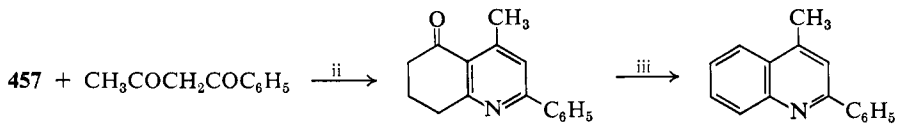


463

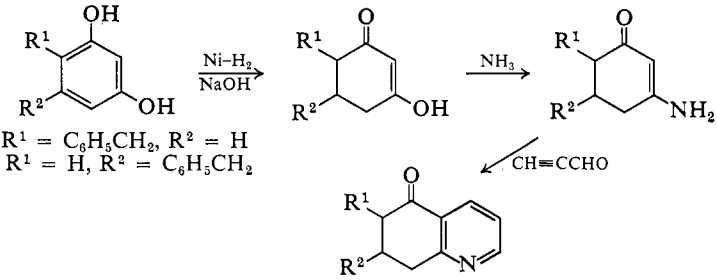
i, *p*-$CH_3C_6H_4SO_3H$, then DMF to 160 °C.
ii, *p*-$CH_3C_6H_4SO_3H$.
iii, Wolff–Kishner, then Pd-C.



464

the enamino-ketone (**457**) to give the quinolin-5-ones (**463**) and (**464**), respectively.[502] In some cases the quinolin-5-ones have been reduced by the Wolff–Kishner procedure, and the resulting tetrahydroquinolines have been dehydrogenated to the quinolines; in the example given,[502] the quinolines obtained were more easily available by other methods.

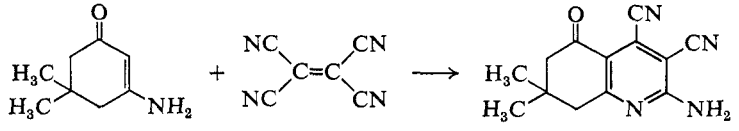
The propargylaldehyde procedure has proved useful in a synthesis of quinolines carrying a 6- or a 7-benzyl substituent,[503] starting from the appropriate benzylresorcinol (**465**) or (**466**).



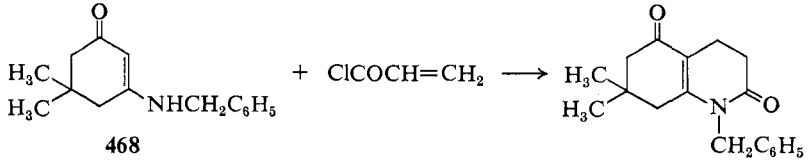
465, $R^1 = C_6H_5CH_2$, R^2 = H
466, R^1 = H, $R^2 = C_6H_5CH_2$

The enamine (**459**) from dimedone reacted with tetracyanoethylene to give the highly substituted quinolin-5-one (**467**);[504] the *N*-substituted enamine (**468**) with acryloyl chloride in boiling benzene gave compound (**469**).[505] The *N*-unsubstituted

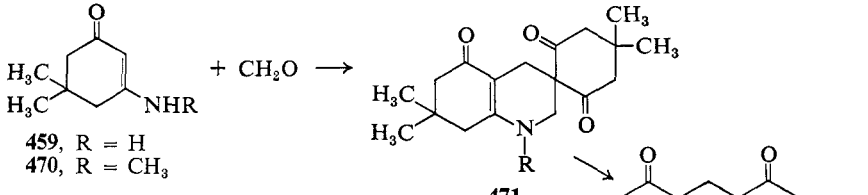
enamine (**459**) or the *N*-methyl derivative (**470**) gave spiro-derivatives (**471**) with formaldehyde and acid at room temperature; it was also possible to isolate tricyclic derivatives of type (**472**); and similar results were obtained with acetaldehyde and benzaldehyde.[506]



459 **467**



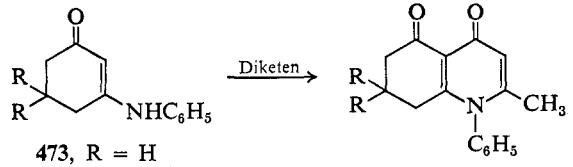
468 **469**



459, R = H
470, R = CH_3

471 **472**

Finally, with diketen the *N*-phenyl-substituted enamino-ketones (**473**) and (**474**) gave quinoline-4,5-dione derivatives (**475**) and (**476**).[493]

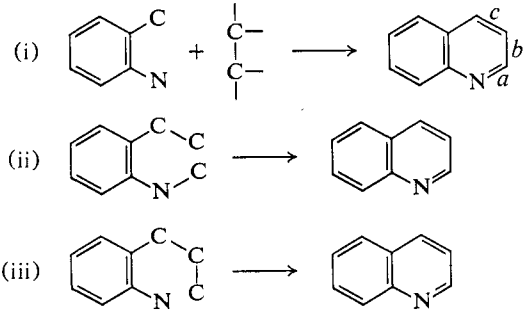


473, R = H
474, R = CH_3

475, R = H
476, R = CH_3

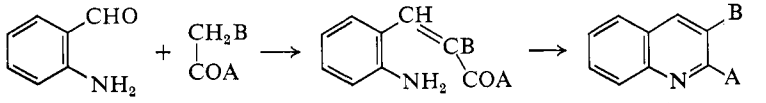
III. Cyclizations of *ortho*-Substituted Benzenes where Both Substituents Form Part of the Heterocyclic Ring

These syntheses are of the general types (i)–(iii). In syntheses of type (i), which make up the bulk of those dealt with, bonds *a* and *c* are formed (Friedländer and related syntheses); in type (ii), bond *b* is formed (Camps); and, in type (iii), bond *a* is formed (reductive cyclization of nitrocinnamaldehydes).



1. Condensations between *o*-Amino-carbonyl Compounds and a Second Carbonyl Component

In 1882 Friedländer reported that *o*-aminobenzaldehyde reacted with sodium acetate and acetic anhydride to give carbostyril (2-quinolone).[507] He also noted that *o*-aminobenzaldehyde and acetaldehyde with a drop of sodium hydroxide at 40–50° gave a compound with a strong odour of quinoline, and suggested an aldol condensation with subsequent cyclization of the cinnamaldehyde (**477**). In a subsequent paper Friedländer and Gohring indicated the scope of the new synthesis.[508] Generalizing the reaction scheme as shown, *o*-aminobenzaldehyde with acetone, acetophenone, or



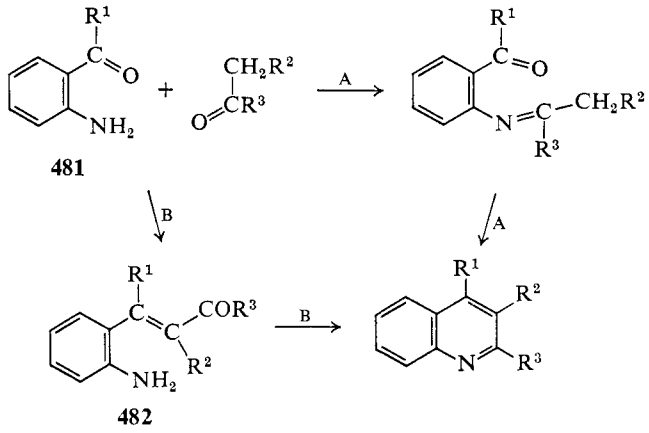
477

	A	B
478,	CH_3	H
479,	C_6H_5	H
480,	H	C_6H_5

phenylacetaldehyde gave the appropriate quinolines (**478**)–(**480**). Friedländer and Gohring also noted the possibility of an alternative cyclization when β-keto-esters were used (p. 187). The synthesis was subsequently extended to include *o*-aminophenyl ketones, particularly acetophenone and benzophenone, and these are dealt with in the first section below. The Pfitzinger modification, and the von Niementovski and Camps syntheses are dealt with in a subsequent section.

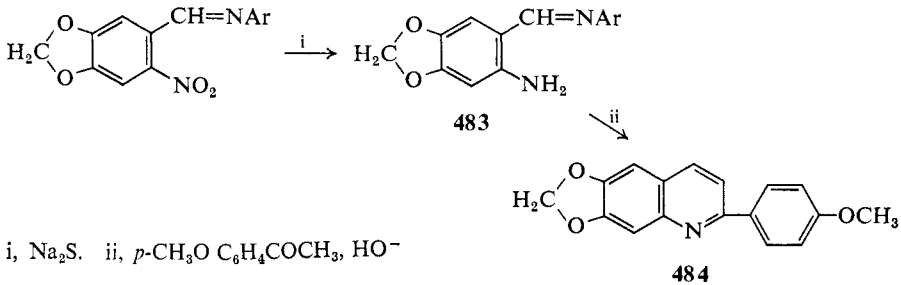
A. The Friedländer Synthesis: Condensation between an o-Amino-aldehyde or -ketone and a Second Aldehyde or Ketone

Of the mechanism of the traditional base-catalysed Friedländer synthesis remarkably little is known. It seems probable that the initial condensation is between the aromatic amine (**481**) and the carbonyl group of the second component (path A); in one of the few cases where an intermediate has been isolated it was such a Schiff base.[509] Should the reaction proceed by the alternative mechanism (path B) it is unlikely to involve the cinnamoyl derivative (**482**), as there is evidence to suggest that the more stable *trans*-cinnamoyl derivative will not cyclize.[510] The strongly basic conditions used in the original Friedländer synthesis causes difficulties when the second carbonyl



component is itself susceptible to aldol condensation, and much resin may be formed. For this reason the acid-catalysed procedure, first reported by Clemo and Felton[511] but much developed by Kempter and his co-workers[512–516] and by Fehnel[517–519] has considerable advantages.

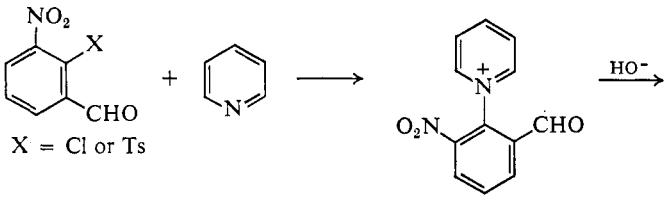
a. Scope and Limitations of the Friedländer Synthesis. The major limitation to the application of Friedländer's synthesis, and to the closely related syntheses described in subsequent sections, comes from the difficulty of preparing the required *o*-aminobenzaldehydes or *o*-aminophenyl ketones, and from the instability of such compounds in the free-base form. Thus *o*-aminobenzaldehyde is difficult to prepare in quantity[520] and rapidly condenses to a diazocine on warming. The problem of instability is overcome partially in the acid-catalysed procedure, although the higher temperature used must allow some dissociation to free base. Another solution to the problem of instability of *o*-aminobenzaldehydes has been the use of *o*-aminobenzanils such as (**483**); these are readily prepared by reduction of the corresponding *o*-nitrobenzanils and have been reported to give improved yields when used in place of the free aldehyde, as in the preparation of the 2-arylquinoline (**484**).[256, 521]



i, Na_2S. ii, *p*-$CH_3O\ C_6H_4COCH_3$, HO^-

Most of the substituted *o*-aminobenzaldehydes used have carried electron-donating groups, usually methoxy- or methylenedioxy-groups, since the usual approach has been by nitration of the substituted aromatic aldehyde, with subsequent reduction of either the nitrobenzaldehyde or the anil of the nitrobenzaldehyde. A free phenolic hydroxyl group does not interfere with the synthesis; successful Friedländer syntheses

have been reported using 2-aminovanillin.[522] An unusual, but limited, approach to nitroquinolines discovered by Allan and Loudon[523] used a nitrophenylpyridinium salt (**485**); cleavage of the pyridine ring under basic conditions was followed by



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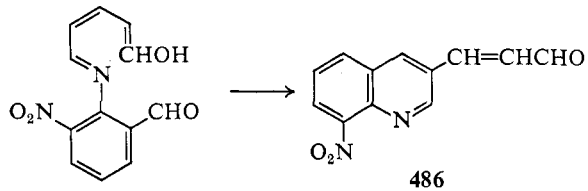

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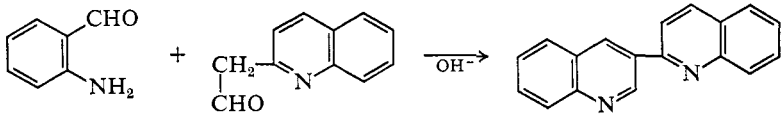
cyclization, giving a nitroquinolyl-acraldehyde (**486**);[523] it was not always necessary to isolate the pyridinium salt; ketones required greater activation, and the synthesis was only successful with 3,5-dinitro-aceto- or -benzophenone.

The major value of the Friedländer synthesis lies in the variations that are possible in the second carbonyl component, leading to a wide range of 2-, 3-, and 4-substituted quinolines. The range is smallest for the 4-substituents, mainly hydrogen, methyl, or phenyl groups (the Pfitzinger modification gives quinoline-4-carboxylic acids, p. 197). The simplest modification of Friedländer's original experiment was the use of higher homologues of acetaldehyde to provide 3-alkylquinolines. The sensitivity of aliphatic aldehydes towards base makes this approach unprofitable, except for arylacetaldehydes, as for example in the synthesis of the biquinolyl (**487**).[524] Fortunately the use of higher temperatures without added base gave satisfactory results, as illustrated by the synthesis of 3-*n*-pentylquinoline (**488**).[525]



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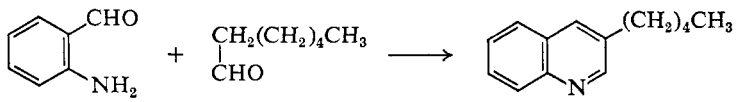

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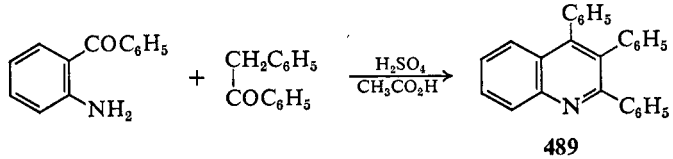
When symmetrical aliphatic or alicyclic ketones are used, making the direction of condensation immaterial and the results unambiguous, good yields of 2-substituted quinolines or 2,4-disubstituted quinolines (from acetone), or of 2,3-disubstituted or 2,3,4-trisubstituted quinolines (from other ketones) have been obtained. A similarly

unambiguous situation exists when aralkyl ketones are used, and 2-aryl-[526] or 2-aryl-3-alkyl-quinolines have been obtained in high yield. An example of such a reaction, acid-catalysed, is provided by the synthesis of compound (**489**).[517] Unsaturated ketones have been used to provide quinolines with an unsaturated side chain in the 2-position,[521, 527] giving, for example, 2-isobutenylquinoline (**490**) in 70% yield from mesityl oxide if the anil was used[527] (only 40% if the free aldehyde



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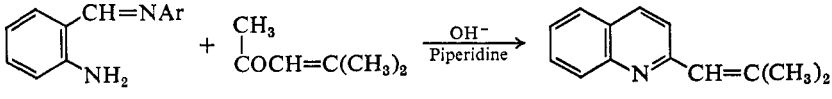

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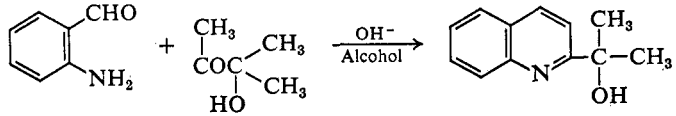

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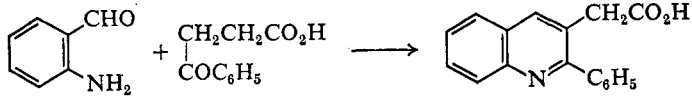
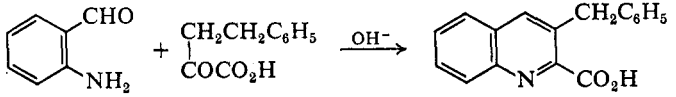


492

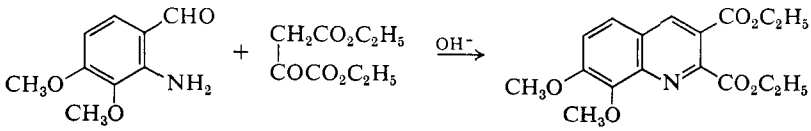
was used[521]). Other substituents successfully introduced in side chains by Friedländer syntheses include the hydroxyl group in compound (**491**) from the corresponding α-hydroxy-ketone,[528] and the carboxyl group (as an acetic acid residue) in compound (**492**), derived from β-benzoylpropionic acid.[529] Quinoline-2-carboxylic acids such as the 3-benzyl derivative (**493**) have been obtained from substituted pyruvic acids,[530]



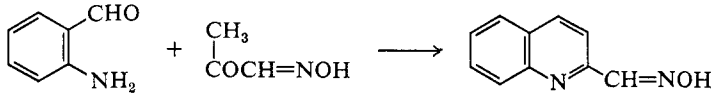
493

and quinoline-2,3-dicarboxylic esters such as (**494**) from alkoxaloacetates.[522] Pyruvaldehyde monoxime reacted with *o*-aminobenzaldehyde to give the hydroxyiminomethylquinoline (**495**);[531] the anil of 6-aminopiperonal has also been used with pyruvaldehyde monoxime.[532] The glyoxal bisulphite compound with *o*-aminobenzaldehyde or its *N*-methyl derivative gave, in the presence of cyanide ion, the 3-hydroxy-4-quinolones (**496**) and (**497**);[533] this reaction would appear to involve a benzoin condensation in one stage.

When unsymmetrical aliphatic, alicyclic, or heterocyclic ketones are used two modes of condensation may be possible and both products may be formed. As an



494; 75%



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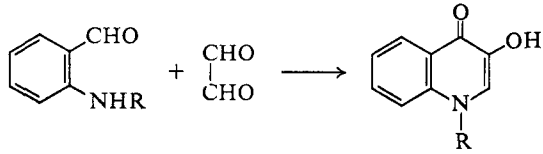
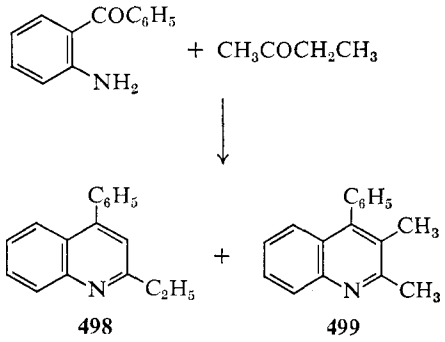


496, R = H
497, R = CH_3

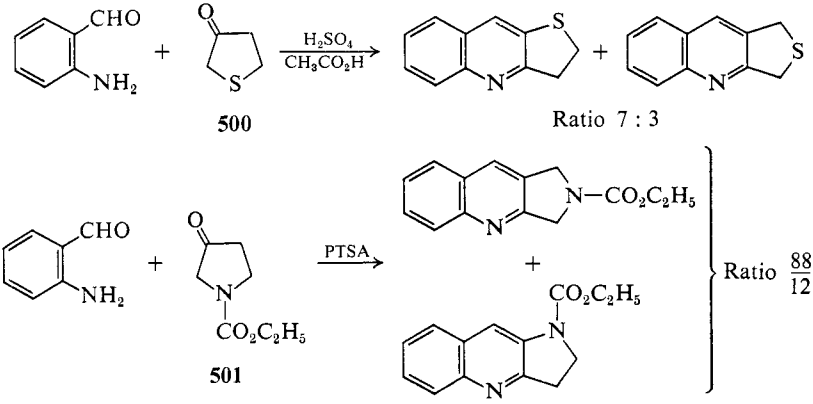
example, ethyl methyl ketone gave predominantly the 2-ethylquinoline (**498**) under basic condensation conditions, but an appreciable amount (11%) of the isomeric 2,3-dimethylquinoline (**499**) was formed, and the value of the synthesis was correspondingly diminished.[517] From methyl ketones under acid-catalysed conditions 3-alkyl-2-methylquinolines are the normal products;[513, 517, 534] for example, ethyl



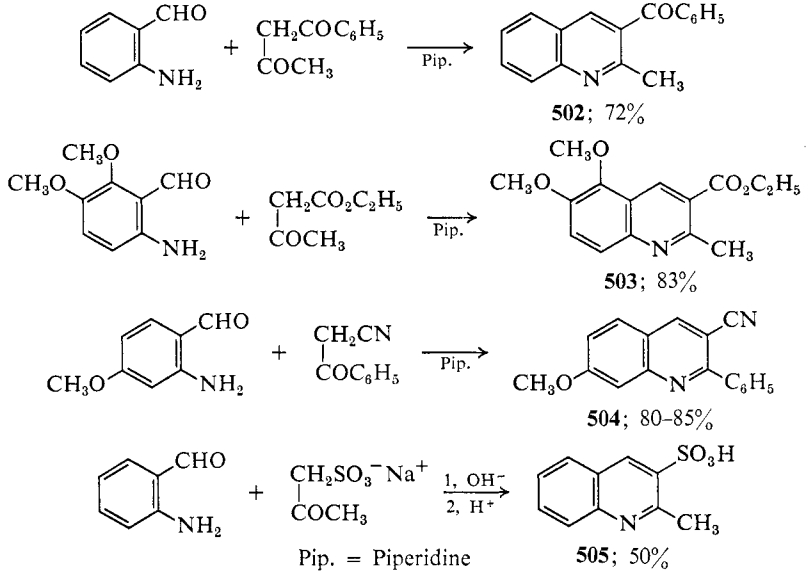
498 **499**

methyl ketone was reported to give almost entirely the 2,3-dimethylquinoline (**499**) when acid-catalysed.[517] Reports of base-catalysed condensations show contradictory results; in some reactions the pattern of acid-catalysed condensations was observed[535, 536] but in others the 3-unsubstituted 2-alkylquinoline was formed.[534] Fehnel has discussed the directional effect exercised by the ketone on the basis of enolization but reached no firm conclusion.[517] When unsymmetrical cyclic ketones are used a mixture almost always results if two directions of condensation are possible, even in the acid-catalysed procedure which seems to give greater specificity in the acyclic series. Two examples using the heterocyclic ketones (**500**)[537] and (**501**)[538] provide rare examples of the use of acid catalysis with *o*-aminobenzaldehyde.

The direction of condensation using an unsymmetrical ketone becomes once more unambiguous if the acidity of one α-methylene group is greatly increased (that is, a



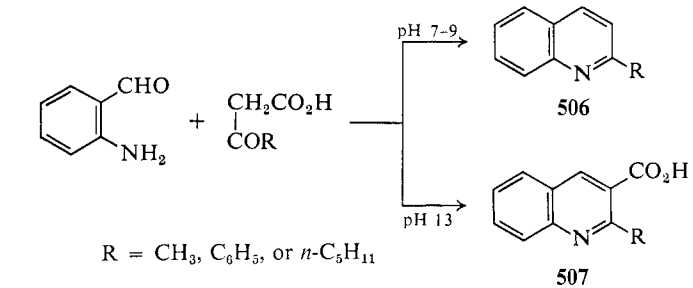
greatly preferred direction of enolization). Such activation is provided in 1,3-diketones,[513, 518, 522, 535, 539-543] giving quinoline-3-ketones such as compound (**502**);[540] in β-keto-esters,[508, 522, 529, 532, 542, 543-547] giving quinoline-3-carboxylates [example (**503**)[542]]; β-keto-amides, giving quinoline-3-carboxamides;[546] β-keto-nitriles,[522, 542, 545, 546, 548] giving 3-cyanoquinolines such as compound (**504**);[522] and



β-keto-sulphonyl derivatives, giving 3-sulphonylquinolines, or, in one case, (**505**) quinoline-3-sulphonic acid.[549]

The production of compound (**502**) rather than the isomeric 3-methyl-2-phenylquinoline illustrates the general rule that condensation occurs between the amino-group and the more reactive of the carbonyl groups in a β-diketone; thus the aroyl group appears always at the 3-position. The β-diketones and β-keto-esters are susceptible to hydrolysis under prolonged basic treatment; Friedländer and

Gohring[508] reported that condensation between *o*-aminobenzaldehyde and ethyl β-benzoylacetate gave only 2-phenylquinoline, presumably because hydrolysis of the keto-ester to acetophenone was faster than the condensation. Free β-keto-acids have been shown[536] to decarboxylate, giving 2-substituted quinolines (**506**) rather than the



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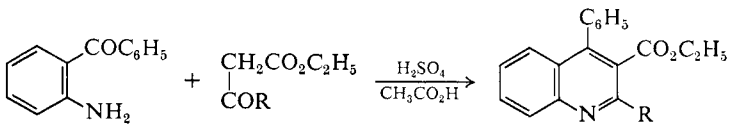


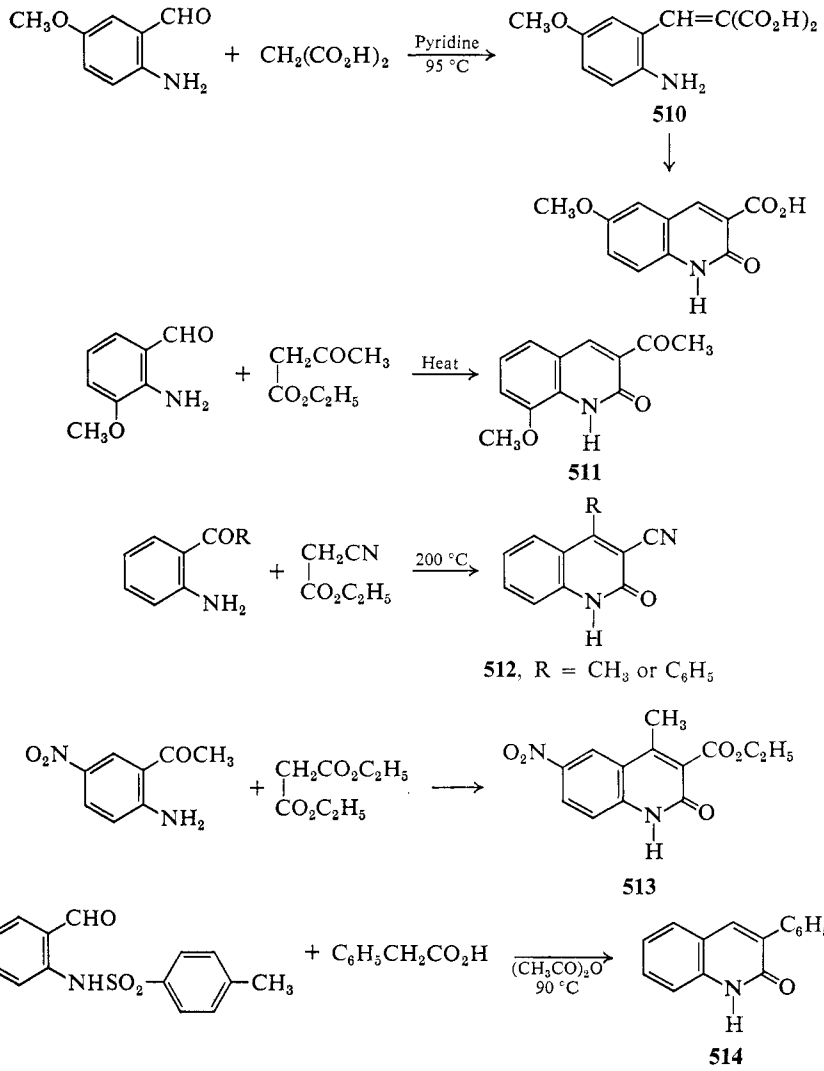
508, R = CH_3
509, R = C_6H_5

corresponding quinoline-3-carboxylic acids (**507**). The greater reactivity of the methylene group in the difunctional compounds allows the use of the weaker base piperidine as catalyst, often in a non-aqueous solvent, as shown in examples (**502**) to (**504**), and hence hydrolysis need not be a problem. Fehnel[519] has successfully condensed *o*-aminobenzophenone with ethyl acetoacetate or benzoylacetate under acid-catalysed conditions to give the esters (**508**) and (**509**). There are, however, two cases of deacetylation of a phenolic acetate during Friedländer condensation when too much piperidine was used.[522, 542] Ion-exchange resins (IRA 400 OH^-) have also been used in non-aqueous media and should also decrease the risk of hydrolysis.[543]

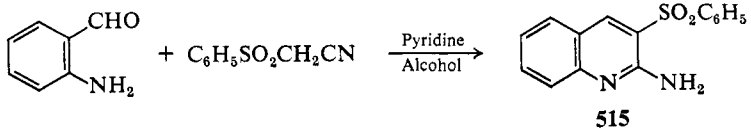
An alternative mode of condensation between *o*-aminobenzaldehyde and β-keto-esters was noted by Friedländer and Gohring.[508] When the reagents were heated together (usually at 130–160°) without a catalyst, condensation occurred between the aromatic amine and the ester group, giving eventually a 2-quinolone.[550] Similar condensations occur with malonic acid derivatives[550–552] and with malonic acid itself.[547] With malonic acid, the condensation was performed under Knoevenagel conditions, and its seems probable that the intermediate was the arylidenemalonic acid (**510**). Other examples of this route to 2-quinolones are provided by the syntheses of compounds (**511**) to **514**).[544, 553–557]

When *o*-aminobenzaldehydes condensed with benzyl cyanide,[547, 558] malonitrile,[545, 547, 559] or sulphonylacetonitriles,[547, 560] 2-aminoquinolines such as compound (**515**) were formed. The aminoquinolines were probably formed via the intermediate cinnamonitrile, since Pschorr has shown[561] that cinnamonitriles such as (**516**) can cyclize to 2-aminoquinolines under basic conditions. Phosphorus tribromide in chloroform has also been used to produce 2-aminoquinolines (**517**) and (**518**).[559]

It is possible to prepare 3-hydroxy- or 3-alkoxy-quinolines, 3-nitroquinolines, or 3-aminoquinolines by a suitable choice of starting material in the Friedländer synthesis. When α-chloro-[562] or α-bromo-ketones[563, 564] were condensed, under basic



conditions, with *o*-aminobenzaldehyde the products were 3-hydroxyquinolines, such as compound (**519**).[562] With a suitably placed carboxylic acid, such a reaction can give a lactone (**520**).[563] An α-methoxy-ketone such as (**521**) gave a 3-methoxyquinoline (**522**).[565] The Friedländer synthesis offers two approaches to 3-aminoquinolines: in the more direct route an α-phthalimido-ketone is used to give a 3-phthalimidoquinoline, such as (**523**);[564, 566] hydrolysis then gave the 3-aminoquinoline; the alternative route, first reported in a German patent,[567] used methazonic acid (nitroacetaldehyde oxime); this reaction has been carefully investigated by Schofield and Theobald,[509] who showed that an initial acid-catalysed condensation gave a Schiff base (**524**); this cyclized rapidly in a neutral or basic medium, to give a 3-nitroquinoline (**525**). The yields are poor in many cases, as there appear to be a



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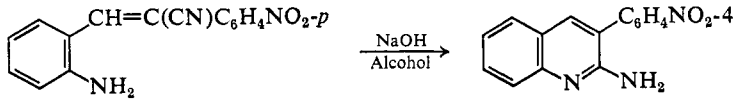

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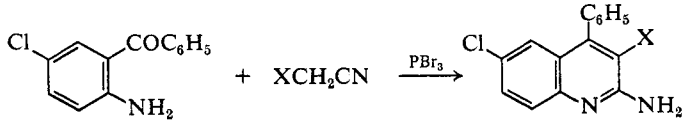
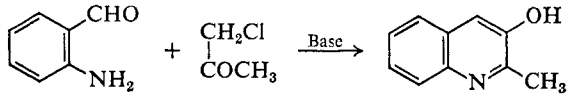


517, X = CN
518, X = $CO_2C_2H_5$



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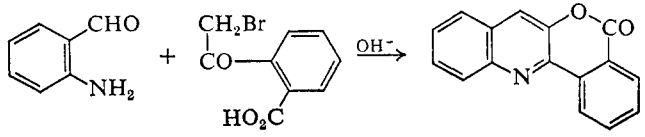

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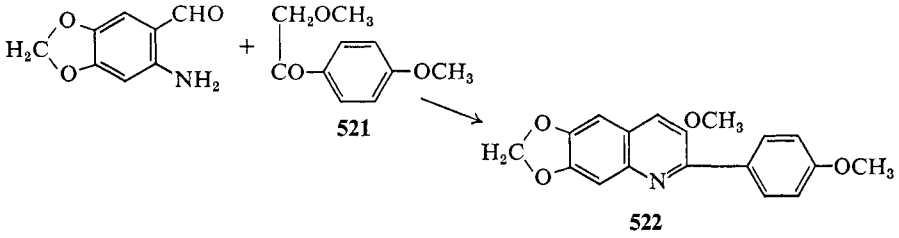

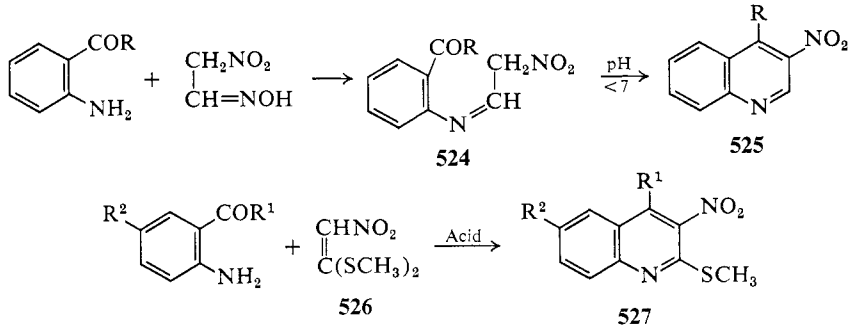

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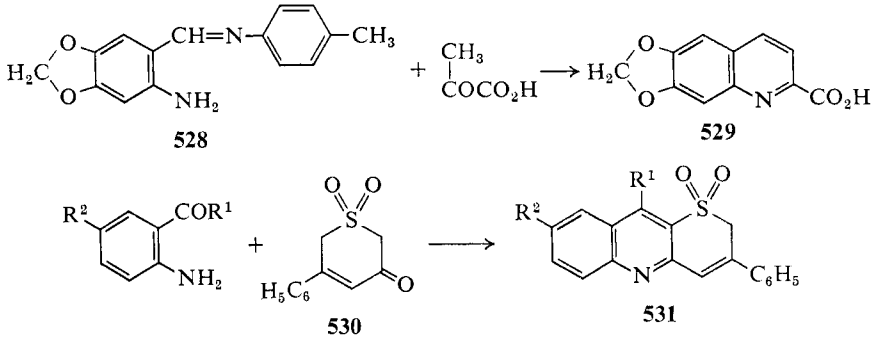
number of competing hydrolyses. The nitroquinolines can readily be reduced to 3-aminoquinolines. A related condensation using the unsaturated nitro-thioketal (**526**) gave 3-nitro-2-(methylthio)quinolines of type (**527**).[568]

A number of aldehydes and ketones have been reported to fail to give quinolines in Friedländer syntheses. Eliasberg and Friedländer[535] reported failure with acetoacetaldehyde and with benzoylacetaldehyde but these were probably too base-sensitive. They also reported failure with deoxybenzoin, which has been successfully condensed with the anil of *o*-aminobenzaldehyde,[245] and under acid-catalysed conditions with *o*-aminobenzophenone[517] and with *o*-aminoacetophenone.[513] One of the few amines that have failed to react was 6-aminopiperonal (with acetaldehyde),[569] but here again the anil (**528**) condensed successfully with pyruvic acid to give the quinoline-2-carboxylic acid (**529**),[532] and it seems probable that the anil would condense also with acetaldehyde. There seem to be no recorded steric restraint on the Friedländer condensation, although there has been no detailed examination. One case where steric effects may have determined the direction of condensation



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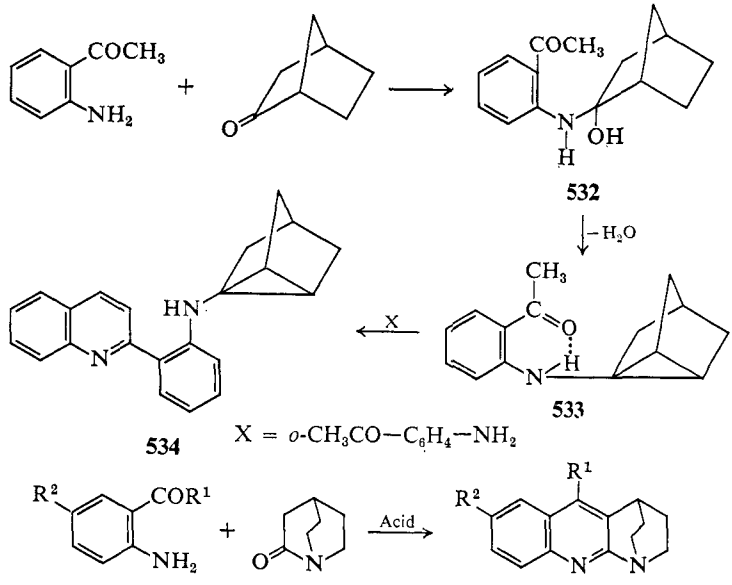
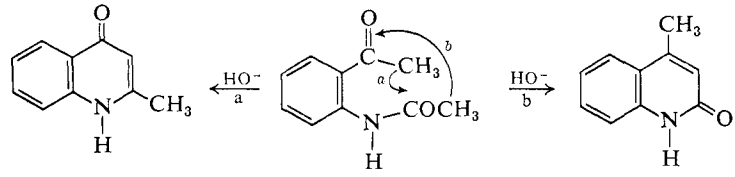
was shown by the reaction of the cyclic sulphone (**530**); here the methylene group α to the carbonyl was preferred to the more hindered vinylogous methylene groups and gave tricyclic compounds (**531**).[570] In the acid-catalysed condensation between *o*-aminoacetophenone and norcamphor the product was the cyclized compound (**533**);[571] the suggested mechanism involves an intermediate aldol (**532**) which undergoes intramolecular dehydration under the acid conditions. It is interesting that the residual acetyl group in compound (**533**) can undergo reaction with more aminoacetophenone to give a flavaniline (**534**) (see Fischer and Rudolph[572]). The normal

Friedlander products were obtained when the superficially similar quinuclidine was condensed with a range of *o*-aminobenzophenones as illustrated.[573]



B. Cyclization of o*-Acetamidoaryl-aldehydes or -ketones: the Camps Modification*

If an *o*-amino-ketone or *o*-aminoaldehyde is acylated, a base-catalysed cyclization becomes possible; if the ketone is of the aralkyl type there are two possible modes of cyclization, both illustrated by the base-catalysed cyclization of *o*-acetylamino-acetophenone (**535**), described in Camps' original paper.[574]



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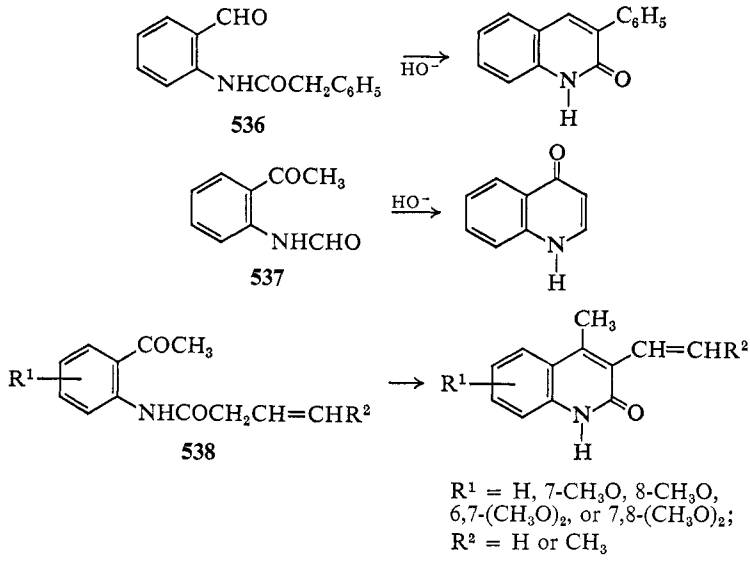
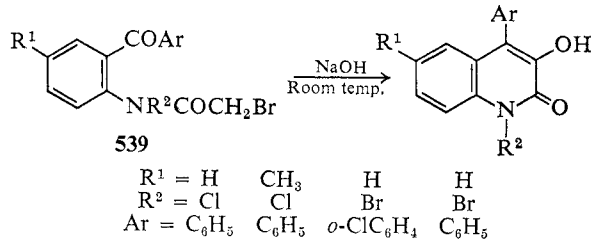
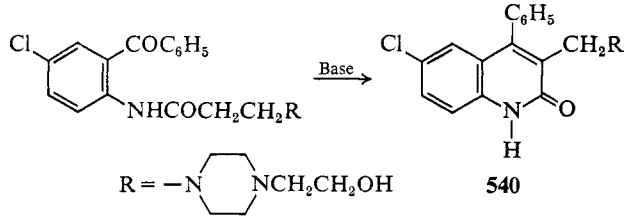
Hydrolysis of the amide is also possible, and the free *o*-aminoacetophenone can itself undergo a Friedländer condensation. The 2-quinolone and the 4-quinolone were easily separated by virtue of the solubility of the 4-quinolone in acid. Earlier papers by Bischler *et al.* had shown ways in which the cyclization could be made unambiguous.[575, 576] Cyclization of an *o*-acylaminobenzaldehyde (**536**)[576] or of a diaryl ketone[577] must give a 2-quinolone, while use of an *o*-aroyl- or an *o*-formyl-amino-derivative (**537**)[578] must give a 4-quinolone. Similarly, if the amide-methylene group carries additional activation, which can be minimal as on the but-3-enoyl-amides (**538**),[579, 580] or in a phenylacetamide,[575] cyclization will give a 4-quinolone.

As in the Friedländer synthesis (p. 189) the use of α-bromo-acetamides, such as (**539**), leads to a quinoline having a hydroxyl substituent in the 3-position.[581] A

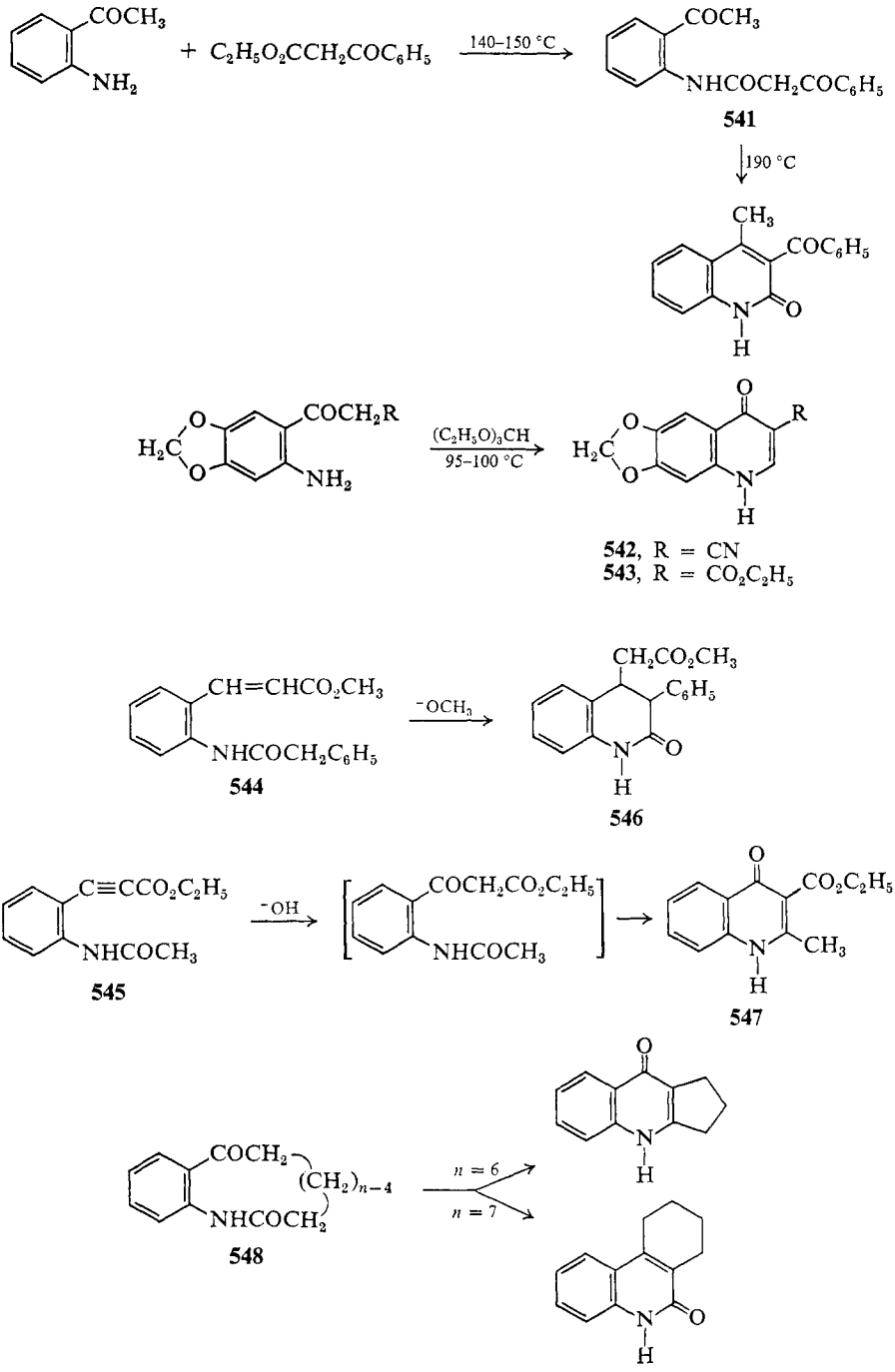


3-aminopropionamide was used to produce a 3-(aminomethyl)quinolone (**540**),[582] while a phthalimidoacetanilide gave a 3-phthalimido-2-quinolone.[583] When malonates, β-keto-esters, or cyanoacetates were used in the Friedländer synthesis, direct heating of the two components gave 3-substituted 2-quinolones (p. 187). Camps showed that at lower temperatures (140–150 °C instead of 190–200 °C) the



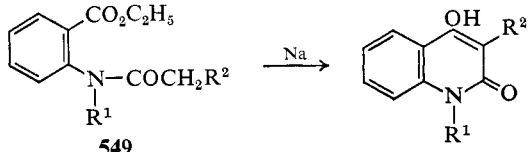


intermediate amide such as (**541**) could be isolated, and it subsequently cyclized on further heating or on base-treatment; sodium hydroxide[553] or calcium hydroxide[554] have been used. In another modification an *o*-aminobenzoyl-acetonitrile or -acetate was heated with ethyl orthoformate to give a 3-cyano-4-quinolone (**542**)[584] or a 4-quinolone-3-carboxylate (**543**).[585] This procedure has been extended to produce 3-sulphonamido- and 3-(dialkoxyphosphino)-quinolines.[586]


COCH3
NH2
+ C2H5O2CCH2COC6H5
140–150 °C
COCH3
NHCOCH2COC6H5
541
190 °C
CH3
COC6H5
N
H
O
COCH2R
H2C
O
NH2
(C2H5O)3CH
95–100 °C
R
542, R = CN
543, R = CO2C2H5
CH=CHCO2CH3
NHCOCH2C6H5
544
-OCH3
CH2CO2CH3
C6H5
546
C≡CCO2C2H5
NHCOCH3
545
-OH
COCH2CO2C2H5
CO2C2H5
CH3
547
COCH2
(CH2)n-4
n = 6
n = 7
548

Contrasting modes of reaction were shown by the *o*-(acylamino)phenylacrylates, e.g. (**544**),[587] and by the corresponding acetylenic esters (**545**).[588] In the former, a "vinylogous Camps" cyclization gave the dihydro-2-quinolone 4-acetic ester (**546**). In the latter, the product was the 4-quinolone (**547**), presumably formed by hydration of the acetylenic bond, with cyclization of the resulting active-methylene derivative. A conformationally controlled change from 4-quinolone to 2-quinolone has been observed in the intramolecular Camps cyclization of the bicyclic ketolactams (**548**).[589]

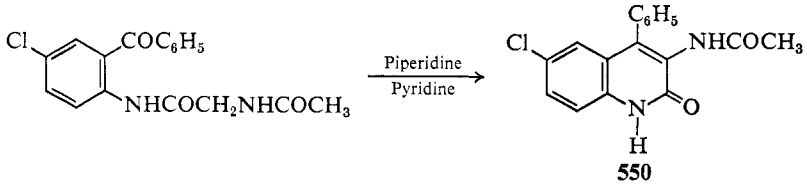
The basic catalyst most commonly used in the Camps cyclization has been aqueous or aqueous-alcoholic sodium or potassium hydroxide, or calcium hydroxide.[554] There may be an advantage in the use of a non-aqueous base (sodium



549

R^1 = H, R^2 = C_6H_5;
or R^1 = various groups,
R^2 = CH_2CO_2R or $CH_2CH_2CO_2R$

ethoxide and triphenylmethylsodium have been used[590]) since hydrolysis of the amide can lower the yield of quinolone. A non-aqueous base must be used when cyclization of an *o*-amido-ester (**549**) is to be performed.[563, 591, 592] Piperidine in



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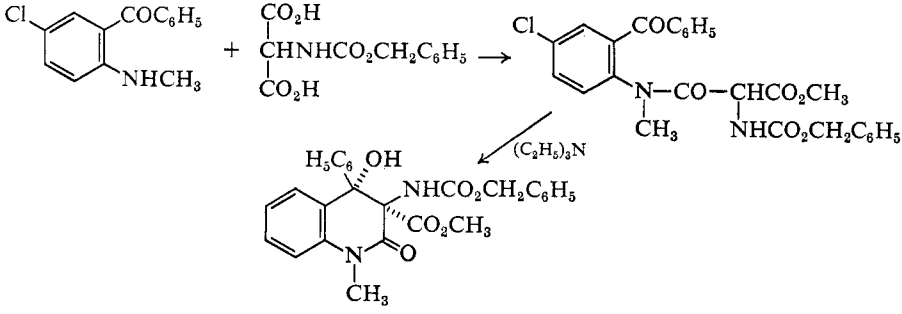
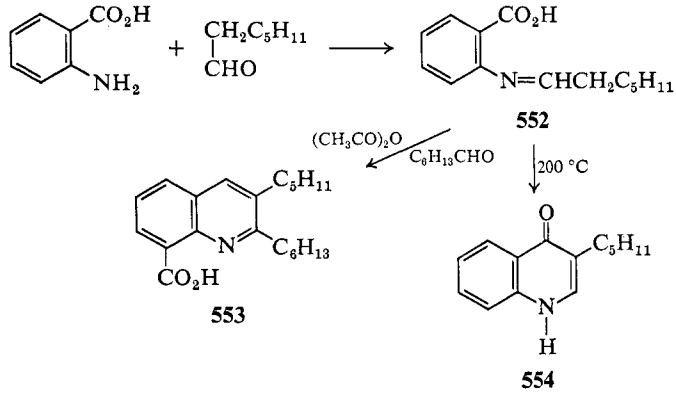


551

pyridine has been used to afford 3-acetamido-2-quinolones such as (**550**).[593] Dihydro-2-quinolones have been obtained by using triethylamine as cyclization catalyst when amethine rather than a methylene group was available for cyclization, as in example (**551**).[594]

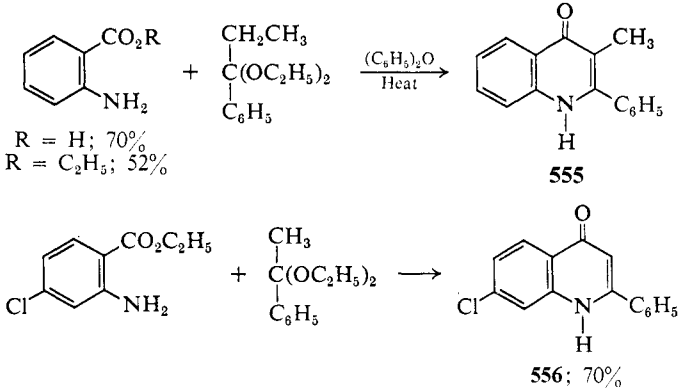
C. Condensation between Anthranilic Acid Derivatives and Carbonyl Components, giving 4-Quinolones: the von Niementovski Modification

von Niementovski reported poor yields of 4-quinolones when anthranilic or 4-methylanthranilic acid was heated with acetophenone.[595] Subsequently, von Niementovski and Orzechovski reported that anthranilic acid reacted with aldehydes to give Schiff bases, such as (**552**), but attempts to cyclize these gave usually the



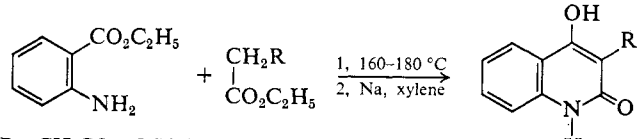
Doebner–von Miller product (**553**);[596] in one case the 4-quinolone (**554**) was obtained. In general, the von Niementovski variation is less versatile than the original Friedländer synthesis.

Anthranilic acid or its esters can be used in the synthesis, and the amino-group may be primary or secondary, but on the whole indifferent yields have been obtained from anthranilic acids and ketones. Fuson and Burness reported much improved yields when the acetal or vinyl ether was used in place of the free ketone, but in only one case (**555**) was the yield better with the free acid than with the anthranilate.[597] Very few substituted anthranilic acids have been used, but ethyl 4-chloroanthranilate



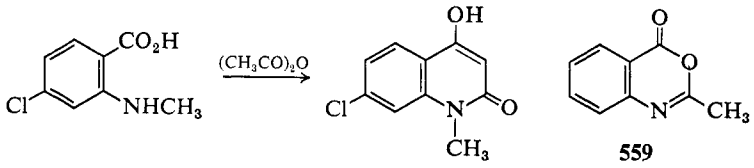
gave an unambiguous entry into the 7-chloro-4-quinolone series, as with compound (**556**).[597] The kinetics of the reaction between methyl anthranilate and ethoxystyrene (giving 2-phenyl-4-quinolone) have been studied.[598]

The reaction failed with 3,5-dibromoanthranilic acid, possibly owing to reduced basicity of the amine, and also when 3-aminopyridine-2-carboxylic acid was used, because of the ready decarboxylation of the acid. Many successful syntheses have started from the anthranilate. Preliminary formation of an acyl or an imino-derivative can then be followed by a Claisen condensation on use of sodium in an inert solvent, or an alkoxide. Many 4-hydroxy-2-quinolones have been prepared and the synthesis is most useful when the methylene group carries additional activation as in the series represented by formula (**557**).[599] A synthesis of 4-hydroxy-2-quinolone was achieved in excellent yield by using methyl anthranilate and diketen.[554] The same method has given *N*-substituted 4-hydroxy-2-quinolones, but these, for example (**558**), are conveniently prepared from *N*-alkyl-[600] or *N*-aryl-anthranilic acids[600, 601] with acetic anhydride. A range of 4-hydroxy-2-quinolones were prepared from anthranilic acid

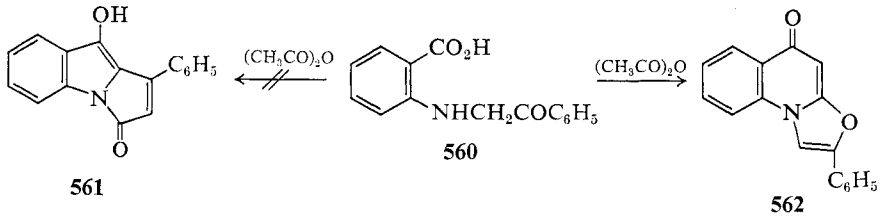


R	CH_3CO	C_3H_7CO	$(CH_3)_2CHCH_2CO$	C_6H_5CO
%	30	59	14	26

557



558 **559**

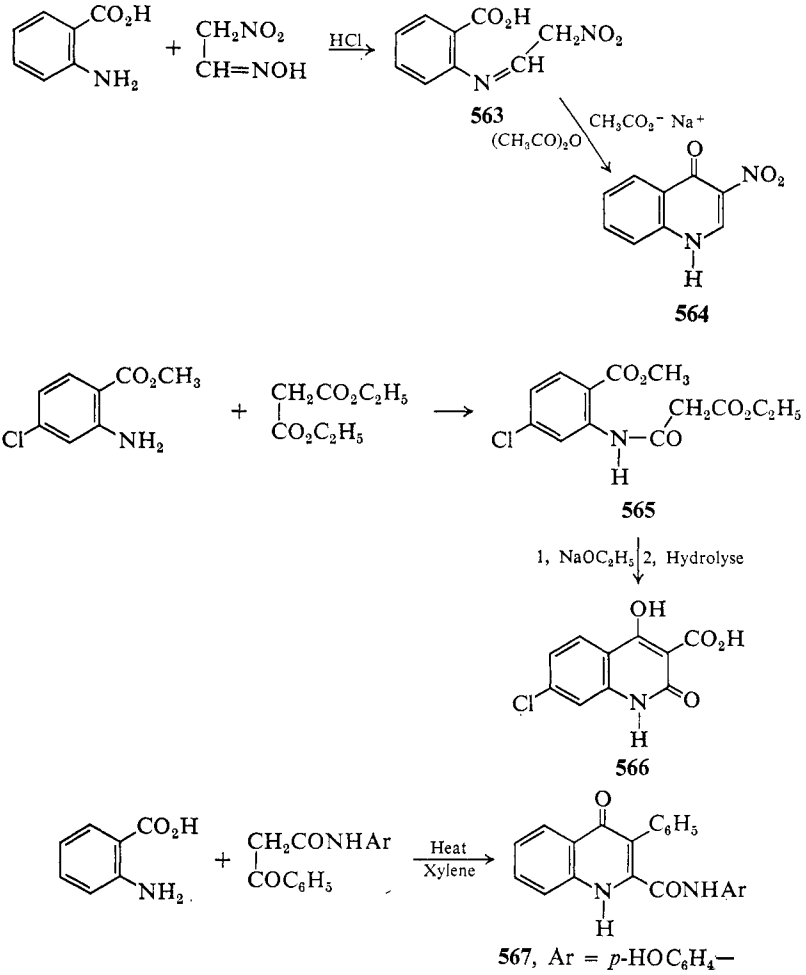


561 **560** **562**

and acetic anhydride, or from acetanthranil (**559**) by use of sodium methoxide in xylene.[602] Acetic anhydride treatment of the *N*-substituted anthranilic acid (**560**) was reported to give the tricyclic compound (**561**),[603] but later the structure was corrected to (**562**).[604]

Anthranilic acids react with methazonic acid under acidic[605, 606] or basic[607] conditions to give an anil (**563**). This anil was cyclized by sodium acetate in boiling acetic anhydride to give 40–45% yields of 3-nitro-4-quinolone (**564**). The alkali-metal acetates gave superior yields in the cyclization when compared with other salts or with organic bases.

Anthranilic acid or anthranilates could, in theory, undergo three types of reaction with β-keto-esters, and two with malonates. If the anthranilates are condensed with esters at 160–180 °C, an amide such as (**565**) is formed; subsequent cyclization with sodium in toluene, or with sodium ethoxide, then leads unambiguously to the 3-acyl-4-quinolone or to the 3-alkoxycarbonyl-4-hydroxy-2-quinolone and thence to the

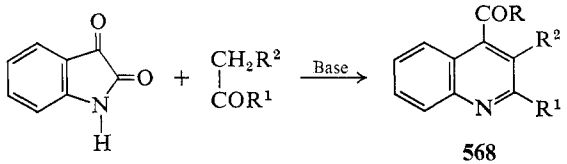


acid (**566**).[599, 608] In an attempt to improve the direct reaction between anthranilic acid and β-keto-amides, Moszev and Kolasa heated the reagents in xylene with removal of water, but the yields were still between 10 and 15%, as in example (**567**).[609]

D. Condensation between Isatins and Carbonyl Compounds to give Quinoline-4-carboxylic Acids: the Pfitzinger Modification

The most widely used modification of the Friedländer synthesis is that due to Pfitzinger,[610–612] in which an aldehyde or ketone is condensed with isatin in a basic medium. The simplicity of the procedure, and the high yields of quinoline-4-carboxylic acids (**568**, R = OH) usually obtained, account for its popularity. As with any synthesis in which the nitrogen atom and the carbon atom at position 4 of the quinoline are provided by an *ortho*-disubstituted benzene, the synthesis is unambiguous with respect to substitution on the "benzoid" ring of the quinoline.

Ambiguities in the "pyridine" ring are discussed at length below (p. 200). The usual basic medium is a concentrated aqueous or aqueous-alcoholic sodium or potassium hydroxide solution; occasionally ammonia has been used, and the product may be the amide (**568**; R = NH_2).



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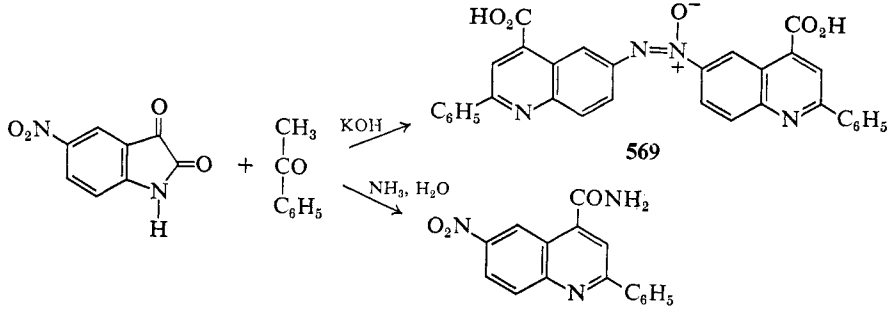
There is surprisingly little detail reported on the mechanism of the Pfitzinger condensation. The five-membered ring of isatin is known to open in base to give *o*-aminophenylglyoxylate, and this presumably then acts as an *o*-aminophenyl ketone in the normal Friedländer reaction.

a. Scope and Limitations. Very little variation in the isatin component has been reported, primarily because of the general difficulty associated with the synthesis of trisubstituted benzenes. Isatins substituted in the 4-, 5-, 6-, or 7-position have been used. No steric inhibition was shown by isatins carrying a substituent in the 7-position; failure has been reported in some condensations between 4-substituted isatins and masked β-keto-aldehydes, but this was not certainly a steric effect (p. 201).[613] Most substituted isatins carry 5- or 5,7-substituents, prepared by direct substitution of isatin or by synthesis from *para-* or *ortho,para*-substituted anilines. Although more difficult to prepare, 6-substituted isatins are important, because they provide unambiguous syntheses of 7-substituted quinolines. Substituted isatins used have contained halogen (fluorine,[614] chlorine,[254, 615-618] bromine,[617] iodine[619, 620]) alkyl[621] and aryl,[622] nitro,[623, 624] alkoxyl,[616, 625] carboxyl,[626, 627] acetamido,[628] and sulpho[629] groups. Of these the only difficulty was observed with 5-nitroisatin;[623] if the usual reagent (concentrated potassium hydroxide solution) was used, the azoxydiquinoline (**569**) was obtained. The use of aqueous ammonia gave the 6-nitroquinoline-4-carboxamide (**570**).



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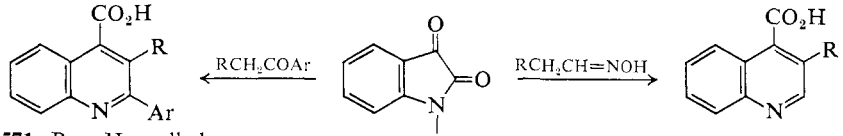
Most of the obvious variations possible with the carbonyl component were noted by Pfitzinger in his papers.[610-612] The majority of quinolines prepared by this synthesis have been obtained from ketones, usually of the type that allows only one mode of cyclization. Acetophenones and other acyl-aromatics and -heterocycles

give uniformly high yields of 2-arylquinoline-4-carboxylic acids (**571**), while deoxybenzoins give 2,3-diarylquinoline-4-carboxylic acids (**572**). The huge range of these derivatives is indicated in Table III (p. 274). As in the Friedländer synthesis, aldehydes are normally too unstable for successful use in the very basic medium, but

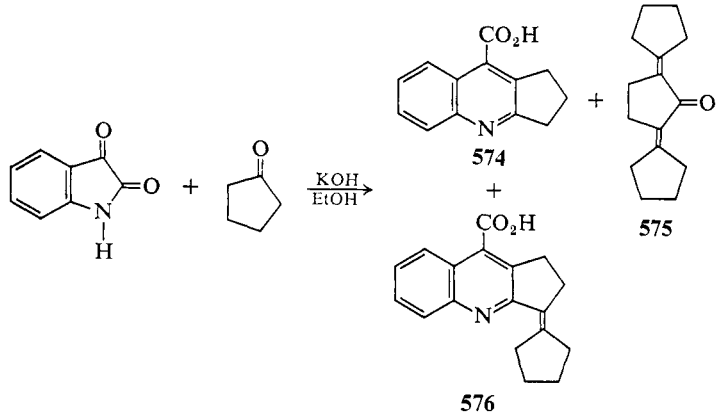


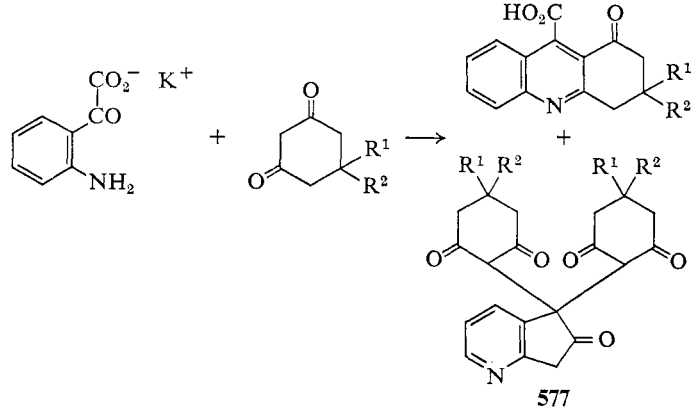
571, R = H or alkyl
572, R = Aryl

573

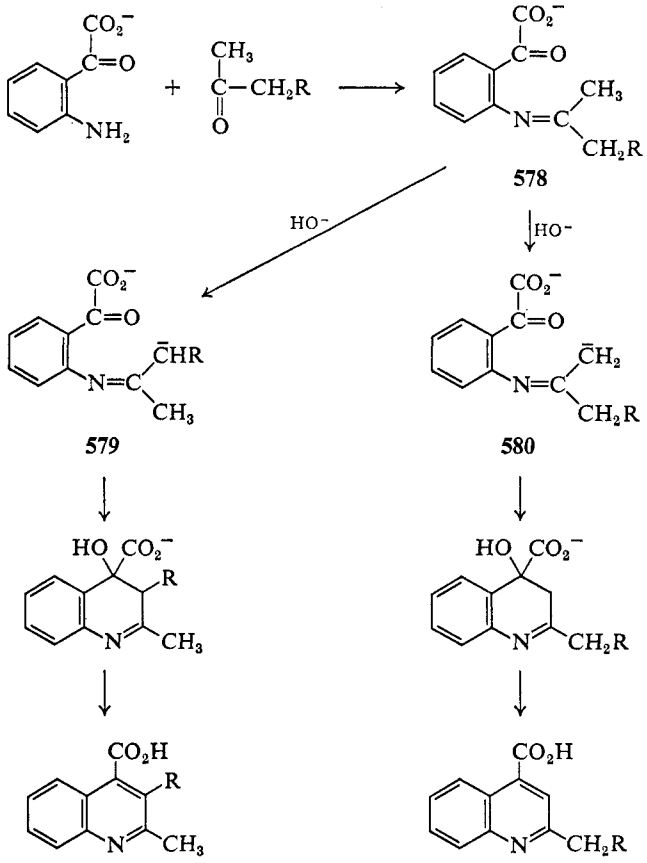
Pfitzinger reported[531] that aldoximes gave satisfactory yields, and these have been widely used[630–633] to give 3-substituted quinoline-4-carboxylic acids (**573**).

Cyclopentanone also readily undergoes aldol condensation, and competing reactions in a Pfitzinger synthesis with cyclopentanone have given a mixture of the three products (**574**)–(**576**).[634] Dibenzoylmethane was hydrolysed under normal Pfitzinger conditions;[635] it appears that the only satisfactory procedure, with enolizable β-diketones has been the use of potassium isatinate[636] with no solvent. Even with this procedure, cyclohexane-1,3-diones gave some products of type (**577**).





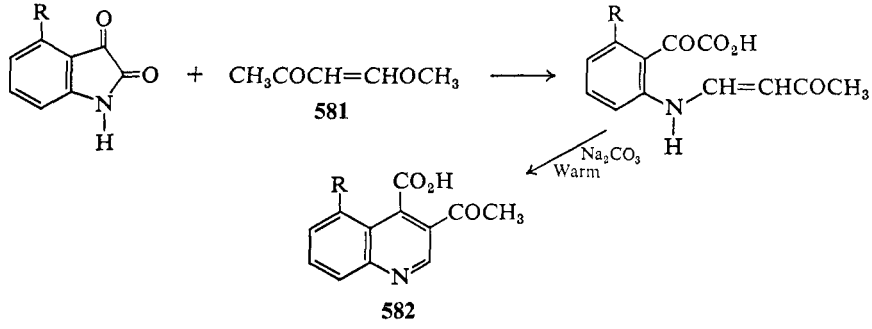
A major difficulty occurs if the ketone to be used has two available activated methylene (or methyl) groups, either of which could take part in the condensation. In the accepted mechanism for the Pfitzinger reaction, the isatinate reacts with the carbonyl group of the second component to give an imine—intermediates such as (**578**) have been isolated.[621] Palmer and McIntyre[637] have studied the product distribution in condensations between isatin and a series of methyl ketones. They suggested that the imine so formed can yield two ions (**579**) and (**580**) and discussed



the reasons for the preference for one against the other. The observed preferences for (**579**) over (**580**) with alkyl substituents were thought to be due to steric interference in the anion. However, this effect could be overcome by electronic influences when the substituent was an aryl group or an oxygen function (OR). It seems probable that very few, if any, ketones having two available condensation sites will give a single product.

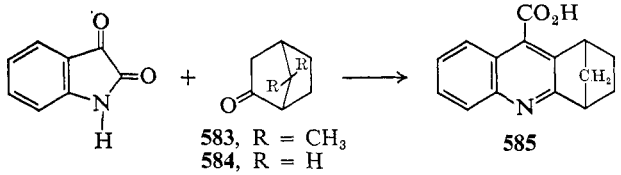
Steric inhibition of the Pfitzinger reaction has been exhaustively discussed, notably by Buu-Hoï and his associates and the major conclusions were summarized in two papers.[638, 639] Steric hindrance was assigned almost entirely to the ketone component, although a hindered 4-substituted isatin can make a bad situation worse—there is one

case of a modified Pfitzinger reaction (**581**) → (**582**), where a 4-substituent (R ≠ H) was said to stop the reaction entirely.[613]



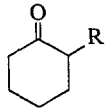
582

In series of simple *n*-alkyl phenyl ketones, RCH_2COAr, Buu-Hoï and Cagniant reported inhibition of the Pfitzinger synthesis when R was an *n*-propyl or a longer alkyl chain.[638] There appears no logical basis for this report, and subsequently[640, 641] it has been shown that such ketones (for example, hexanophenone) can react with isatin to give quinoline-4-carboxylic acids. The other features reported by Buu-Hoï and Cagniant,[638] and by others, to cause steric inhibition of the Pfitzinger reaction were α- or β-branching (for example, where R was an isopropyl group[639]) and the presence of bulky *ortho*-groups in either benzene ring, when R was a second phenyl group. There are a number of cyclic ketones, notably terpenes,[642, 643] where Pfitzinger reactions were said to fail because of steric inhibition. An interesting contrast was provided by camphor (**583**) which failed and norcamphor (**584**) which



583, R = CH_3
584, R = H

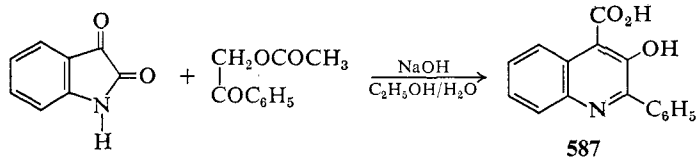
585



586, R = alkyl groups > propyl

gave a 10–12% yield of the quinoline (**585**).[644] Cyclic ketones from cyclobutanone[645] to cyclopentadecanone[646] reacted successfully with isatin; α- or β-branching can dramatically reduce the yields, as has been shown for some cyclohexanones[647] and α-tetralones.[639, 648] Thus compounds (**586**) failed to react with isatin.

Functional groups in the α-position of a ketone usually appear, although not always unchanged, in the 3-position of the quinoline. Thus have been prepared 3-hydroxyquinoline-4-carboxylic acids (**587**) (from hydroxy-,[635] acetoxy-,[649, 650] or halo-ketones[622, 651–654]). The use of halopyruvic acids[652] led directly to 3-hydroxyquinoline-4-carboxylic acids (**588**), not to the 2,4-dicarboxylic acids; comparison of the yields obtained in this reaction suggests that chloropyruvic acid is superior to bromopyruvic acid. There is no comparable report on halo-ketones, but it has been noted that ω-iodoacetophenone is useless.[651]



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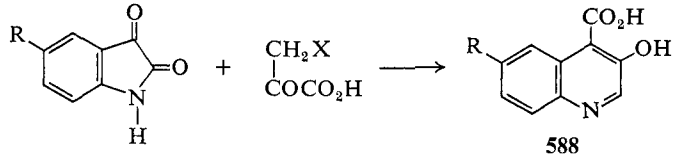
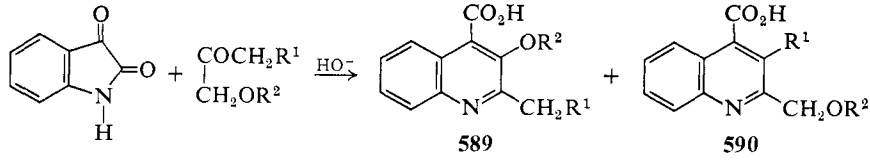


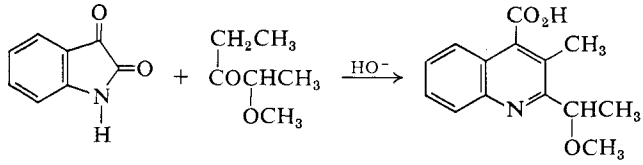
588

R	H	Cl	CH_3	CH_3
X	Cl	Cl	Cl	Br
%	71	79	24	14

When aryloxy-[655-660] or alkoxy-ketones[661-663] were used there was evidence that both possible isomers (**589**) and (**590**) were formed. The 3-aryloxy- or 3-alkoxy-quinoline (**589**) usually predominates, though it has been shown by nmr examination



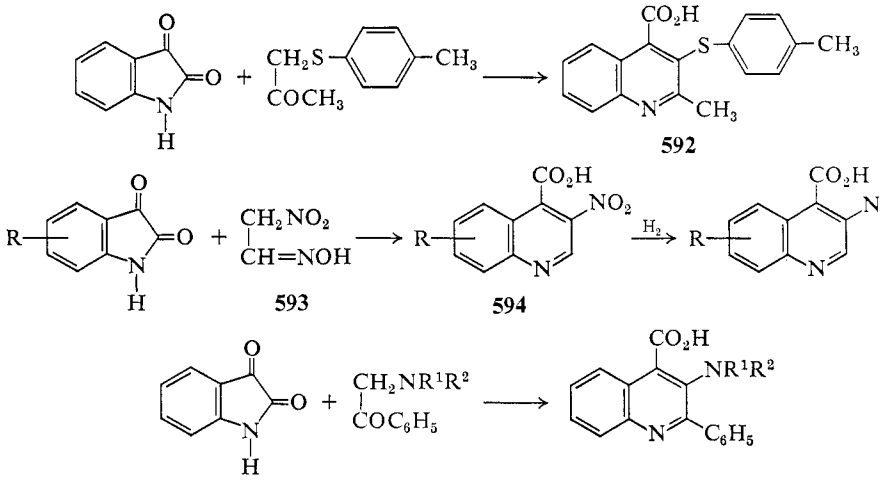
589 590



591; 74%

of the crude reaction mixture[637] as well as by isolation of the isomers[655] that there are also substantial amounts of the isomer (**590**). In cases where the 2-alkoxyalkyl isomers predominates, as for example with (**591**), there was steric control through α-branching.[664, 665]

From the limited evidence available[666-668] α-arylthio-substituents on a ketone also lead predominantly to this 3-substituent at position 3 of the quinoline (**592**).[567] Methazonic acid (**593**),[567] which can be prepared *in situ* from nitromethane by the basic medium,[669, 670] condensed with isatin to give 3-nitroquinolone-4-carboxylic acids (**594**), and hence by reduction the 3-aminoquinoline-4-carboxylic acids. There is a patent report[671] that ω-aminoacetophenone can be used in the Pfitzinger synthesis to give 3-amino-2-phenylquinoline-4-carboxylic acid (**595**); ω-piperidino-acetophenone gave the amine (**596**),[672] and ω-anilinoacetophenone gave the 3-anilinoquinoline (**597**).[673-676] Other workers have preferred to use ω-phthalimido-acetophenone[677, 678] or *N*-benzoylaminoacetophenone[679] and to hydrolyse the 3-imido- or 3-amidoquinoline, (**598**) or (**599**), to produce the 3-aminoquinoline.

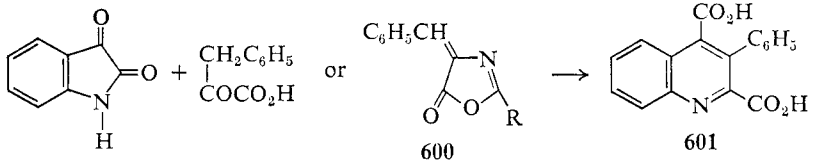


592

593 594

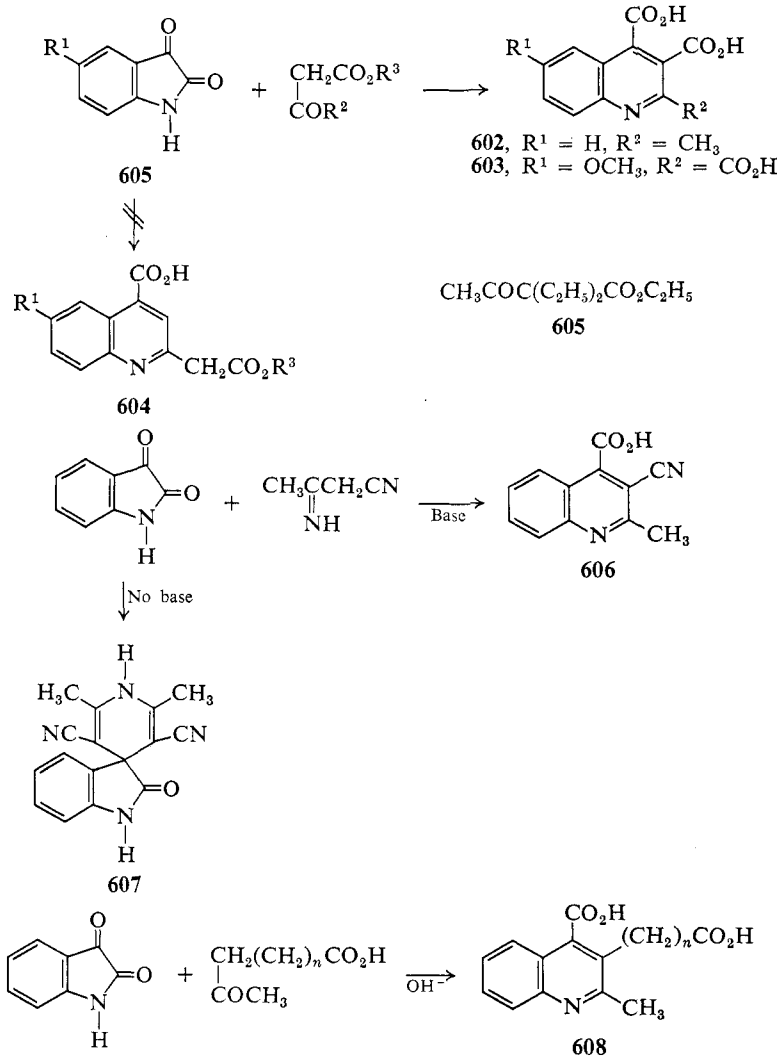
595, $R^1 = R^2 = H$
596, $R^1, R^2 = -[CH_2]_5-$
597, $R^1 = H, R^2 = C_6H_5$
598, $R^1, R^2 = OCC_6H_4CO$
599, $R^1 = H, R^2 = NHCOC_6H_5$

A variety of usefully substituted quinoline-4-carboxylic acids can be produced by using keto-acids or keto-esters in the Pfitzinger synthesis. Pyruvic acids[612, 680-686] and substituted pyruvic acids[530, 687] gave quinoline-2,4-dicarboxylic acids (except in the case, previously noted, of halopyruvic acids, p. 202). Thus phenylpyruvic acid gave 3-phenylquinoline-2,4-dicarboxylic acid (**601**);[530] the same compound was obtained from the oxazolone (**600**) which is a masked pyruvic acid.[688]



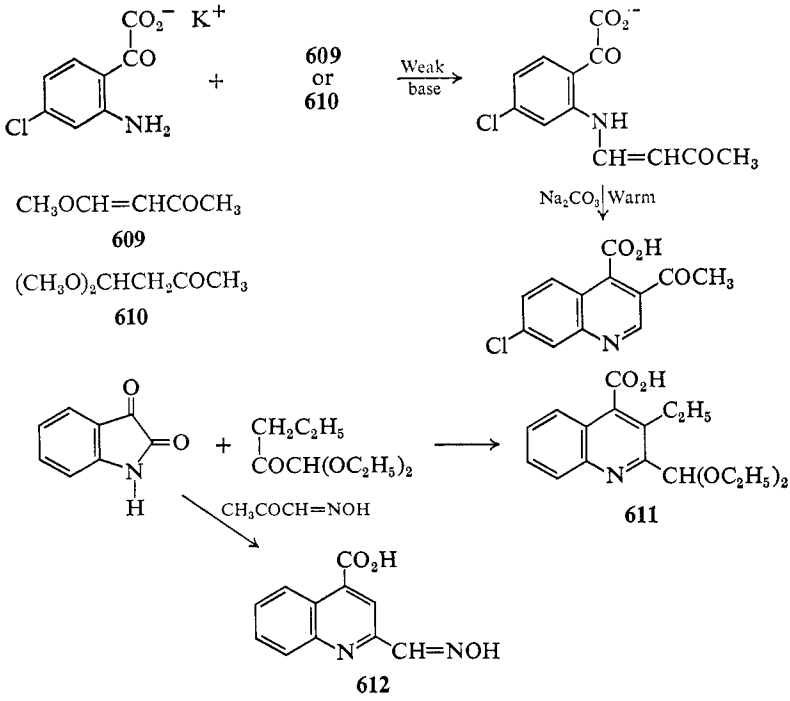
600 601

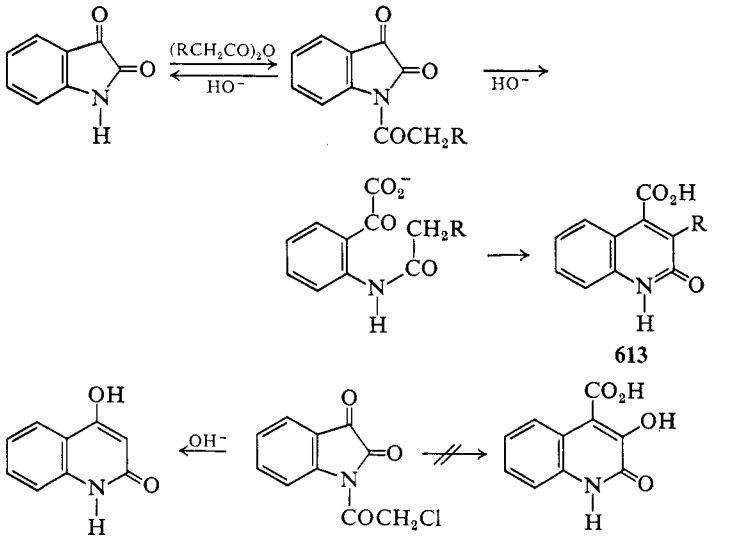
When a β-keto-acid[689] or -ester[685, 689] was used in the Pfitzinger synthesis, the product was a quinoline-3,4-dicarboxylic acid (**602**); with oxaloacetate the product was quinoline-2,3,4-tricarboxylic acid (**603**).[680] In view of the great reactivity of the methylene group flanked by ketone and carboxylate groups, it is not surprising that none of the isomeric product (**604**) was formed when β-keto-esters were used; an attempt to force the reaction in this direction by the use of a dialkylacetoacetate (**605**) failed;[689] however, it must be noted that the keto-ester (**605**) is as sterically obstructed as methyl *tert*-butyl ketone which also fails to undergo the Pfitzinger condensation.[259] The "dinitriles" are masked β-keto-nitriles and therefore give 3-cyanoquinoline-4-carboxylic acids such as (**606**);[548, 690] in this case, if the medium is not basic, condensation can occur with the intact isatin, to give a spiro-compound (**607**). Laevulic acids[689, 691, 692] and keto-acids with more than two methylene groups between the ketone and the carboxyl function[693] gave acids of type (**608**).



The synthesis of 2-substituted 3-acyl(or 3-aroyl)quinoline-4-carboxylic acids from 1,3-diketones has been mentioned on p. 199.[636] Under similar mildly basic conditions methoxyvinyl ketones (**609**) or the acetals (**610**) of β-keto-aldehydes gave 3-acyl (or 3-aroyl)quinoline-4-carboxylic acids without a substituent in position 2.[613, 621] The acetals of β-keto-aldehydes gave acetals of quinoline-2-aldehydes, such as (**611**);[694] the oxime of pyruvaldehyde was reported by Pfitzinger to give the oxime (**612**).[531]

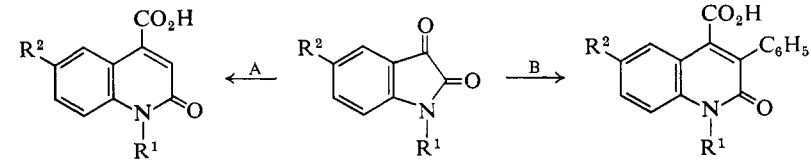
In a combination of Camps' and Pfitzinger's syntheses, an acylated isatin can be treated with base, whereupon it undergoes ring-opening and subsequent intramolecular cyclization to give a 2-quinolone-4-carboxylic acid (**613**). An alternative approach is to condense isatin with a carboxylic acid or a derivative having an active methylene group. The *N*-acylisatins have usually been prepared by the use of


609
or
610
Weak base
Na_2CO_3 | Warm
$CH_3OCH=CHCOCH_3$
609
$(CH_3O)_2CHCH_2COCH_3$
610
611
$CH_3COCH=NOH$
612


$(RCH_2CO)_2O$
HO^-
613
OH^-
614
615

the appropriate anhydride;[630, 680, 695–700] occasionally the sodium derivative of isatin has been treated with an acid chloride.[701] The base-catalysed conversion into 2-quinolone-4-carboxylic acids has given high yields, although some isatin has usually been recovered owing to hydrolysis of the *N*-acyl group. A curious, and unexplained, anomaly is that chloroacetylisatin (**614**) gave 4-hydroxy-2-quinolone, not the expected quinoline-4-carboxylic acid (**615**).[702]

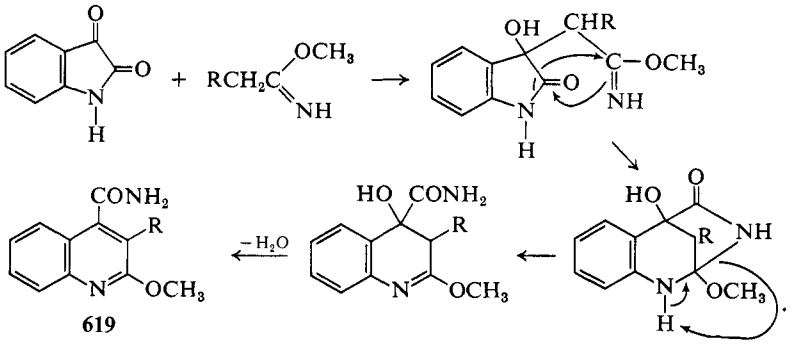
Isatins react with malonic acid in acetic acid, with or without sodium acetate, to give 2-quinolone-4-carboxylic acids;[697, 698, 703–705] an example is the synthesis of compound (**616**).[703] When *N*-substituted isatins were used, the 1-methyl-2-quinolones such as compound (**617**) were obtained.[704] Phenylacetic acid reacted with isatin to give 3-phenyl-2-quinolone-4-carboxylic acid (**618**).[697, 698, 706]



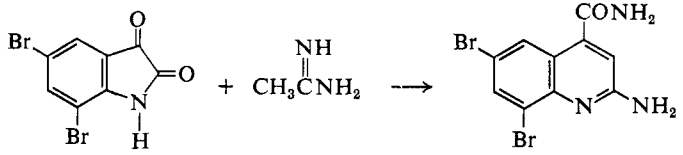
616, R^1 = H, R^2 = I; 100%
617, R^1 = CH_2CH_2CN, R^2 = H

618, R^1 = H, R^2 = I

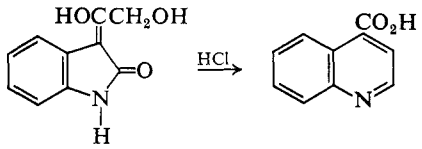
A = $CH_2(CO_2H)_2$ B = $C_6H_5CH_2CO_2H/CH_3O^-$



619



620



621

Ried and Kohlhaas[708, 709] and Arima and his co-workers[710] have reported that imino-ethers reacted with isatins to give 2-alkoxyquinoline-4-carboxamides, such as compound (**619**),[708, 709] and that amidines gave 2-aminoquinoline-4-carboxamides,

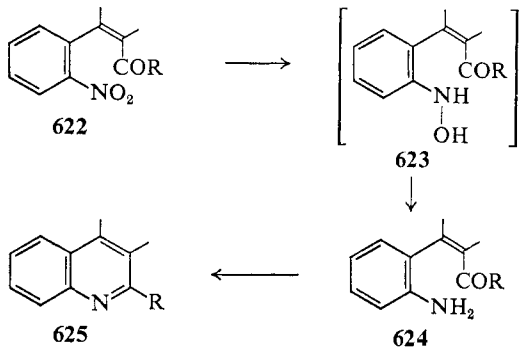
such as compound (**620**).[709] The mechanism suggested for these reactions implies attack on the unopened isatin system, giving an intermediate reminiscent of those considered and discarded for the normal Pfitzinger synthesis. The reaction using imino-ethers failed when R was a nitro, cyano, or ethoxycarbonyl group. In this context Wenkert and Blossey showed that the isatin derivative (**621**), when treated with acid, gave quinoline-4-carboxylic acid.[711]

2. Cyclization of *ortho*-Substituted Nitrobenzenes

It was noted early that the juxtaposition of an aromatic amino-group with an *ortho*-situated three-carbon chain having a terminal carbonyl group would provide a synthesis of 2-substituted quinolines, notably of 2-quinolones. Chiozza,[712] in 1852, reduced *o*-nitrocinnamic acid (mixed with *p*-nitrocinnamic acid, since it was obtained by direct nitration of cinnamic acid) and obtained some 2-quinolone, thus establishing the most popular route to the necessary *o*-amino-cinnamic or -hydrocinnamic acid derivatives. It has since been shown that an *ortho*-placed nitro-group can take part in a quinoline synthesis either by reduction or by direct cyclization; these two processes will be dealt with successively.

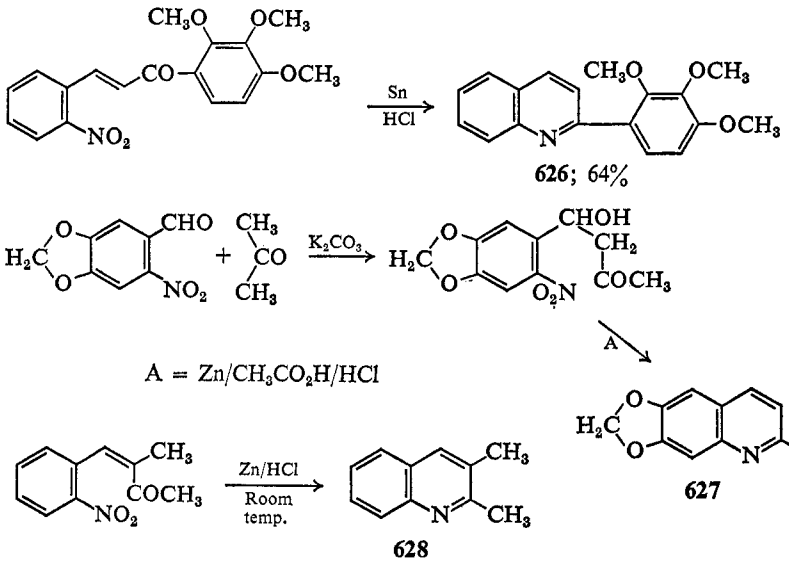
A. Reduction Procedures

The generalized scheme for the production of quinolines by reduction of *o*-nitrostyrene derivatives is shown (**622**) → (**625**). The hydroxylamine (**623**) has often been

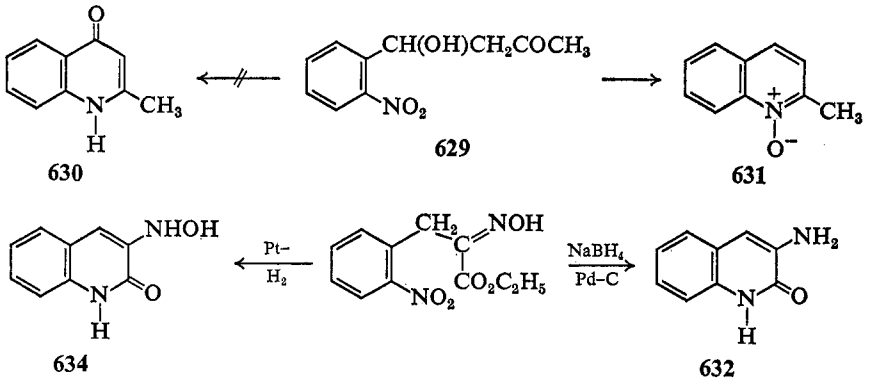


suggested as intermediate but rarely isolated. The starting materials have been aldehydes (R = H), ketones (R = alkyl or aryl), acids or esters (R = OH or OR′); the products are then respectively unsubstituted at position 2, 2-alkyl- or 2-aryl-quinolines, or 2-quinolones. The simplest possible case where *o*-nitrocinnamaldehyde was reduced to give quinoline was reported by Baeyer in 1883;[713] a number of *o*-nitrostyryl ketones have been reduced to give 2-alkyl-, or, occasionally, 2,3-dialkyl-quinolines, as exemplified by the syntheses of compounds (**626**).[714] (**627**),[715] and (**628**).[716]

The synthesis of compound (**627**) illustrates one approach to the preparation of a suitable side chain (by aldol condensation from *o*-nitrobenzaldehyde) and also that reduction of the styrene precursor (the aldol) can be achieved under acid conditions. The alternative approach to an *o*-nitrostyrene, by nitration of a styrene derivative,

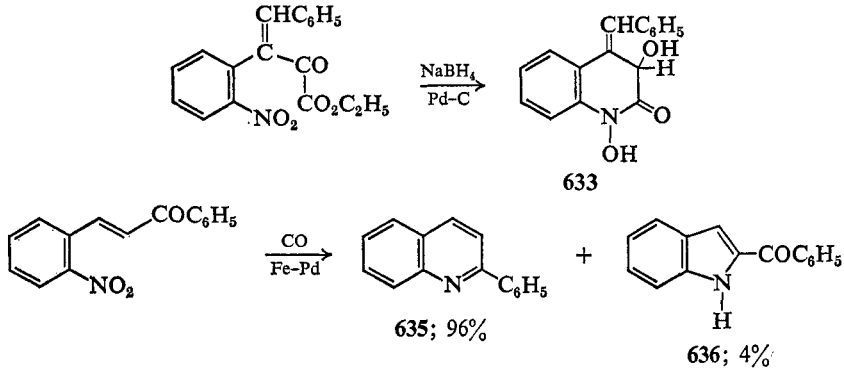


is only efficient if strongly directing groups are present; if the benzene ring is unsubstituted a mixture of *o*- and *p*-nitrostyrene is obtained. Reduction of the nitro-group has been performed with zinc and various mixtures of hydrochloric and acetic acids,[715-718] tin[714] or stannous chloride[719-723] and hydrochloric acid, sodium in ethanol,[718] iron and acid,[724, 725] ferrous sulphate and ammonia,[718, 726] sodium borohydride and palladium charcoal,[726, 727] and catalytically with nickel or palladium.[723] Catalytic reduction with platinum as catalyst has given tetrahydroquinolines.[723] An early report that reduction of the aldol (**629**), using zinc and acetic acid, gave 2-methyl-4-quinolone[728] (**630**) was corrected; the abnormal product was the N-oxide

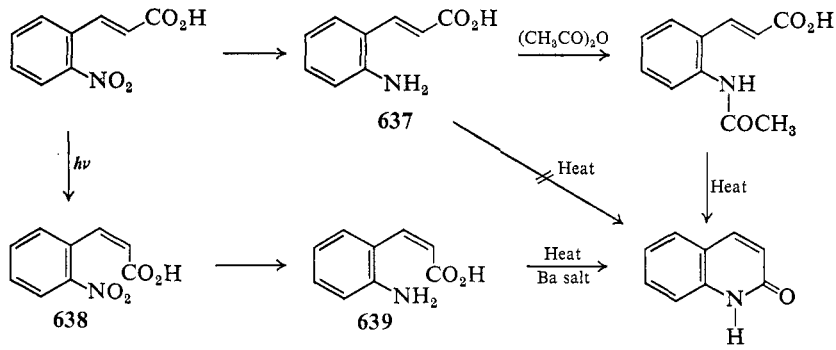


(**631**).[729] Reduction by borohydride is solvent-dependent, giving 2-quinolones in methanol, but in dioxan gives mixtures containing 2-quinolones and some 3,4-dihydro-2-quinolones.[726] Some substituted 2-quinolones, notably the 3-amino-2-quinolone (**632**) and the benzylidene derivative (**633**), have been obtained by reduction with borohydride and palladized charcoal of the *o*-nitrophenylpyruvates

shown;[727] it was suggested that catalytic reduction of the oxime gave the 3-(hydroxyamino)-2-quinolone (**634**). A method of reduction reported to give mainly 2-phenylquinoline (**635**), using a high pressure of carbon monoxide with iron and palladium catalysts, gave as a by-product 2-benzoylindole (**636**).[730]

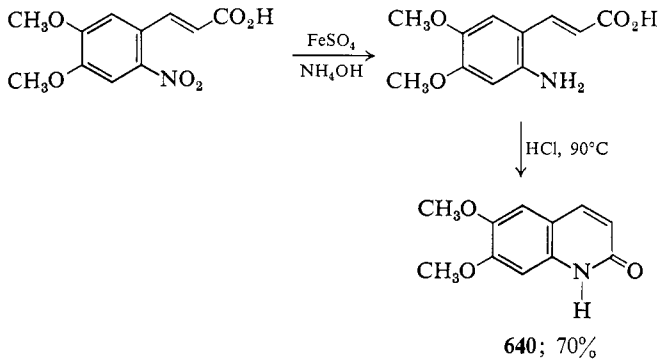


Most reductive cyclizations of *o*-nitrostyryl compounds have involved use of cinnamic acid derivatives, generally giving 2-quinolones. The originator of the synthesis, Chiozza, obtained 2-quinolone from *o*-nitrocinnamic acid by using ammonium sulphide.[712] Baeyer and Jackson[731] used tin and hydrochloric acid as the reducing agent and were able to isolate the *o*-aminocinnamic acid (**637**); they showed that this amino-acid decomposed rather than cyclized when heated, although the *N*-acetylamine could be cyclized. With a clearer view of the preferred *trans*-geometry about the double bond it is obvious why the intermediate (**637**) could be cyclized in high yield by heating it in a dilute acid solution or as a salt,[732] since this provides the opportunity for the necessary *trans–cis*-isomerism. In an early use of photochemistry by Stoermer and Heymann,[733] the normal *trans-o*-nitrocinnamic acid was converted



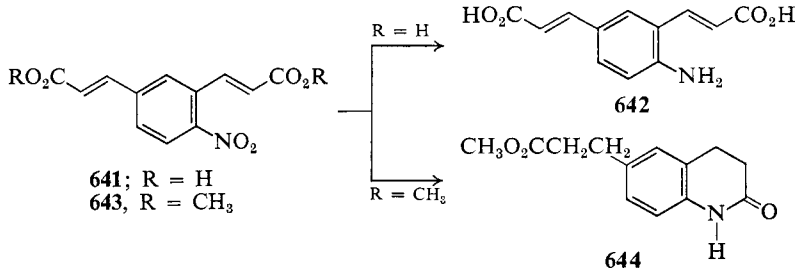
into the *cis*-cinnamic acid (**638**) and then reduced by ferrous sulphate and ammonia to the *cis-o*-aminocinnamic acid (**639**), and this was cyclized by heating the barium salt.

In a more common procedure the *o*-nitrocinnamic acid was reduced by ferrous sulphate and ammonia, then cyclized in good yield by using boiling hydrochloric acid,[734–737] as exemplified by preparation of the dimethoxy-2-quinolone (**640**).[736]



640; 70%

Catalytic reduction has been used, although under some conditions the dihydro-2-quinolone (or the hydrocinnamic acid) was obtained. Ruggli and Staub reported[738] that the nitro-di(carboxyvinyl) derivative (**641**) could be reduced to the unsaturated amino-acid (**642**), while the ester (**643**) gave the dihydro-2-quinolone (**644**).

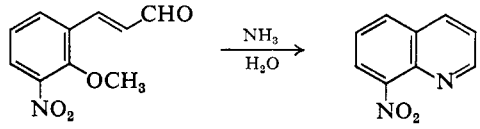


641; R = H
643, R = CH_3

642

644

There are a few cases where the *o*-aminocinnamic acid[739] (or cinnamaldehyde[740]) has been obtained by nucleophilic displacement rather than by reduction of a nitro-group. The methoxynitrocinnamaldehyde (**645**) was sufficiently activated to

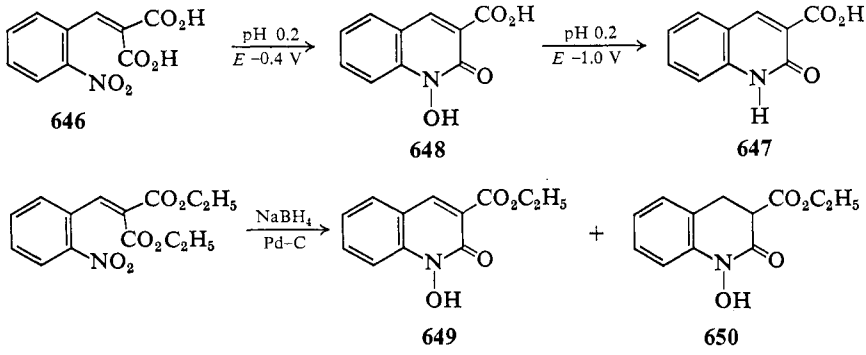


645

give 8-nitro-2-quinoline when heated with ammonia (130–140 °);[739] and the unactivated *o*-chlorocinnamic acid gave with ammonia *o*-aminocinnamic acid, or at higher temperatures 2-quinolone.[740]

The cyclization, after reduction, of *o*-nitrobenzylidene-malonic or -cyanoacetic acids gives 2-quinolone-3-carboxylic acids or 3-substituted 2-aminoquinolines. Reduction of *o*-nitrobenzylidenemalonic acid (**646**) with ferrous sulphate and ammonia gave 2-quinolone-3-carboxylic acid (**647**);[741] on controlled electrolytic reduction an intermediate *N*-hydroxy-2-quinolone (**648**) was isolated, further reduced at increased voltage to the 2-quinolone (**647**).[742] Reduction of diethyl *o*-nitrobenzylidenemalonate by sodium borohydride and palladized charcoal also

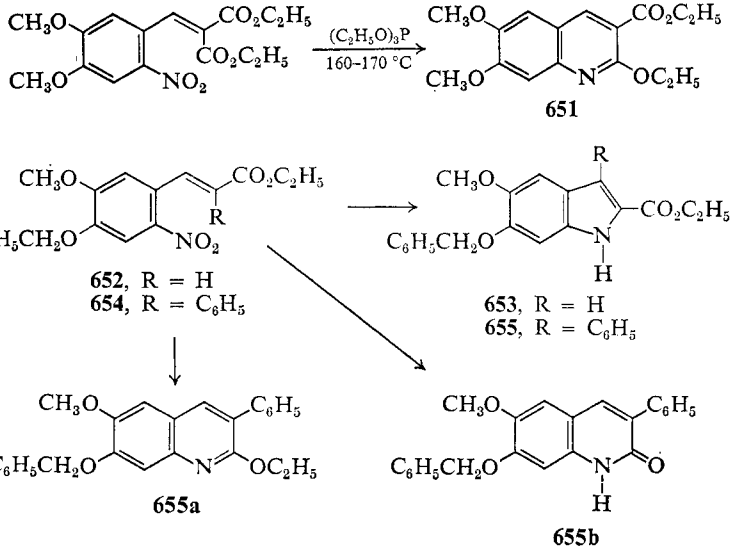
gave an *N*-hydroxy-2-quinolone (**649**) in methanol as solvent, but gave a mixture of compound (**649**) with the dihydro-derivative (**650**) when dioxan was used.[726]



646 **648** **647**

649 **650**

A number of benzylidenemalonates and cinnamates, have been cyclized by deoxygenation of the nitro-group by means of triethyl phosphite.[743-745] Yields of between 40% and 70% were recorded, the products being either 2-ethoxy-compounds, such as compound (**651**), or the 2-quinolones. It was noted that a reaction using the cinnamate (**652**), of established *trans*-geometry, gave not the 2-quinolone but an indole (**653**), a well-known nitrene insertion product. The phenyl-substituted



651

652, R = H
654, R = C_6H_5

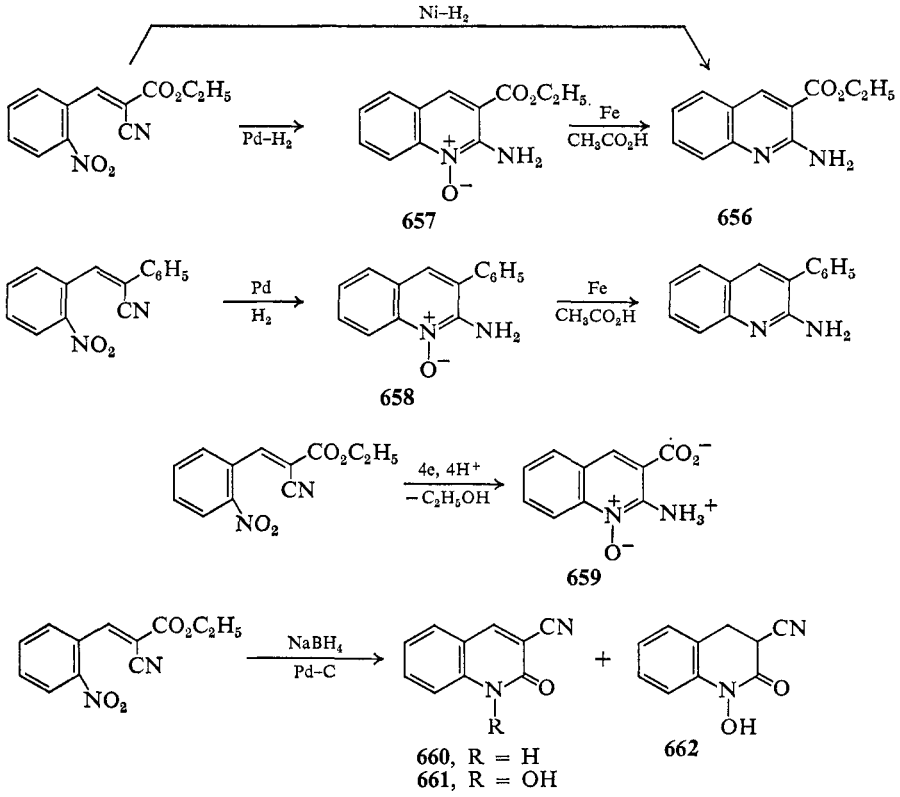
653, R = H
655, R = C_6H_5

655a **655b**

cinnamate (**654**) gave the indole (**655**) and the appropriate 2-ethoxy-3-phenylquinoline (**655a**) and 3-phenyl-2-quinolone (**655b**), presumably reflecting the mixed stereochemistry of the starting material.[746]

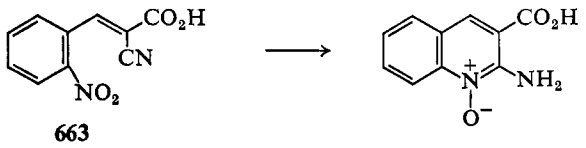
The full variety of products dependent on the *cis*- or *trans*-arrangement around the double bond is reflected in the reported reduction of 2-cyano-2-*o*-nitrobenzylideneacetates. Early reports[747, 748] showed that on catalytic reduction with nickel[747]

cyclization involved the cyano-group, giving the 2-aminoquinoline (**656**); when palladium on kieselguhr[748] was used, the *N*-oxide (**657**) was obtained, further reduced by iron and acetic acid. The *o*-nitrocinnamonitrile similarly gave an *N*-oxide (**658**), which could be further reduced.[748] Electrochemical reduction of the cyanoacetate resulted in loss of ethanol, with formation of the zwitterionic *N*-oxide (**659**).[749] By



contrast, reduction of cyano-*o*-nitrobenzylidene acetate with borohydride and palladium–charcoal resulted in cyclization exclusively to the ethoxycarbonyl group,[726] as does deoxygenation by triethyl phosphite;[750, 751] in the former case the products obtained depend on temperature and the solvent used; reduction in methanol gave, at low temperatures, 3-cyano-2-quinolone (**660**) with some of the *N*-hydroxy-compound (**661**); at 25 °C some dihydro-2-quinolone (**662**) appeared, and it became the sole product in dioxan.[726] Reduction of the cyano-acetic acid (**663**), in contrast, gave 2-aminoquinoline-3-carboxylic acid *N*-oxide in any solvent.[726] Deoxygenation of a series of ethyl cyano-*o*-nitrobenzylidene acetates with triethyl phosphite gave exclusively the 3-cyano-2-ethoxyquinolines (**664**), although the starting materials were said to be *trans*-cinnamates.[750, 751]

Related to these cyclizations is that of 3-(*o*-nitrobenzylidene)pentane-2,4-dione; electrochemical reduction gave the *N*-oxide (**665**), the reaction being said to proceed through the intermediate hydroxylamine (**666**).[749] Reduction of the 2-cyano-2-(nitrobenzylidene)acetanilides (**667**, R = C_6H_5 or *p*-$CH_3C_6H_4$), using zinc and



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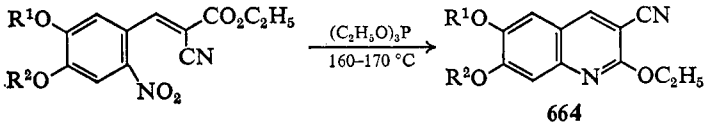

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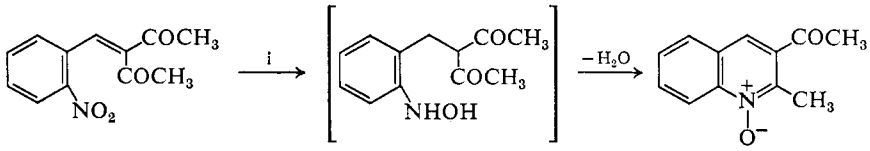
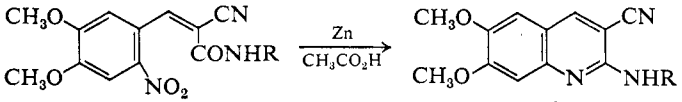


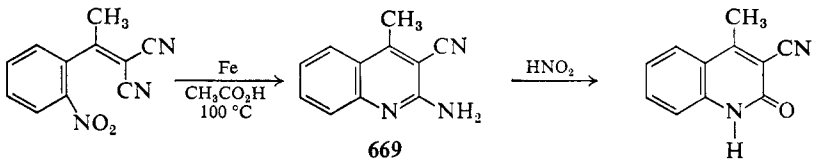
i, 4e, 4H$^+$; pH 0.2; $E-0.4$ V

666 665



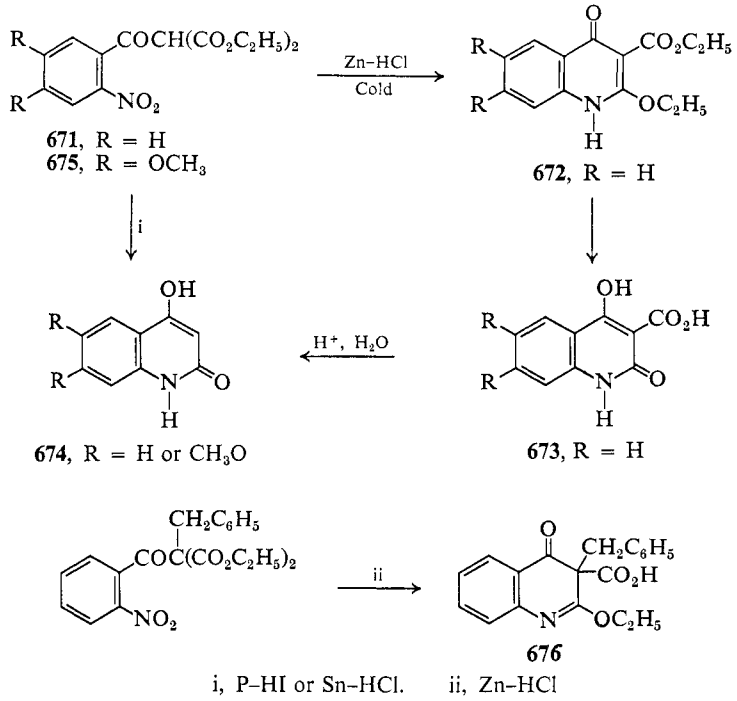
667 668

acetic acid, gave the respective 3-cyanoquinolines (**668**).[752] Reduction of *o*-nitrobenzylidenemalonitriles was again unambiguous, giving 2-amino-3-cyanoquinolines such as compound (**669**).[753] The 2-aminoquinolines were readily converted into 2-quinolones (**670**) on treatment with nitrous acid.

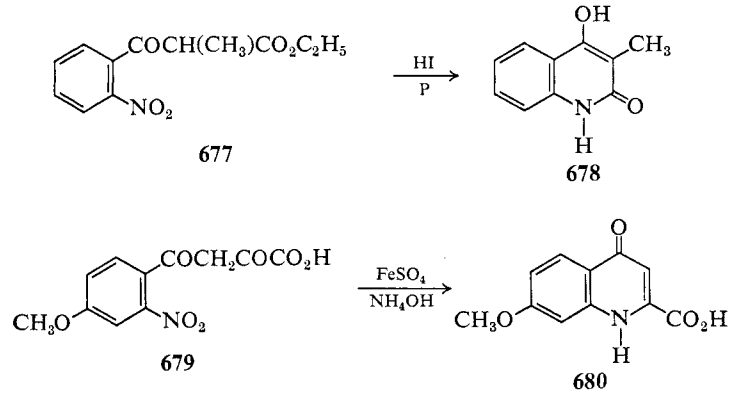


669 670

Another variant of this general synthesis is in the reduction of *o*-nitrobenzoylacetates and related compounds to give 4-hydroxy-2-quinolones. Reaction between *o*-nitrobenzoyl chloride and diethyl sodiomalonate gave the malonate (**671**), which was reductively cyclized by zinc and hydrogen chloride in cold dry alcohol to the 2-ethoxy-4-quinolone (**672**).[754] After reaction at room temperature or above, the product was the carboxylic acid (**673**), which was readily decarboxylated in aqueous acid to the 4-hydroxy-2-quinolone (**674**).[754] Reduction of the malonate (**671**)[755] or of substituted malonates[756] by phosphorus and hydriodic acid gave directly the 4-hydroxy-2-quinolone, as did reduction of some *ortho*-nitrodimethoxybenzoylmalonates, e.g. (**675**), with tin and concentrated hydrochloric acid.[757] Cyclization of a disubstituted malonate is also possible, as shown by the synthesis of the 3,3-disubstituted quinoline (**676**).[754]

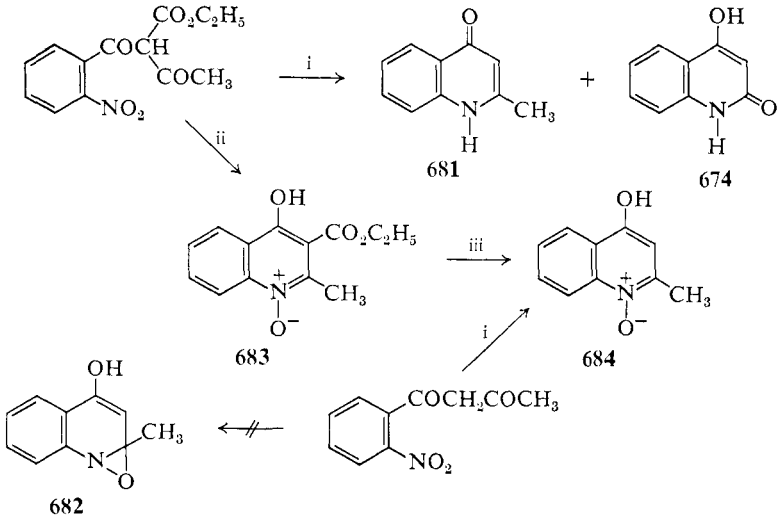


Probably because of the availability of 4-hydroxy-2-quinolones directly from the malonates, there have been few examples of reductive cyclization from the *o*-nitro-derivatives of simple β-diketones or β-keto-esters. Reduction with phosphorus and hydriodic acid of the 2-benzoylpropionate (**677**) gave 4-hydroxy-3-methyl-2-quinolone (**678**),[758] and reduction by ferrous sulphate and ammonia of the benzoyl-



pyruvate (**679**) gave the acid (**680**).[759] Ethyl *o*-aminobenzoylacetate, prepared by a Claisen condensation from methyl anthranilate and ethyl acetate, was said to be unstable, readily cyclizing to 4-hydroxy-2-quinolone (**674**).[760]

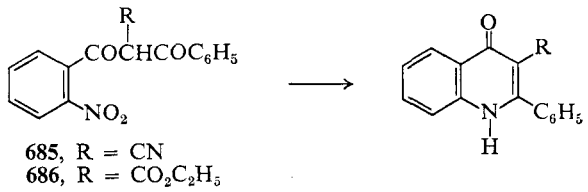
Cyclization of *o*-nitrobenzoyl-acetoacetates or -benzoylacetates could give 2-quinolones, but in practice the more reactive ketonic carbonyl group takes part in the cyclization, giving 2-alkyl- or 2-aryl-4-quinolones. Gabriel and Gerhard[758] reported that reduction of ethyl *o*-nitrobenzoylacetoacetate by phosphorus and hydriodic acid gave 2-methyl-4-quinolone (**681**) with some 4-hydroxy-2-quinolone (**674**); similar reduction of *o*-nitrobenzoylacetone was reported to give compound



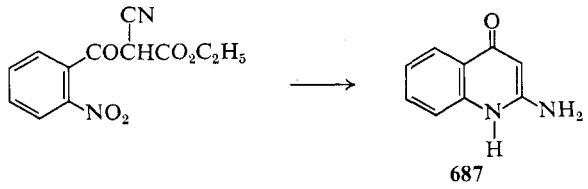
i, HI–P. ii, $SnCl_2$–HCl. iii, H^+, H_2O, $-CO_2$

(**682**);[758] it was, however, subsequently shown[761] that reduction of the acetoacetate by stannous chloride and dry hydrogen chloride in acetic acid gave the *N*-oxide (**683**), which could be hydrolysed and decarboxylated to give the *N*-oxide (**684**), identical with Gabriel and Gerhard's compound reputedly (**682**).

Reduction of the *o*-nitrobenzoyl(benzoylacetic acid) derivatives (**685**) and (**686**) gave 2-phenyl-4-quinolones,[762] but similar reduction of ethyl 2-cyano-2-(*o*-nitrobenzoyl)-acetate gave 2-amino-4-quinolone (**687**).[755]

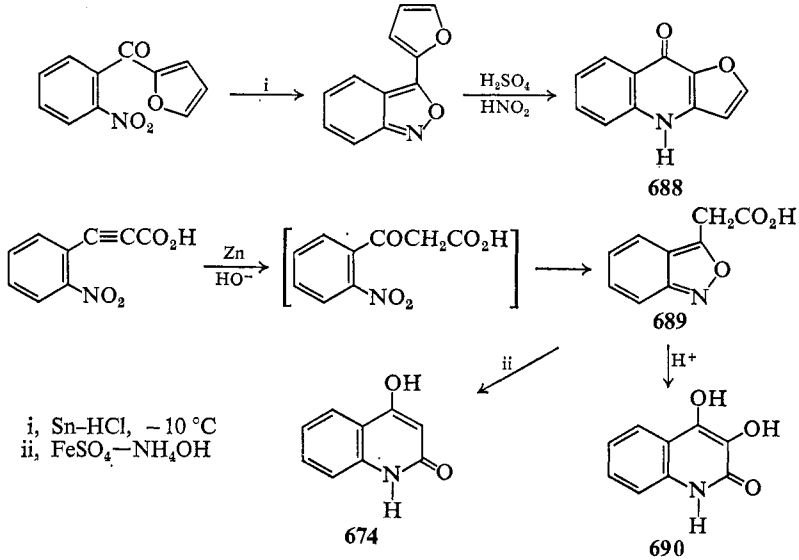


685, R = CN
686, R = $CO_2C_2H_5$



687

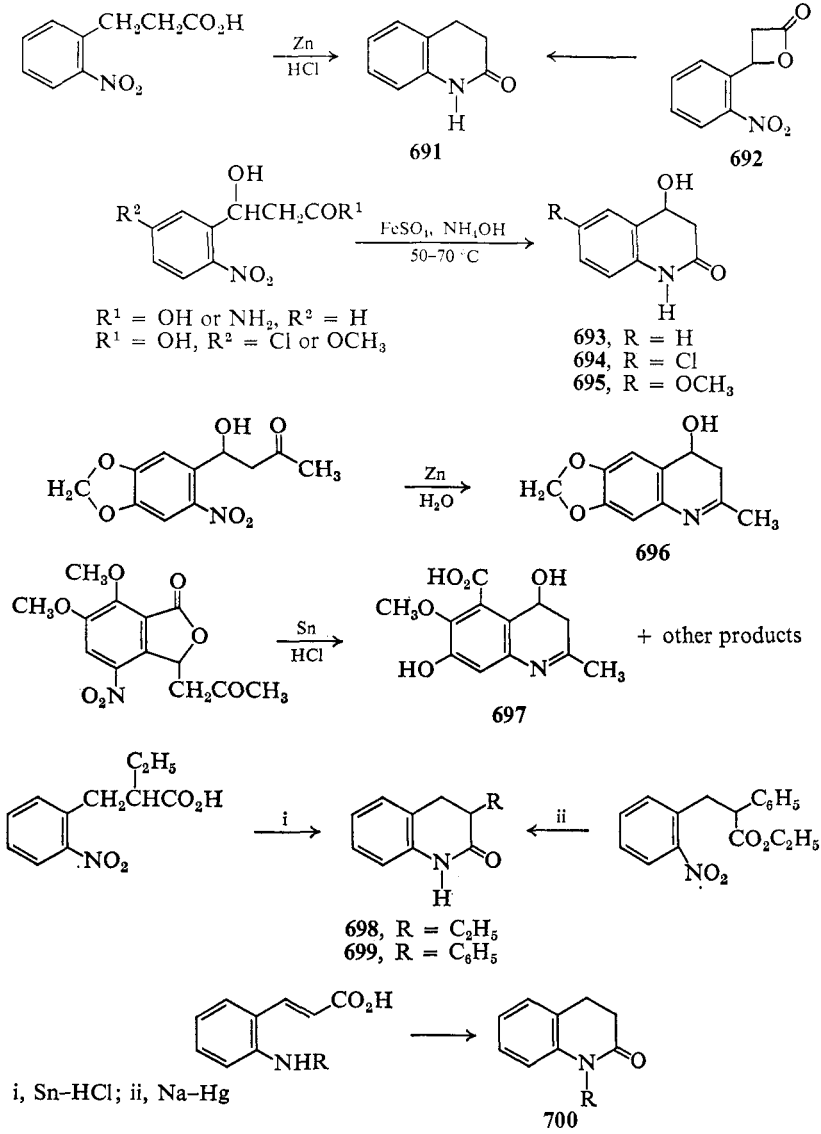
When a carbonyl group is in an *ortho*-relationship with the nitro-group, reduction can lead to anthranils (2,1-benzisoxazoles). Examples of this are provided by the reduction of *o*-nitrobenzoylfuran, giving after further treatment the furoquinolone (**688**),[763] and by the reduction of *o*-nitrophenylpropiolic acid with zinc and alkali (in which the probable intermediate was *o*-nitrobenzoylacetic acid), giving the anthranil



(**689**).[764] The anthranil (**689**) was converted by further treatment either into 4-hydroxy-2-quinolone (**674**) or into 3,4-dihydroxy-2-quinolone (**690**). By using preformed *o*-aminophenylpropiolic acid Baeyer and Bloehm[765] obtained 4-hydroxy-, 4-chloro-, or 4-bromo-2-quinolones, with sulphuric, hydrochloric, or hydrobromic acids, respectively, as cyclizing agents; these observations seem to confirm the view that the cyclization to anthranils occurs from the nitro-compounds or some intermediate between the nitro- and the amino-compounds.

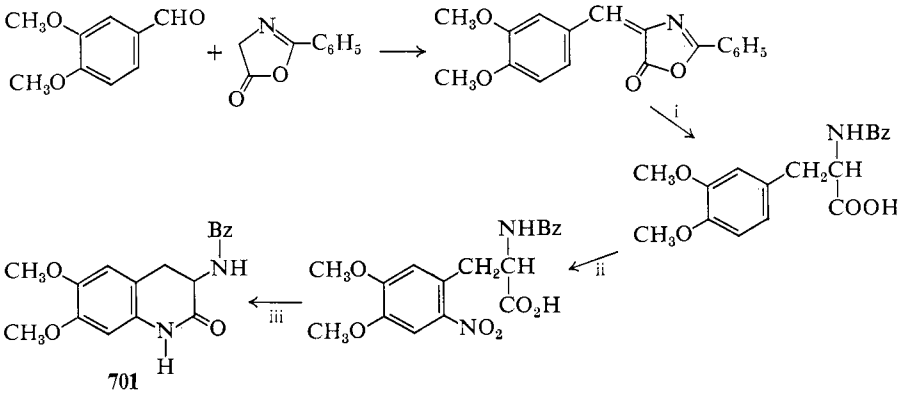
The cyclization of *o*-aminophenylpropionic acid derivatives gives 3,4-dihydro-2-quinolones. Baeyer synthesized 3,4-dihydro-2-quinolone (**691**) by this method in 1879.[766] Einhorn obtained the same compound from the β-lactone (**692**),[767] and, more surprisingly (see p. 207) 3,4-dihydro-4-hydroxy-2-quinolone (**693**) from 3-hydroxy-3-(*o*-nitrophenyl)propionic acid or its amide.[768] Other examples, (**694**) and (**695**), were subsequently reported.[769] Even more surprising was the reported isolation of the 1,2-dihydro-4-hydroxyquinoline (**696**) by reduction of a 4-(*o*-nitrophenyl)butan-2-one;[770] a similar, if superficially more complex, case was the synthesis of the compound (**697**).[771, 772] Jackson showed[773] that zinc and hydrochloric acid reduced the nitration product from 4-phenylbutan-2-one to 1,2,3,4-tetrahydro-2-methylquinoline.

Catalytic reduction of *o*-nitrophenylpropionic acids[774] or of the esters[734] has been reported; tin and hydrochloric acid were used to produce the 3-ethyl-2-quinolone derivative (**698**).[731] Sodium amalgam has been used to reduce *o*-nitrocinnamic acids to the dihydro-2-quinolones such as compound (**699**),[775] but whether the reduction of the double bond occurs before or after cyclization is unknown. By this method *N*-ethyl- and *N*-amino-3,4-dihydro-2-quinolones (**700**, R = C_2H_5 or NH_2) were obtained.[776] A number of 3-amino- and 4-amino-3,4-dihydro-2-quinolones have been



prepared by reduction (using ferrous sulphate and ammonia) of the appropriate aminophenylpropionic acids.[777, 778] A representative sequence leads to the synthesis of a 3-(benzoylamino)quinolone (**701**).[777] The cyclic dimer of glycine condensed with *o*-nitrobenzaldehyde to give a bis derivative (**702**); reduction of this gave 3-amino-3,4-dihydro-2-quinolone (**703**).[779]

Reductive cyclization of *o*-nitrobenzylmalonates with zinc and acetic acid[780] or with zinc and hydrochloric acid[781] gave ethyl dihydro-2-quinolone-3-carboxylates such as compound (**704**). Several groups of workers have investigated the reductive cyclization of diethyl bis-(*o*-nitrobenzyl)malonate to give the spiro-compound



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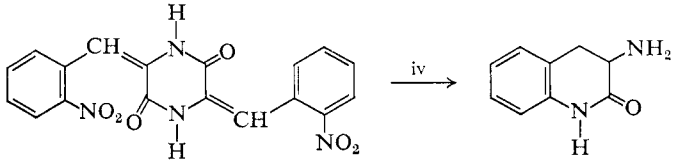
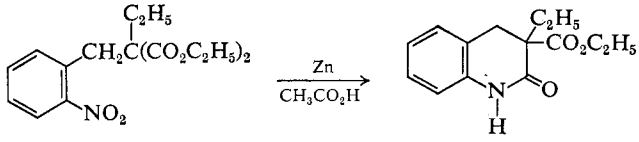


702 703

Bz = COC_6H_5. i, KOH, then reduce. ii, HNO_3.
iii, $FeSO_4$–NH_4OH. iv, HI–P.



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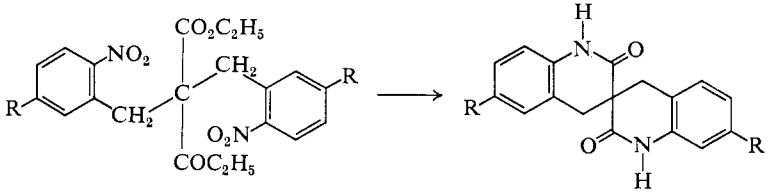
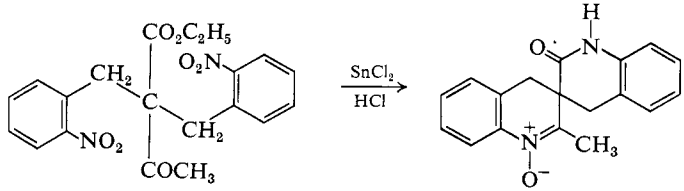


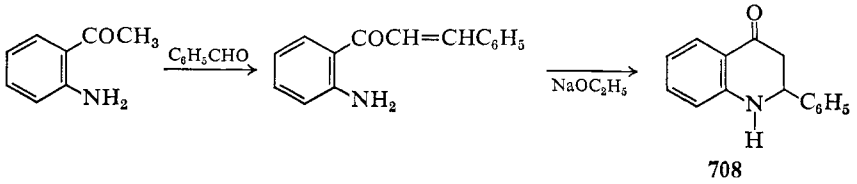
705, R = H
706, R = OH



707

(**705**).[780, 782, 783] Leuchs and Von Katinszky[783] obtained an 80% yield of the pure spiran by reducing the malonate with zinc and alcoholic hydrogen chloride at 0 °C; under other conditions they reported many side-products, including the phenol (**706**), which was formed by an aminophenol rearrangement of the intermediate hydroxylamine. Ethyl bis(*o*-nitrobenzyl)acetoacetate gave, on reduction with stannous chloride and hydrochloric acid, the spiro-compound (**707**).[784]

The *o*-amino group has been introduced by other methods than by reduction of a nitro-group. Copper and ammonia solution at 140–160° converted 3-(*o*-chlorophenyl)propionic acid into dihydro-2-quinolone (**691**).[739] Three examples of cyclization between an amino-group and an *ortho*-placed chain containing a double bond differ from the previous reactions. An intramolecular β-addition gave 2,3-dihydro-2-phenyl-4-quinolone (**708**),[785] and a cyclization initiated by a mercury salt converted *o*-(but-1-enyl)-*N*-methylaniline into a mixture of the tetrahydroquinoline (**709**) and



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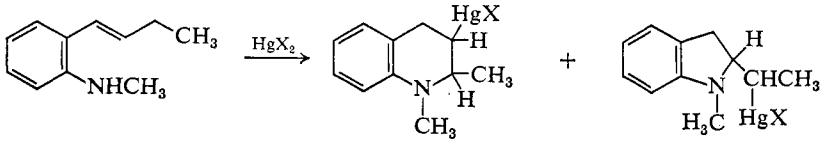
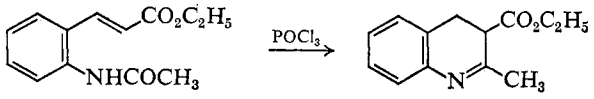


709 **710**



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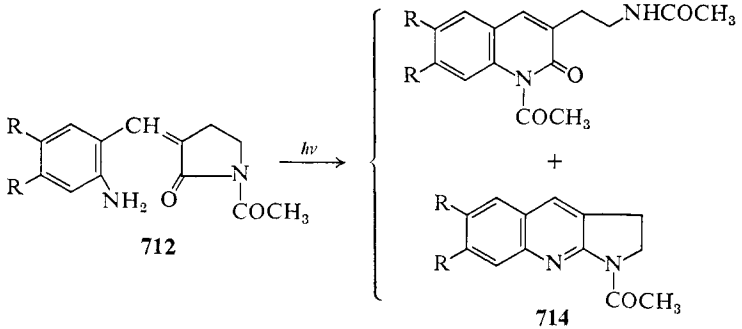
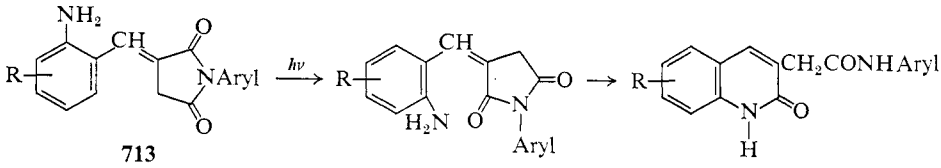


712 **714**

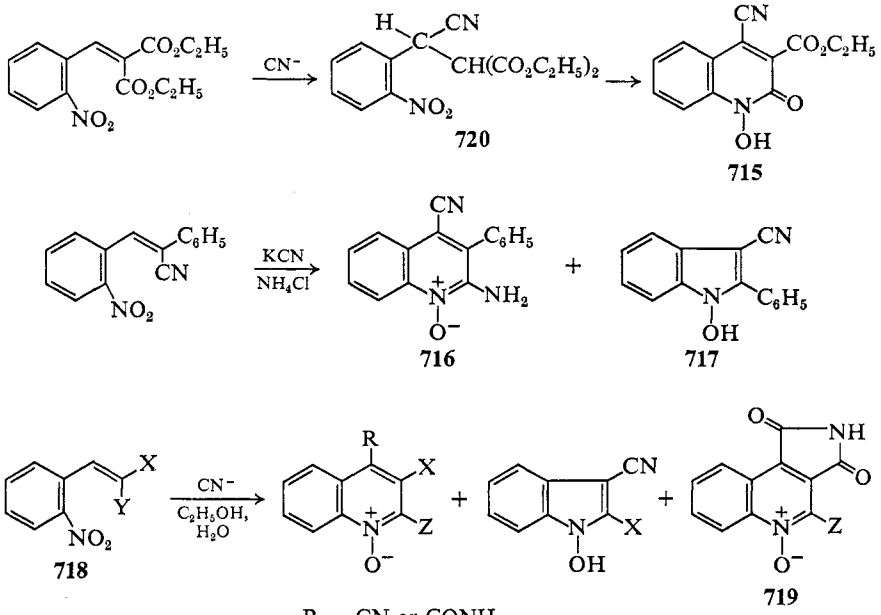


713

the indoline (**710**).[786] A similar principle was involved in the use of phosphoryl chloride to cyclize ethyl 2-acetamidocinnamate (**711**) by intramolecular electrophilic addition;[787] simple *o*-acetamidostyrenes have been similarly cyclized to give 2-substituted or 2,3-disubstituted quinolines.[788, 789] The photochemical cyclizations of *o*-aminobenzylidenepyrrolidones (**712**) and of *o*-aminobenzylidenepyrrolidinediones (**713**) have given excellent yields of 2-quinolones, in the former case mixed with dihydropyrroloquinolines (**714**).[790, 791] The *N*-acetyl group was found to be essential for cyclization in the case of compounds (**712**).[790]

B. Direct Cyclizations Using the Nitro-group

Loudon and his co-workers, in 1960, reported that *o*-nitrocinnamic acid derivatives could be cyclized etiher by cyanide ions[792, 793] or by acid (hydrogen chloride or hydrogen bromide).[794, 795] When cyanide was used, the quinolines, for example compounds (**715**)[792] and (**716**),[793] possessed a 4-cyano-substituent; indoles such as



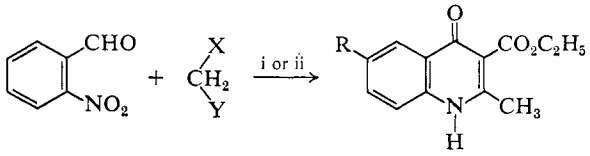
R = CN or $CONH_2$

compound (**717**)[793] were also formed. The balance between quinoline and indole formation was carefully studied by Sword,[796] for the general case (**718**). Quinoline formation was favoured by strongly electron-withdrawing X and Y groups in the starting material, and also by strong base; in a given case the use of sodium carbonate reduced the quinoline : indole ratio from 3 : 1 to 2 : 1. Occasionally, an imide of type (**719**) was isolated.

The mechanism of the cyanide-induced cyclization, which presumably proceeds through intermediates of type (**720**), has been discussed in a review[797] without firm conclusions, though it was suggested that internal oxidation–reduction was involved, with hydrogen-transfer from the side chain and formation of an intermediate nitroso-compound.

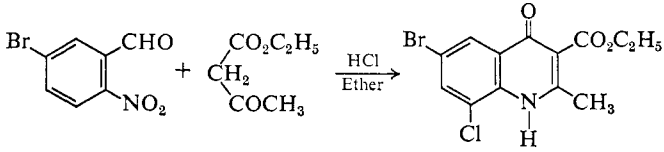
The acid-catalysed cyclizations were reported to occur when *o*-nitrobenzaldehyde was treated with a compound having an active methylene group, in the presence of

hydrogen chloride or hydrogen bromide in ether. Ethyl acetoacetate, acetylacetone, and diethyl acetonedicarboxylate were successfully cyclized; deoxybenzoin and ethyl benzoylacetate failed to give cyclic products.[794] The most interesting point was the involvement of the acid; for example, Loudon and Wellings[794] showed that the products obtained when hydrogen chloride was used possessed a 6-chloro-substituent, as in compound (**721**). Subsequently, Loudon and Tennant[795] obtained a chlorine-free product (**722**) from *o*-nitrobenzaldehyde and ethyl acetoacetate by using hydrogen chloride and quinol. They also noted that even without quinol hydrogen bromide gave halogen-free products such as compound (**722**), but that 5-bromo-2-nitrobenzaldehyde, ethyl acetoacetate, and hydrogen chloride gave the 8-chloroquinolone (**723**).



721

i, HCl-ether; ii, HCl-quinol or HBr-ether. i → **721**, R = Cl
ii → **721**, R = H



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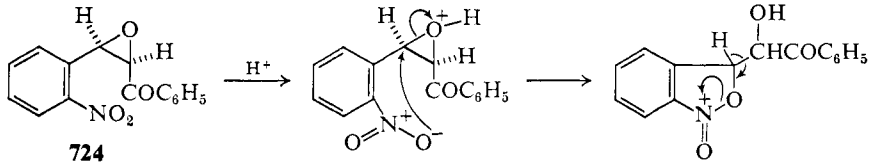

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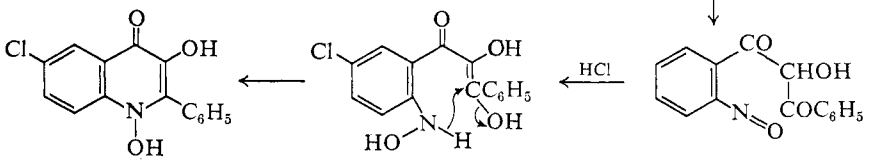

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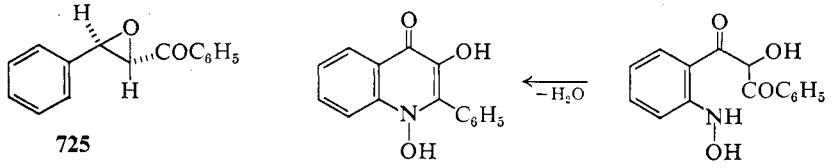

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727

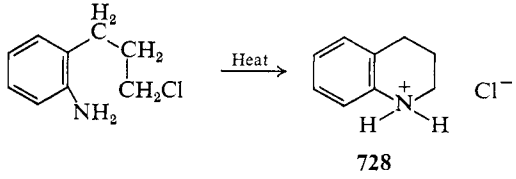
An early suggestion[797] that a carbonium ion intermediate was involved, and that quinol or hydrogen bromide can act as reducing agents whereas hydrogen chloride supplies electrons in the form of chloride ions, has been further elaborated after a study of the cyclization of the oxides formed from the intermediate benzylidene derivatives.[798-800] Spence and Tennant[798, 800] used both stereoisomers (**724**) and (**725**) of the ethylene oxide to investigate steric effects on the reaction and were able to obtain a 90% yield of cyclized material by using the *cis*-isomer (**724**). The suggested mechanism involved positively charged intermediates and led to the 1-hydroxy-4-quinolone (**726**) or the unchlorinated compound (**727**).

3. Miscellaneous Syntheses Involving Ring Closure between *ortho*-Substituents

Grouped in this section are a number of procedures in which the 1,2- or 3,4-bond of the quinoline is formed by some reaction from an *ortho*-disubstituted benzene derivative; excluded from these are the cyclizations of *o*-aminocinnamic acid derivatives which were grouped for convenience with the *o*-nitrocinnamic acid cyclizations (p. 209).

A. Formation of the 1,2-*Bond*

The simplest reaction in this class is the reported cyclization of *o*-(3-chloropropyl)-aniline[801] to 1,2,3,4-tetrahydroquinoline hydrochloride (**728**). Although other routes to the starting material may be available it should be noted that von Braun obtained



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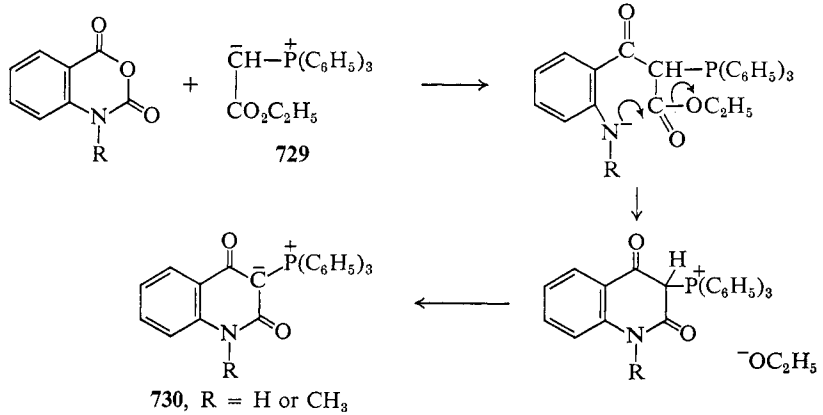
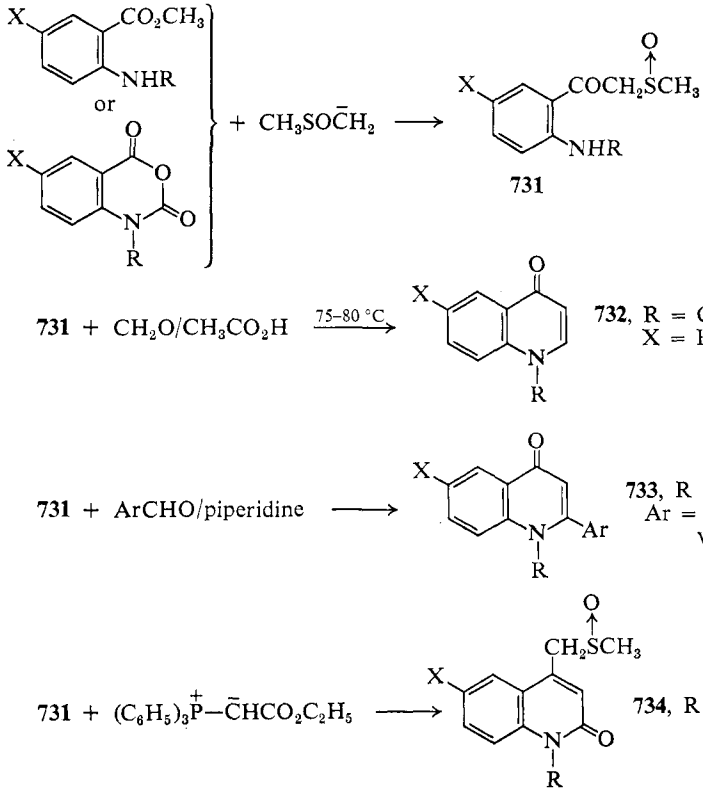


the chloride by degradation of *N*-benzoyltetrahydroquinoline. In a more complex reaction, the phosphonium ylide (**729**) was shown to react with isatoic anhydrides to give the triphenyl-3-quinolylphosphonium ylide (**730**); the intermediate ylide must

cyclize by formation of the 1,2-bond.[802] The ylide (**730**) was found to be too stable for further elaboration at position 3.

In a synthesis that may involve 1,2- or 2,3-bond formation as the final step, the sulphoxide (**731**) was treated with formaldehyde or aromatic aldehydes with acid- or base-catalysis to give 2-quinolones (**732**) and (**733**).[803] The sulphoxides (**731**) were



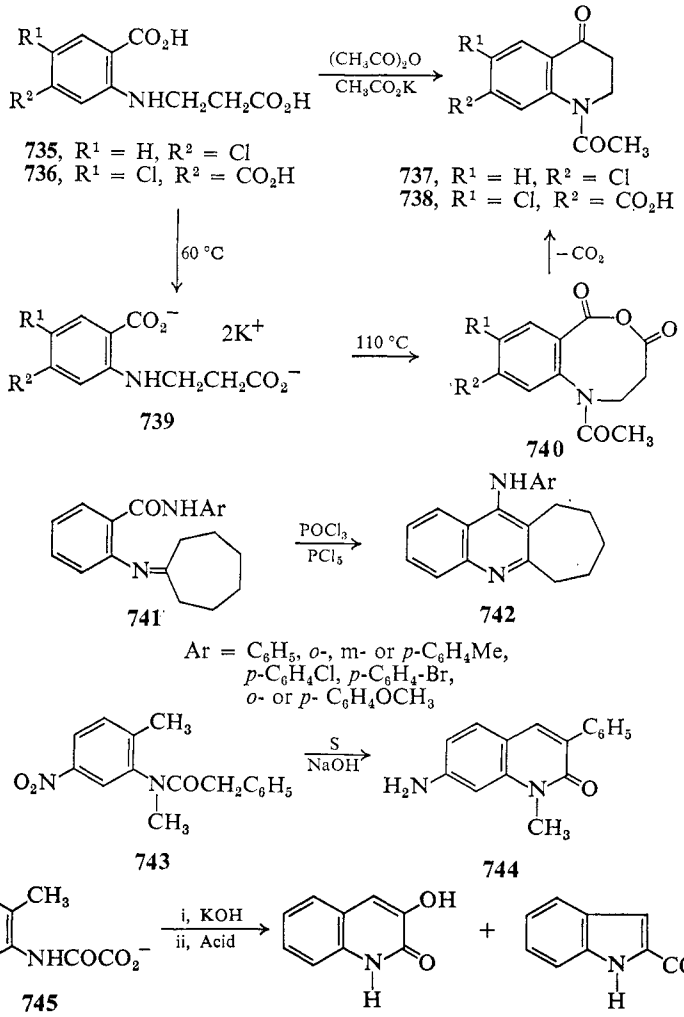
obtained from methyl anthranilates or from isatoic anhydrides. The two syntheses were combined in the preparation of the 2-quinolone (**734**) from the sulphoxide (**731**), R = H, X = Cl) which was treated with the ethoxycarbonylmethylphosphonium ylide.[804]

B. Formation of the 3,4-*Bond*

A number of syntheses of quinolines involve the formation of a 3,4-bond. The Camps synthesis can involve condensation between a carbonyl group and an adjacent activated methylene group; the syntheses described here differ in the type of activation or, in the later examples, involve unsaturated groups *ortho* to the carbonyl function.

The dicarboxylic cids (**735**) and (**736**) have been cyclized by boiling them with acetic anhydride and potassium acetate to give the ketones (**737**) and (**738**).[805, 806] It was established by using lower temperatures that the reaction goes through the

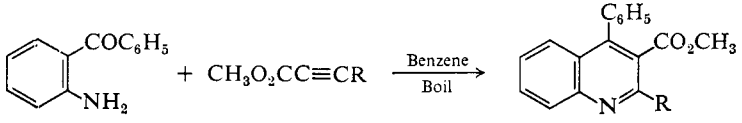
salt (**739**) and the oxazocine (**740**).[805] The amides (**741**) were cyclized by phosphoryl chloride and phosphorus pentachloride to give the 4-arylaminoquinolines (**742**).[807] Although the activation of the methylene group is small in compound (**741**), there is



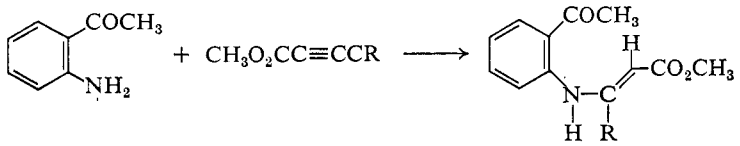
no obvious activation of the groups in compounds of type (**743**), which were reported to cyclize when treated with sulphur and sodium hydroxide, giving 2-quinolones such as compound (**744**) in which the nitro-group has been reduced.[808] Madelung reported that a little 3-hydroxy-2-quinolone was formed when the oxamide salt (**745**) was treated with base; the major product was indole-2-carboxylic acid.[809]

A number of related syntheses proceed from an *o*-aminophenylketone and an acetylene, with an intermediate of aminoacrylate type. In the simplest cases, *o*-aminobenzophenones reacted with acetylenedicarboxylates[810] or methyl propiolates[811] to give quinoline-2,3-dicarboxylates such as compound (**746**) or quinoline-3-carboxylates (**747**), respectively. In both cases, the use of *o*-aminoacetophenone

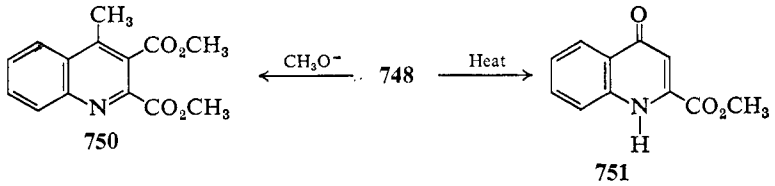
allowed the isolation of the intermediate aminoacrylate (**748**) or (**749**); the former intermediate could be cyclized to the dicarboxylate (**750**) by sodium methoxide but gave a 4-quinolone (**751**) on pyrolysis.[810] A related synthesis, although not strictly analogous, was used to convert methyl *o*-aminophenylacetate into the 3-hydroxyquinoline-2,4-dicarboxylate (**752**).[812]



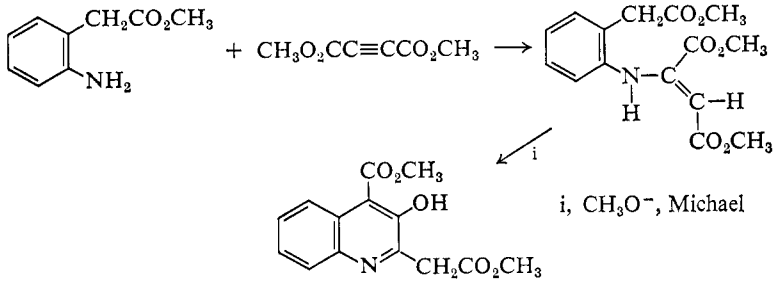
746, R = CO_2CH_3
747, R = H



748, R = CO_2CH_3
749, R = H



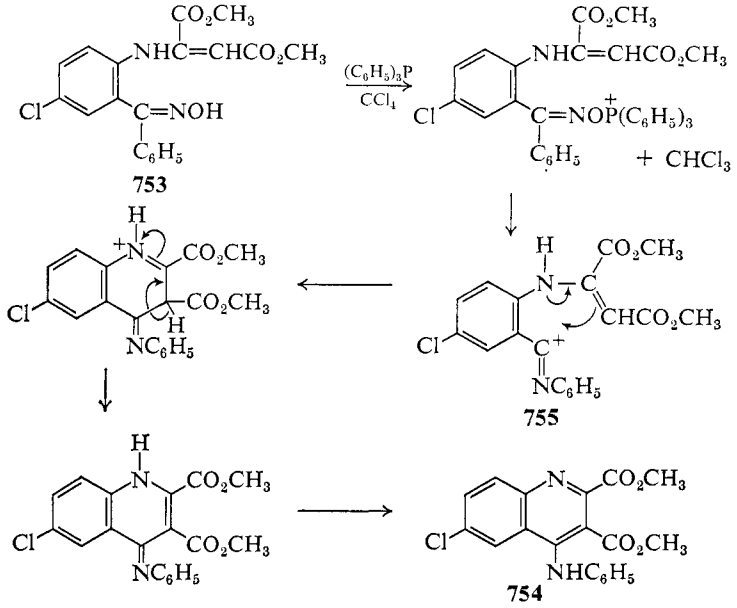
750 **751**



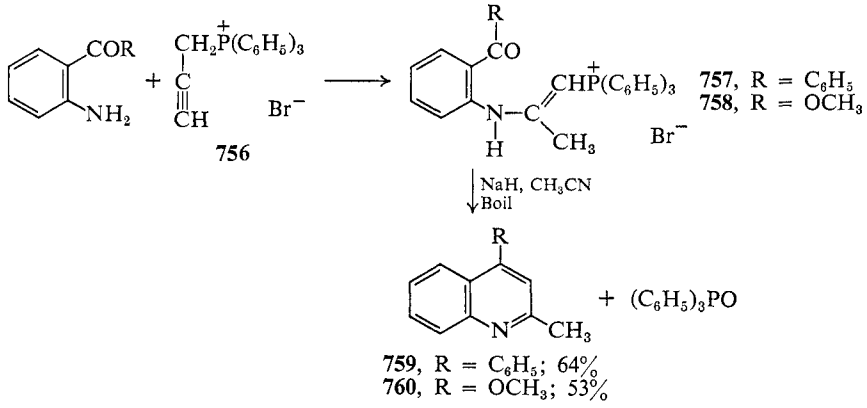
752

Cyclization of the ketoxime (**753**), using triphenylphosphine and carbon tetrachloride, gave the 4-anilinoquinoline-2,3-dicarboxylate (**754**).[813] The mechanism proposed involved a "Beckmann" intermediate (**755**), and Beckmann rearrangement products were isolated. The acetylenic phosphonium salt (**756**) reacted with *o*-aminobenzophenone or methyl anthranilate to give the phosphonium salts (**757**) and (**758**);[814] treatment of these with sodium hydride gave the quinolines (**759**) and (**760**). Ethyl anthranilate reacted with ynamines to give 2-dialkylamino-4-quinolones (**761**) and (**762**), probably via a ketene aminal (**763**).[815] Acetanthranils reacted with enamines to give quinoline-8-carboxylates (**764**),[816] but with ynamines to give predominantly 4-(dialkylamino)quinolines (**765**);[817] a minor product in the ynamine reaction was the dihydro-4-quinolone (**766**). The suggested intermediate for the

ynamine reaction was the dipolar species (**767**), which must cyclize either to the carboxyl group (minor route) or to the carbon atom carrying the carboxyl group, with subsequent decarboxylation.

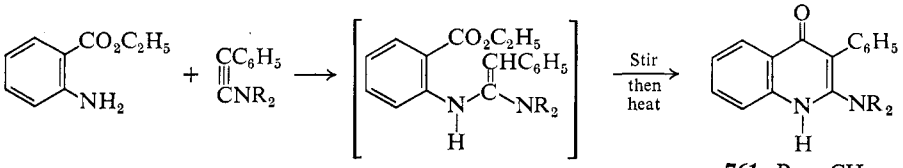


753 **755** **754**



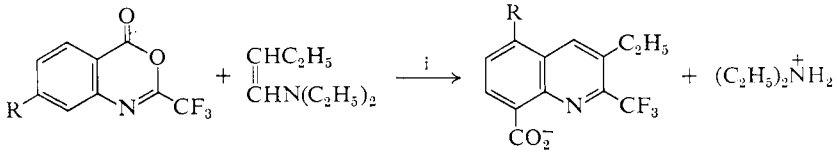
756 **757**, R = C_6H_5 **758**, R = OCH_3

759, R = C_6H_5; 64%
760, R = OCH_3; 53%



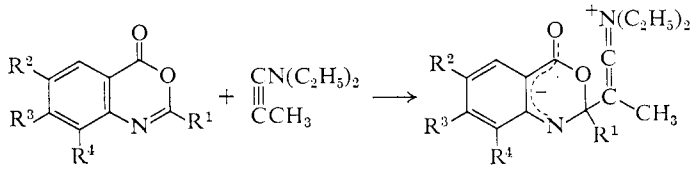
763

761, R = CH_3
762, R = C_2H_5

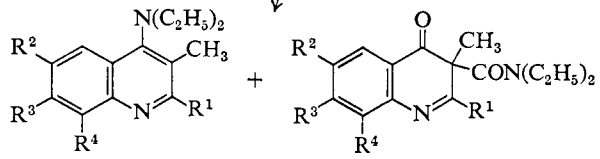


i, Ether, room temp., then acid

764 R: H Cl NO_2
%: 65 48 67



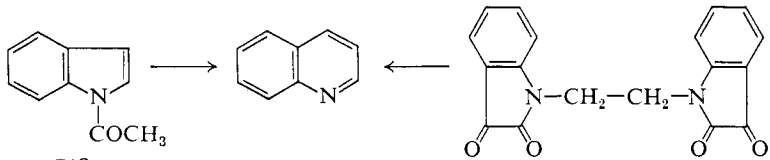
767



765; Seven examples **766**

IV. Syntheses Involving Ring Expansion or Contraction

The early literature contains some examples of the pyrolytic conversion of indoles into quinolines. Fischer and Steche[818] heated 2-methylindole with zinc chloride to obtain a very small yield of quinoline; Pictet[819] obtained a 17% yield of quinoline by passing 2-methylindole through a red-hot tube. Pyrolyses of 1-acetylindole (**768**)[820, 821]



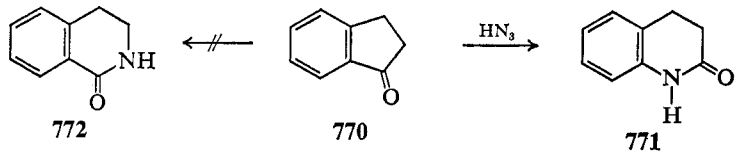
768 **769**

and of the 1,1-ethylenediisatin (**769**)[822] have been reported to give small yields of quinoline. Most ring-expansion syntheses of quinoline proceed by more readily defined pathways and can give appreciable yields. The major classes of reaction involve the expansion of five-membered cyclic ketones (Beckmann, Schmidt rearrangements, diazo-reactions) or insertion reactions into indoles (carbene reactions, azide reactions, oxygen insertion).

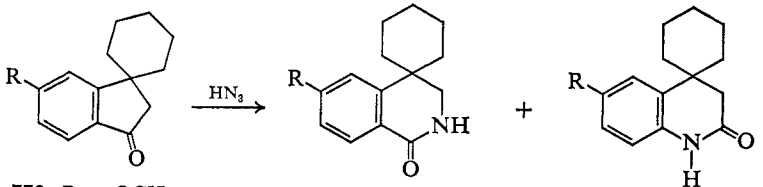
1. Ring Expansions

A. Indanones and Indenones

The simplest reactions, leading normally to dihydro-2-quinolones, are the various rearrangements of indanones and of indanone oximes. Rearrangement of indan-1-one (**770**), by use of hydrazoic acid, gave a 68% yield of 3,4-dihydro-2-quinolone (**771**).[823] It has been reported[824] that aralkyl ketones rearrange preferentially to give aromatic amines, so that the isomeric dihydroisoquinol-1-one (**772**) seems unlikely



772 **770** **771**



773, R = OCH_3
774, R = H

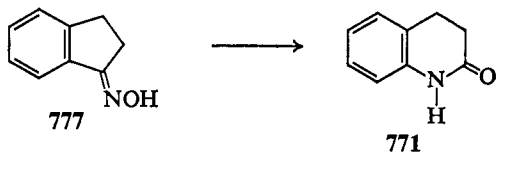
775 **776**

R =	OCH_3	H
%(**775**)	71	7
%(**776**)	6	77

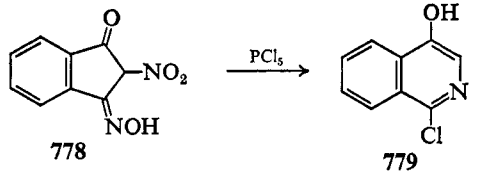
to be formed. That the situation is less clear with cyclic ketones was demonstrated by a study of the Schmidt reaction using the spirocyclic ketones (**773**) and (**774**). When the methoxylated derivative (**773**) was used, the product was largely the isoquinolone (**775**) rather than the quinolone (**776**); with the unsubstituted starting material (**774**) the situation was reversed.[825]

Conventional Beckmann rearrangements of indan-1-one oxime (**777**) gave poor yields of the 2-quinolone (**771**);[826, 827] the more highly substituted oxime (**778**) gave predominantly the isoquinolone (**779**).[828] In a reductive Beckmann rearrangement, using aluminium chloride and lithium aluminium hydride, the oxime (**777**) gave a reported yield of 95%, of which 98% was 1,2,3,4-tetrahydroquinoline (**780**);[829] without the aluminium chloride the yield was only 75%, and the major product 1-aminoindane (**781**).

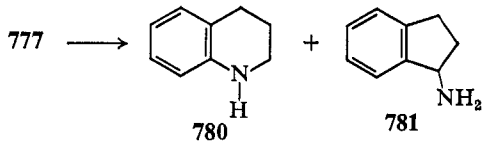
If the Schmidt or Beckmann reaction was performed on indenones, then 2-quinolones rather than the dihydro-derivatives were formed. A number of di-substituted indenones (**782**) have been treated with sodium azide and sulphuric acid to give the corresponding 2-quinolones.[830–833] All successful conversions involved a 3-phenylindenone, giving 4-phenyl-2-quinolones; notable was the synthesis of 3-cyano-4-phenyl-2-quinolone (**783**);[830] the suggested intermediate was of type (**784**).[832] Marsili observed the formation of some isoquinolone (**785**) when 2-ethyl-3-phenylinden-1-one was used;[830] treatment of oxime (**786**) of 2-methyl-3-phenylinden-1-one with polyphosphoric acid gave only the isoquinolone (**787**). A Schmidt reaction on benzoylstyrenes (**788**) which gave trisubstituted quinolines (**789**) was



777 771

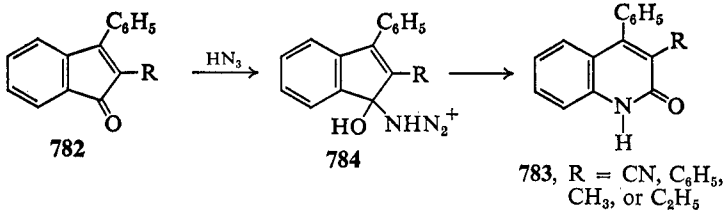


778 779

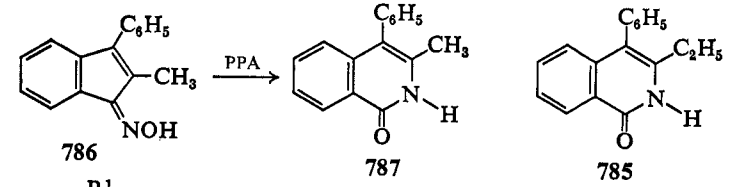


780 781

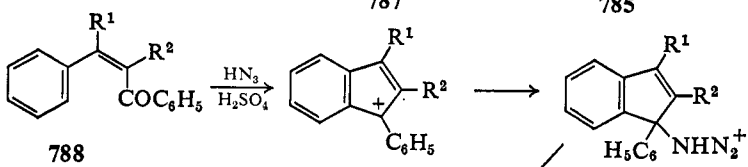
Conditions	%(780)	%(781)
$LiAlH_4$, $AlCl_3$	98	Trace
$LiAlH_4$ only	28	72



782 784 783, R = CN, C_6H_5, CH_3, or C_2H_5

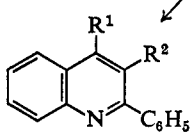


786 787 785



788 790

$R^1 = R^2 = Br$; 30%
$R^1 = R^2 = C_6H_5$; 35%
$R^1 = C_6H_5CO$, $R^2 = C_6H_5$; 53%

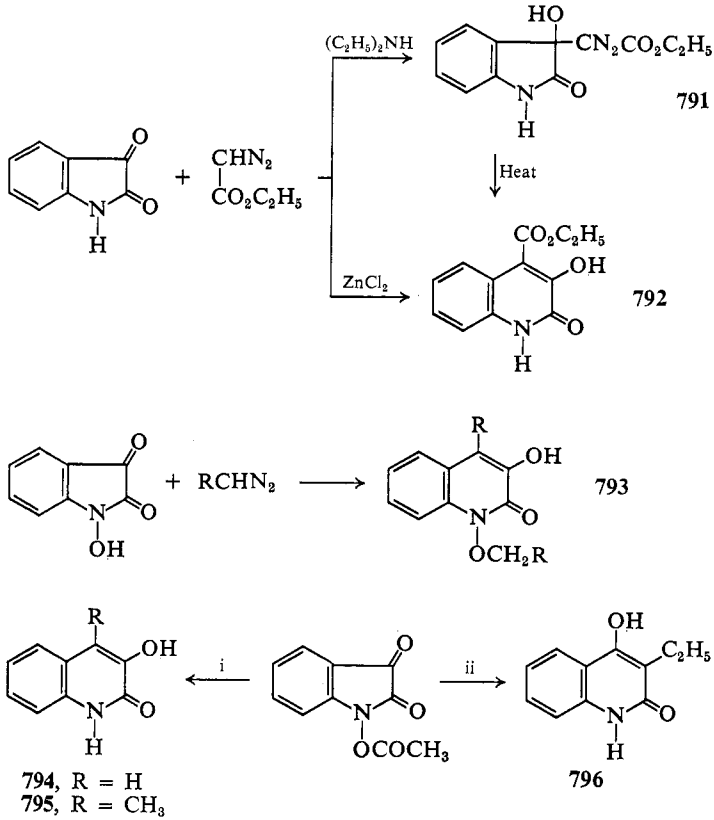


789

suggested to pass through an indene intermediate (**790**) very similar to that (**784**) proposed by Marsili;[832] quenching the reaction after acid-treatment but before addition of azide gave indenes.[834]

B. Isatins with Diazo-compounds

Eistert and his co-workers have reported a series of ring expansion reactions of isatins, using aliphatic diazo-compounds. Successful reactions were achieved when using isatin[835–840] or *N*-methylisatin[836–838] and with *N*-hydroxy- or *N*-acetoxyisatin.[841] Diazo-compounds used were diazomethane,[836, 839, 841] diazoethane,[836, 841] diazopropane,[841] phenyldiazomethanes,[836, 837, 840] pyridyldiazomethanes,[838] ethyldiazoacetate,[836, 837] and acetyl- or benzoyl-diazomethane.[837] In the example shown, the intermediate (**791**) was isolated in high yield and was converted by heat into the 2-quinolone (**792**).[837] The reaction could be done directly in the presence of zinc

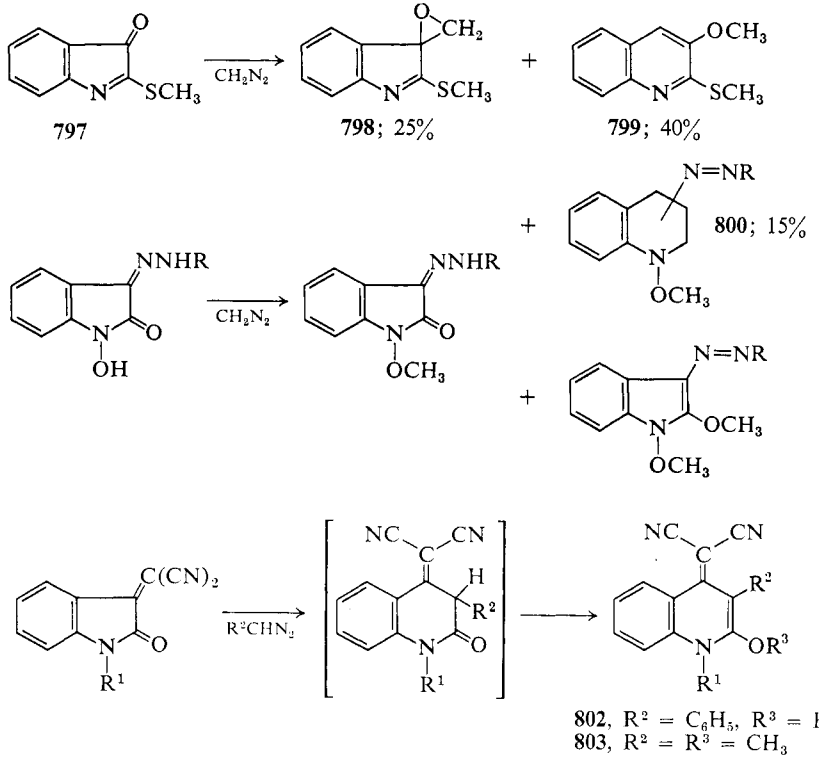


i, CH_2N_2 or CH_3CHN_2. ii, $C_2H_5CHN_2$.

chloride, but the yields were better in the two-stage process. In some cases, when diazomethane was used the 3-methoxy-2-quinolones were obtained.[836] The *N*-oxygenated isatins presented some interesting chemistry; use of *N*-hydroxyisatin gave

the 1-alkoxy-2-quinolones (**793**).[841] Expansion of *N*-acetoxyisatin was normal with diazomethane and diazoethane, giving the 3-hydroxy-2-quinolones (**794**) and (**795**);[841] diazopropane, however, gave the product of the alternative insertion, the 4-hydroxy-2-quinolone (**796**). A similar isomeric pair has been observed in a diazomethane reaction.[839]

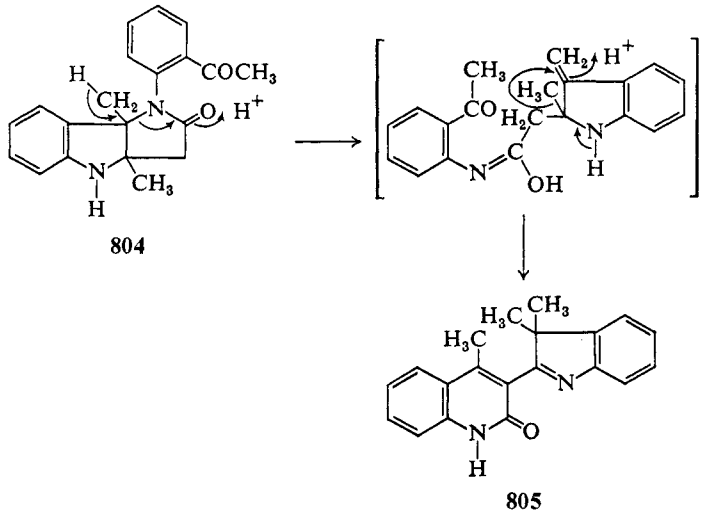
Related ring expansions have been achieved with derivatives of isatin[842, 843] and with the indolenin-3-one (**797**),[844] the latter giving the spiro-compound (**798**) as well as the quinoline (**799**). While the hydrazones of 1-hydroxyisatin gave mixtures when treated with diazo-compounds, in which an azo-compound (**800**) of incompletely



specified structure was a minor component,[842] the isatinylidenemalonitriles (**801**) gave good yields of *N*-substituted 2-hydroxy-4-quinolylidenemalononitriles (**802**) with phenyldiazomethane or the 2-methoxy-derivatives (**803**) with diazomethane itself.[843]

C. Oxygenated Indoles

A number of reactions are known in which an oxygenated indole expands to give a quinoline, or in which indoles or indolenines expand via an oxygenated intermediate. One of the simplest reactions was the acid-catalysed conversion of the 1-(*o*-acetylphenyl)-3,3a,4,4b-tetrahydropyrrolo[3,2-*b*]indol-2(1*H*)-one (**804**) into a 2-quinolone (**805**).[845]



804

805

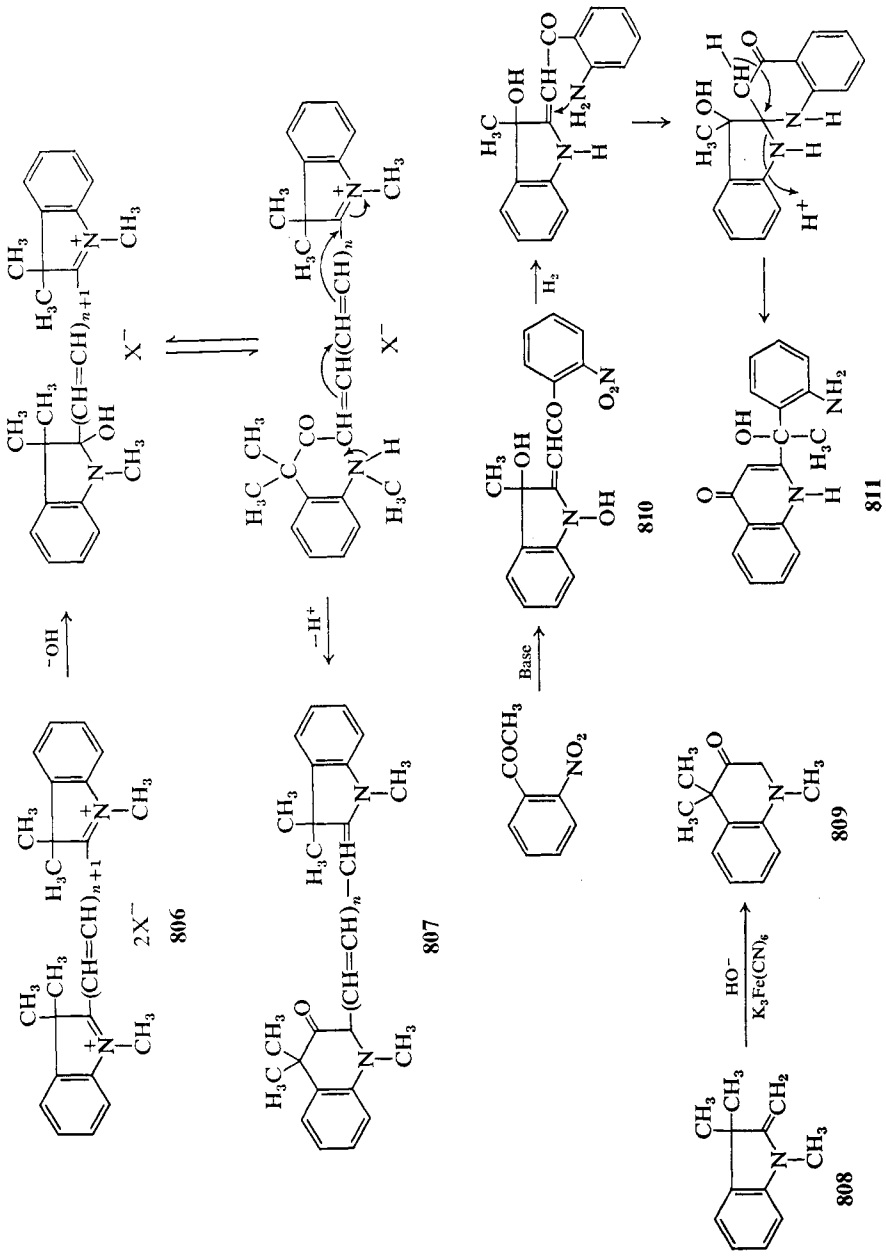
The indoleninium salts (**806**), when treated with bicarbonate, were found to give the 1,4-dihydro-3-quinolones (**807**) in very high yield; the suggested mechanism is shown.[846] The simple indolenine (**808**) similarly gave a 95% yield of the compound (**809**); here the reagent was bicarbonate and ferricyanide. A superficially similar reaction was observed when a compound (**810**) (isolated after treatment of 2-nitroacetophenone with base) was catalytically hydrogenated[847] to give the 4-quinolone (**811**); in fact, however, the "indole"-nitrogen atom does not appear in the quinolone.

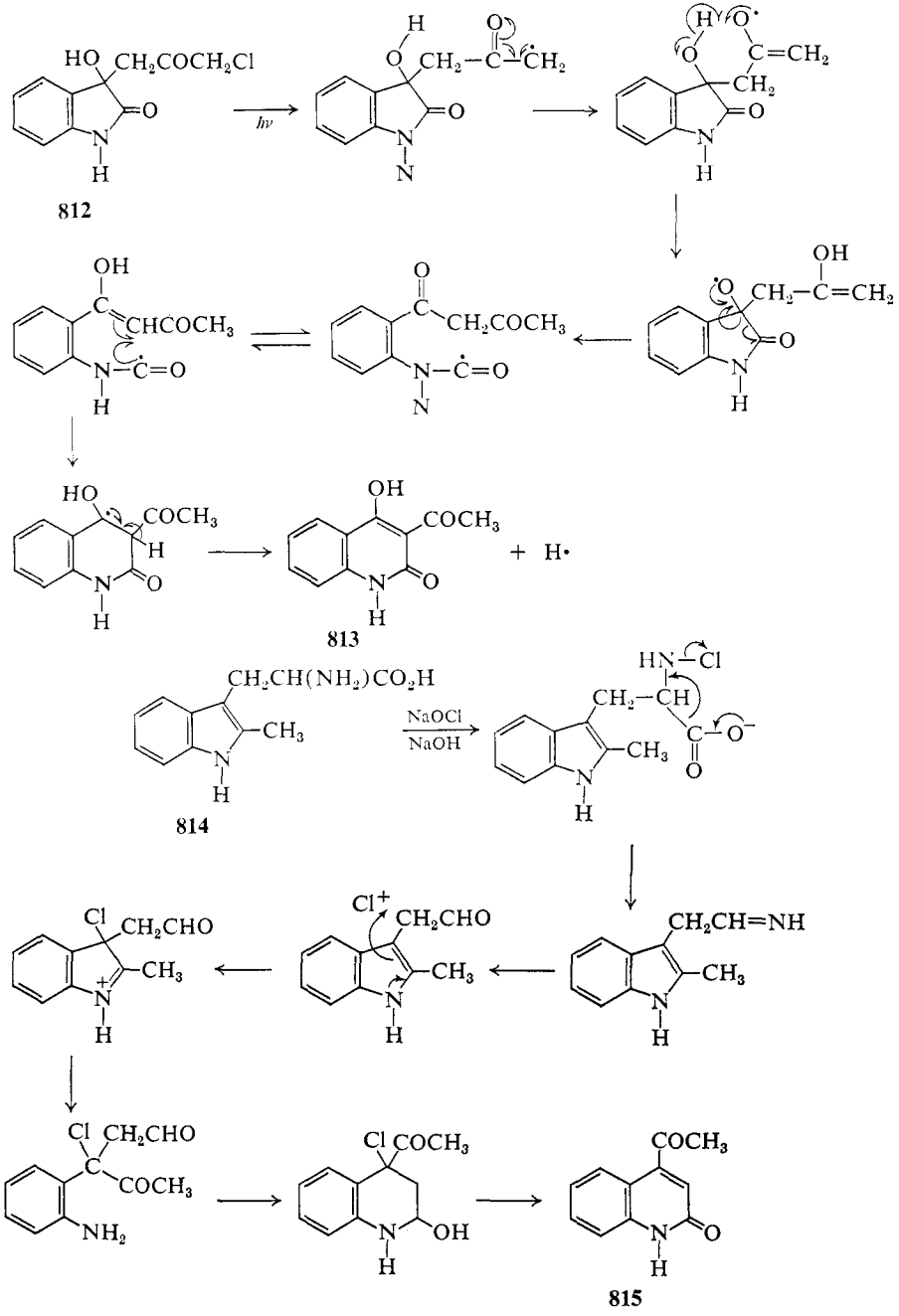
Photolysis of the hydroxyoxindole (**812**) leads, via a series of radical intermediates, to 3-acetyl-4-hydroxy-2-quinolone (**813**).[848] Some stages in the mechanism of a biomimetic procedure for conversion of a tryptophan such as (**814**) into a quinolone such as (**815**) are similar to those in the photolysis, although the biomimetic synthesis does not involve an oxygenated indole[849] (for formulae see p. 234).

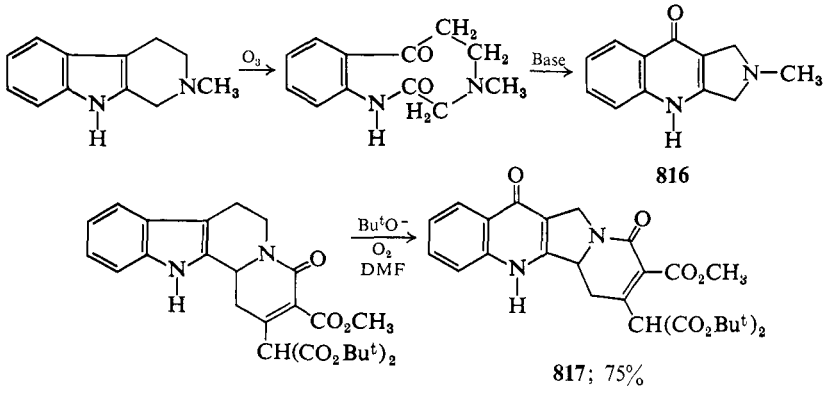
Oxidative procedures have been used to convert indoles into quinoline derivatives. Such oxidative procedures may throw light on the interconversion of tryptophan into kynurenic acid. Various workers have studied the oxidation of indoles and some have reported two-stage[850–853] and one-stage[850, 854–857] methods for the conversion of indoles into 4-quinolones. An example of the two-stage procedure is shown for the preparation of the tricyclic compound (**816**),[850] but Witkop and Goodwyn also reported a one-stage conversion of yohimbine into the corresponding quinolone.[850] Better yields of cleavage products have been obtained from some indoles by oxidation with periodate.[851, 852] The second general procedure is exemplified by the synthesis of a compound (**817**) related to camptothecin[857] (for formulae see p. 235).

D. Non-oxidative Expansion of Indoles

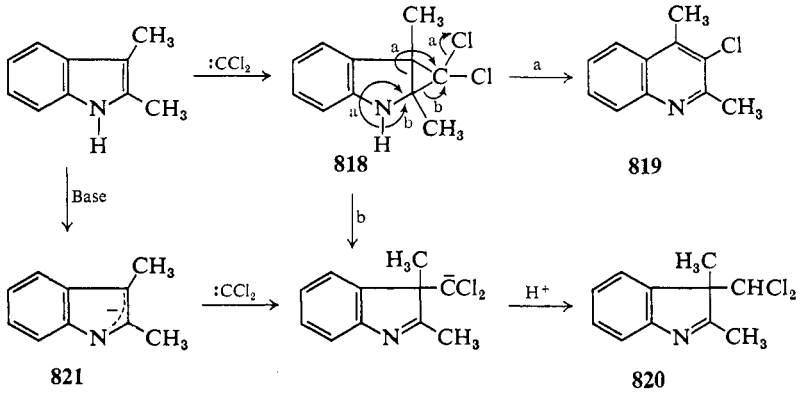
The largest group of reactions in this section is that of carbene expansion of indoles. It has been known since the last century that indole,[858] 2- or 3-methylindole,[859, 860] 2,3-dimethylindole,[861] and tetrahydrocarbazoles[862] react with chloroform and strong bases to give indolenines and 3-chloroquinolines, as pyrroles under similar conditions give pyridines. Similarly, bromoform with 2- or 3-methylindole gave 3-bromo-2-methyl- and 3-bromo-4-methyl-quinoline, respectively.[860] The production of




812
813
814
815
NaOCl
NaOH
hν

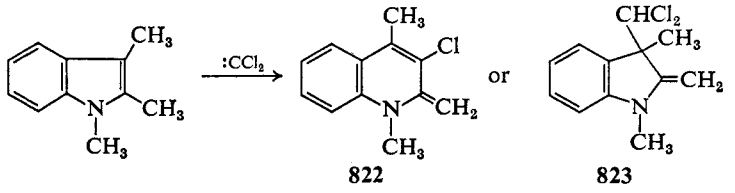


mixtures of indolenines and quinolines was suggested by Nakazaki[863] to be due to a carbene addition, as shown for 2,3-dimethylindole, giving a cyclopropaindole (**818**) which could open either to a quinoline (**819**) or to an indolenine (**820**).



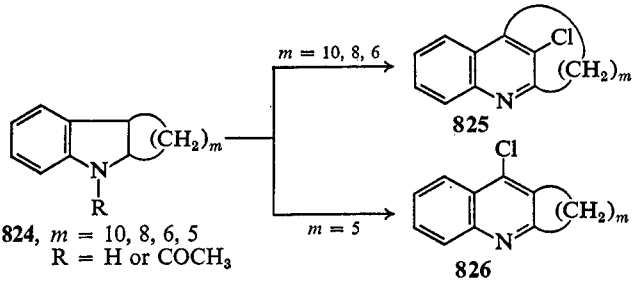
Dobbs[864] reported a number of isotopic labelling experiments that gave inconclusive results; the intermediate proved too unstable for isolation and could not be trapped in quenching experiments. Detailed studies by Robinson[865] and by Rees and Smithen[866–868] led to the suggestion that the indolenine was, not an intermediate on the way to the quinoline (first suggested by Plancher and Carrasco[869]), but the end-product of an alternative mechanistic pathway that involved the indolyl anion, as in formula (**821**). Hence strongly basic reaction conditions favoured indolenine formation. Rees and Smithen also showed[868] that 1,2,3-trimethylindole could undergo ring expansion to the quinoline (**822**) if the carbene was generated from ethyl trichloroacetate, although the indolenine (**823**) was the major product in basic media.[868]

Carbenes used successfully for quinoline preparations were dichlorocarbene,[858–863, 865–868, 1329] dibromocarbene,[860, 868, 1329] bromocarbene,[864] and chlorocarbene;[864, 870] difluorocarbene gave only indolenine with no ring-expansion product.[868] Improved yields of 3-chloro- and of 3-bromo-quinoline were obtained when a phase-transfer catalyst was used with the appropriate haloform and sodium



822 823

hydroxide.[1329] In one case a still better yield was obtained by using dibenzo[18]-crown-6 ether. Chlorocarbene and indole gave a poor yield of quinoline. Dichlorocarbene, generated from phenyl(trichloromethyl)mercury, with the indoles (**824**) gave the quinolinocyclophanes (**825**).[871-873] The reaction gave the 2,3-fused cyclophane (**826**) when $m = 5$.[871, 872] This sequence may throw light on the failure of



tetrahydrocarbazole to undergo ring expansion,[862, 868] the alicyclic ring being too small to bridge the 2,4-position in quinoline.

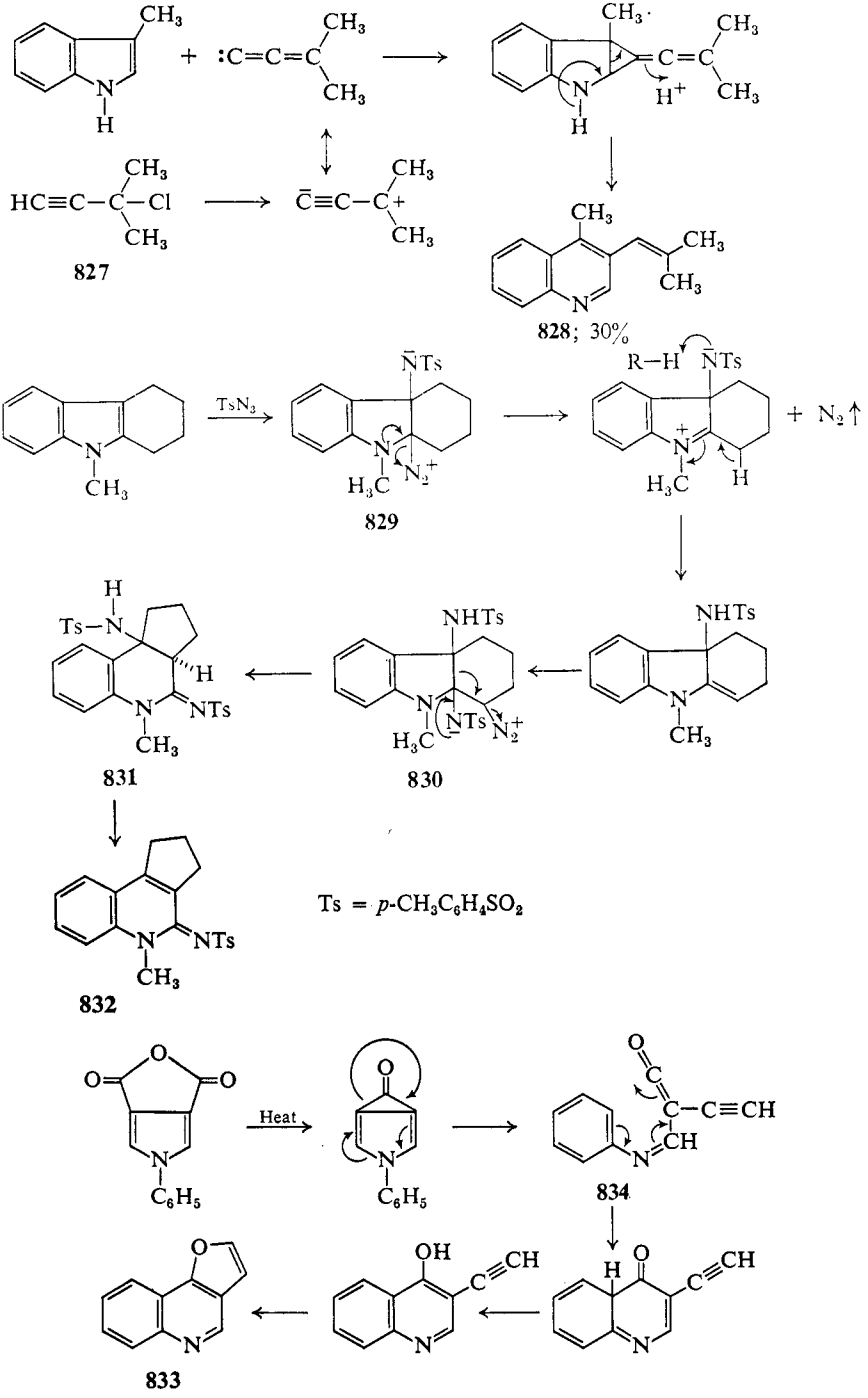
A carbene character in the intermediate was suspected in the reaction between 3-methylindole and the chloroacetylene (**827**) under basic conditions; the product was the vinylquinoline (**828**).[874] Very small yields of quinoline derivatives were obtained when indoles[875] or tetrahydro-*N*-methylcarbazoles[876] were treated with tosyl azide; the suggested intermediates (**829**) and (**830**) are shown for the conversion of tetrahydro-*N*-methylcarbazole into the 2-quinolone derivatives (**831**) and (**832**).[876]

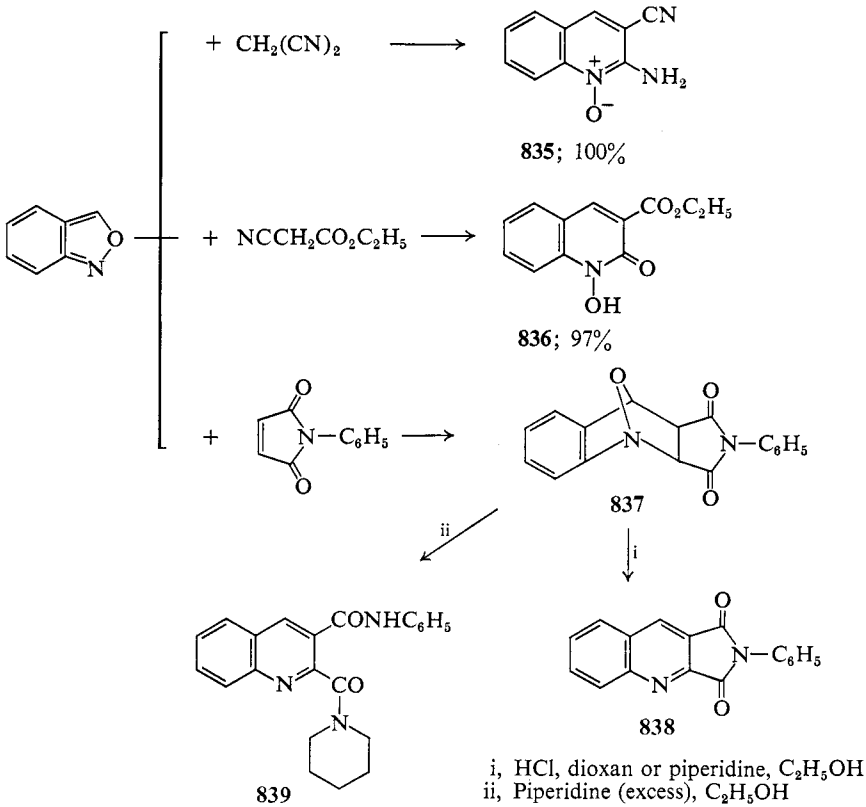
E. Miscellaneous Conversions of Five-membered Ring Heterocycles into Quinolines

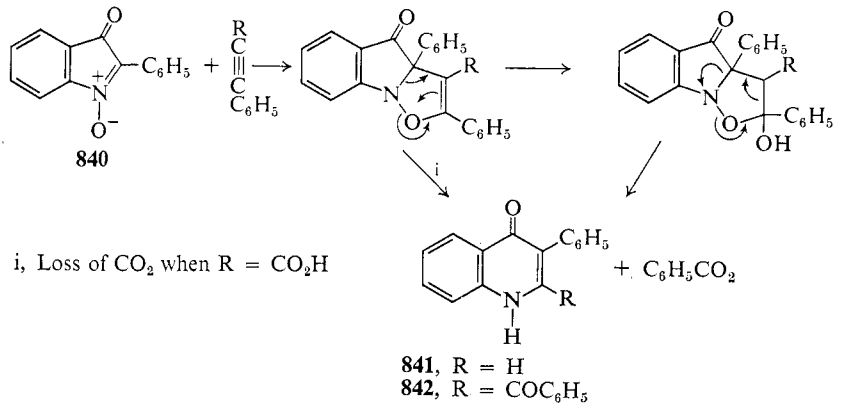
One of the most unexpected reactions in this class is the reported[877] conversion of 1-phenylpyrrole-3,4-dicarboxylic anhydride into the furoquinoline (**833**), in a yield of 81% based on unrecovered starting material. The pyrolysis was thought to proceed through an aniline derivative (**834**).

Reactions using anthranils can be regarded either as ring expansion routes or as involving a masked *o*-nitrobenzaldehyde. Direct reaction of anthranil with active methylene compounds gave the *N*-oxide, such as compound (**835**), or the 1-hydroxy-2-quinolone, such as compound (**836**).[878] Reaction with *N*-phenylmaleimide gave a bridged tetrahydroquinoline (**837**) which was converted into the quinoline-2,3-dicarboxylic acid derivatives (**838**) or (**839**).[879] (cf. formulae on p. 238.)

Isatogen (**840**) reacted with phenylacetylene or phenylpropargylic acid (in xylene with acetic or propionic acid) to give, respectively, 3-phenyl-4-quinolone (**841**) or its 2-benzoyl derivative (**842**).[880, 881]

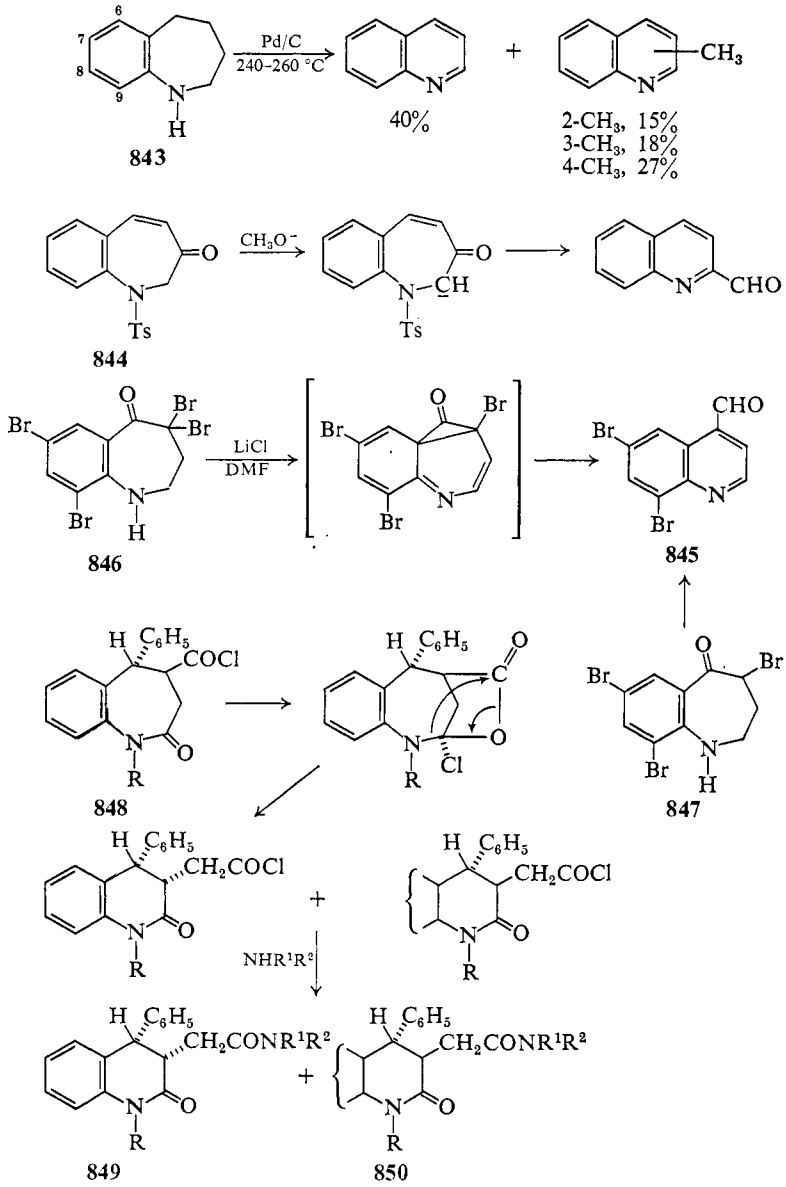

827
828; 30%
829
830
831
832
Ts = p-CH3C6H4SO2
833
834
Heat


+ $CH_2(CN)_2$
CN
NH_2
835; 100%
+ $NCCH_2CO_2C_2H_5$
$CO_2C_2H_5$
OH
836; 97%
+
$N-C_6H_5$
837
ii
i
$CONHC_6H_5$
838
839
i, HCl, dioxan or piperidine, C_2H_5OH
ii, Piperidine (excess), C_2H_5OH

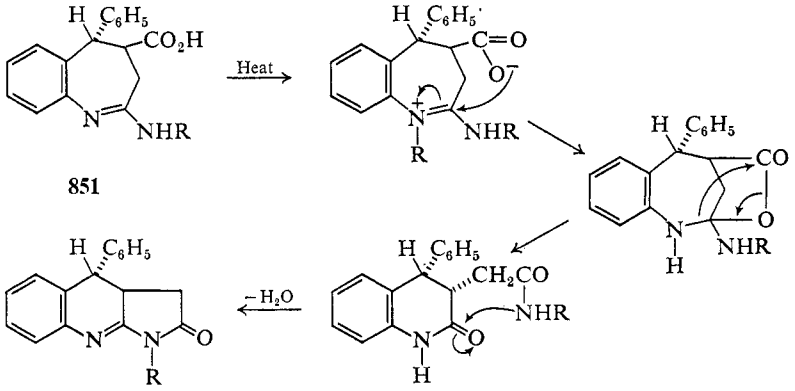

C_6H_5
840
R
C_6H_5
OH
i
i, Loss of CO_2 when R = CO_2H
+ $C_6H_5CO_2$
841, R = H
842, R = COC_6H_5

2. Ring Contractions

A number of reactions have been reported in which an azepine contracts to yield a quinoline derivative. The simplest azepine thus treated was the tetrahydro-1*H*-benzazepine (**843**) which, when heated with palladized charcoal and ethyl cinnamate was converted into a mixture of quinoline and 2-, 3-, and 4-methylquinoline.[882] The 6,8-diethyl derivative of compound (**721**) similarly gave 5,7-diethylquinoline.

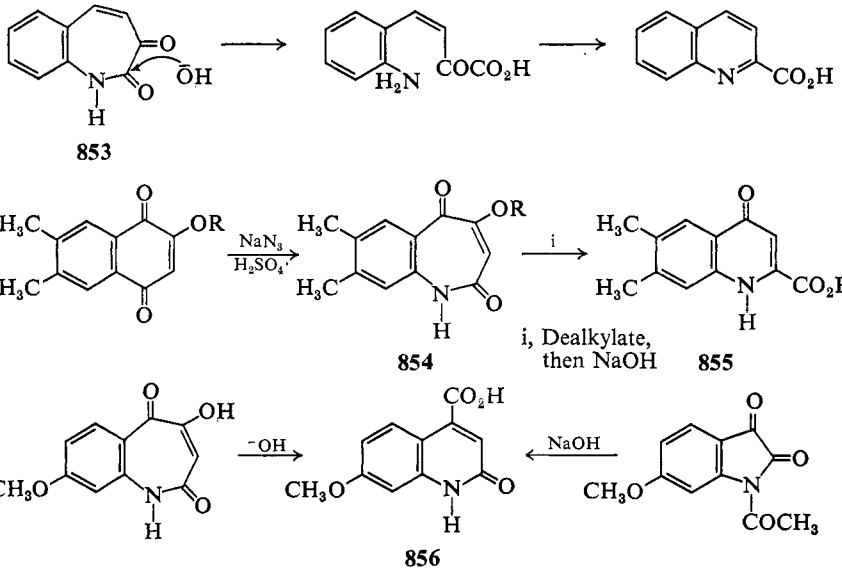


A number of oxygenated benzazepines have been converted into quinolines, mainly under basic conditions; the mechanisms advanced have been often of the Favorskii rearrangement type. Thus the compound (**844**) gave, with sodium methoxide, quinoline-2-carboxaldehyde;[883] the quinoline-4-carboxaldehyde (**845**) was obtained either from the tetrabromo-ketone (**846**) by treatment with lithium chloride and dimethylformamide, or from the tribromo-ketone (**847**) with manganese dioxide.[884] The lactam (**848**), when treated with thionyl chloride and pyridine, was converted into a mixture of stereoisomeric dihydro-2-quinolones, trapped as the amides (**849**) and (**850**).[885] The aminoazepinecarboxylic acid (**851**) gave, when heated, the pyrrolo-[2,3-*b*]quinoline (**852**); the mechanisms suggested for these last three contractions are shown.



851 **852**

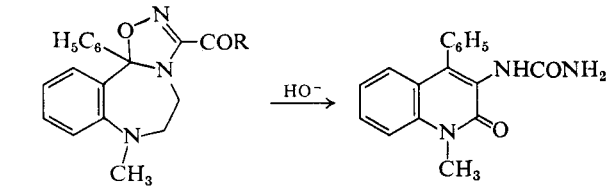
Dioxobenzazepines similarly gave quinolinecarboxylic acids under base-catalysed ring contraction conditions. The keto-lactam (**853**) gave quinoline-2-carboxylic acid on treatment with warm alkali;[886] a more interesting, because more general, sequence



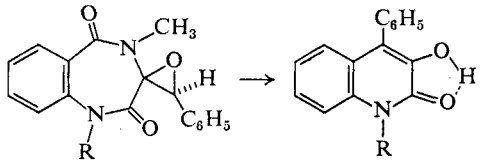
853 **854** **855** **856**

converted naphthoquinones through alkoxybenzazepinediones (**854**) into 4-quinolone-2-carboxylic acids (**855**).[887, 888] In one case the 2-quinolone-4-carboxylic acid (**856**) was formed.[887]

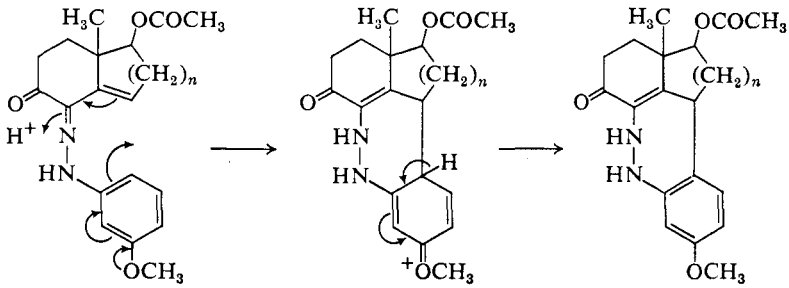
Seven-membered rings containing two heteroatoms in various compounds can contract to give quinoline derivatives. The diazepine (**857**) gave, with base, a 2-quinolone-urea (**858**).[889] Cyclopenin (**859**) gave 3-hydroxy-4-phenyl-2-quinolone (**860**) with acid or with base; the 1-methyl derivative (**861**) gave the 1-methyl-2-quinolone (**862**) with acids only.[890] The 1,2-diazepine (**863**) was described as an



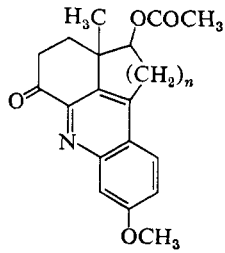
857, R = C_6H_5 or OC_2H_5 **858**



859, R = H **860**, R = H
861, R = CH_3 **862**, R = CH_3



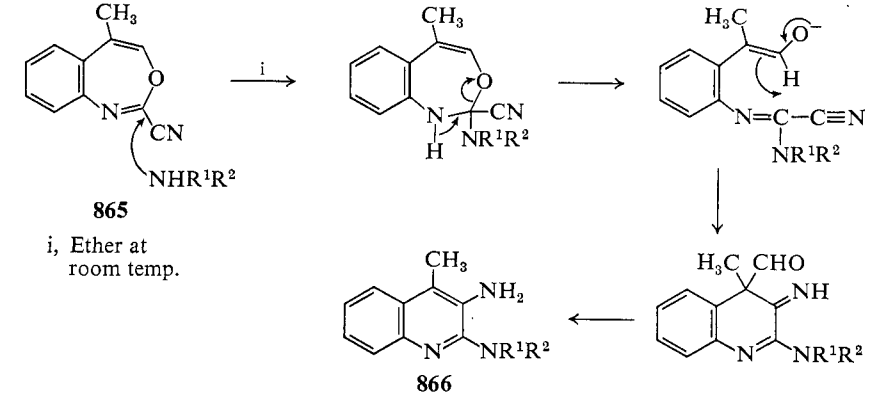
863



864

intermediate in the formation of the tetracyclic system (**864**), via an analogue of the Fischer indole reaction.[891]

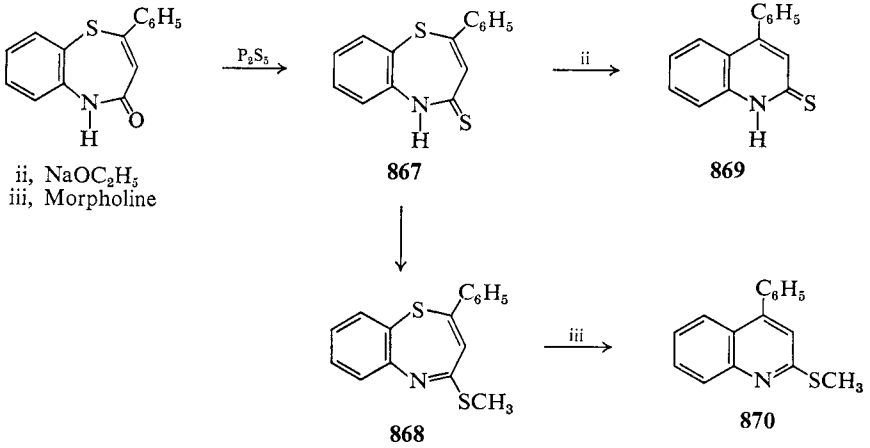
The benzoxazepine (**865**) reacted with a number of amines and with ammonia to give 2,3-diamino-4-methylquinolines (**866**) in fair to good yield.[892] Treatment of the thiazepinethione (**867**) or its methylthio-derivative (**868**) with base gave the quinolinethione (**869**) or the (methylthio)quinoline (**870**), respectively.[893]



865

i, Ether at room temp.

866

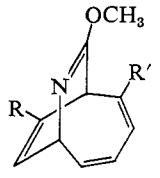


ii, $NaOC_2H_5$
iii, Morpholine

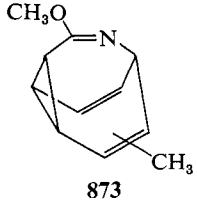
867 **869**

868 **870**

An extraordinary series of rearrangements of the bridged azocine (**871**) gave quinoline and a number of methoxyquinolines. From the methyl derivative (**872**) *all* the methyl quinolines except 2-methylquinoline were obtained, but from the closely related azasemibullvalene (**873**) 2-methylquinoline was the major product.[894]



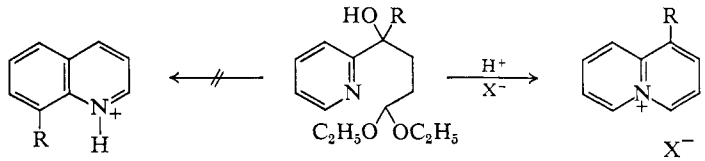
871, R = R′ = H
872, R = CH_3, R′ = H



873

V. Syntheses from Pyridines or Piperidines by Completing the Carbocyclic Ring

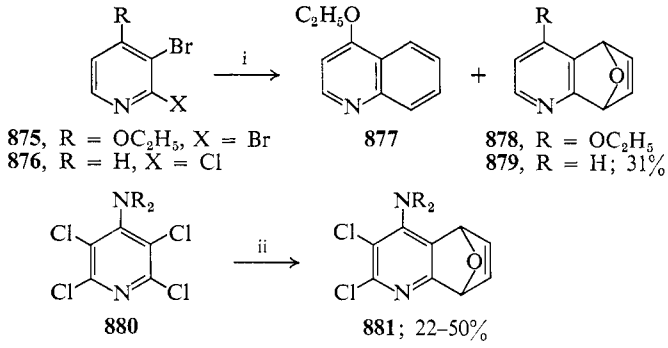
There is a very limited range of syntheses where the starting material is a pyridine or piperidine, and the carbocyclic ring is formed. The limitations of this approach are clearly the relative inaccessibility of suitable 2,3-disubstituted pyridines, and the difficulty of cyclizing a monosubstituted pyridine (2- or 3-substituted) on to the correct adjacent site. As an example of the latter problem, a number of 2-substituted



874

pyridines have been cyclized to give quinolizinium salts (**874**) rather than quinolines. The highest electron density is normally at the nitrogen atom and hence this site is most readily attacked by electrophiles.

Pyridine has been reported to give very low yields of quinoline on pyrolysis (600, 850 °C), possibly through a pyridyne intermediate.[895, 896] Such pyridynes have provided some of the best routes from 2,3-dihalopyridines to quinolines. Treatment of the dihalopyridines (**875**) and (**876**) with lithium amalgam[897, 898] or with *n*-butyllithium[899, 900] in the presence of furan gave the quinoline (**877**) and the epoxydihydroquinolines (**878**) and (**879**). 4-Aminotetrachloropyridines of type (**880**) also



875, R = OC_2H_5, X = Br
876, R = H, X = Cl

877

878, R = OC_2H_5
879, R = H; 31%

880

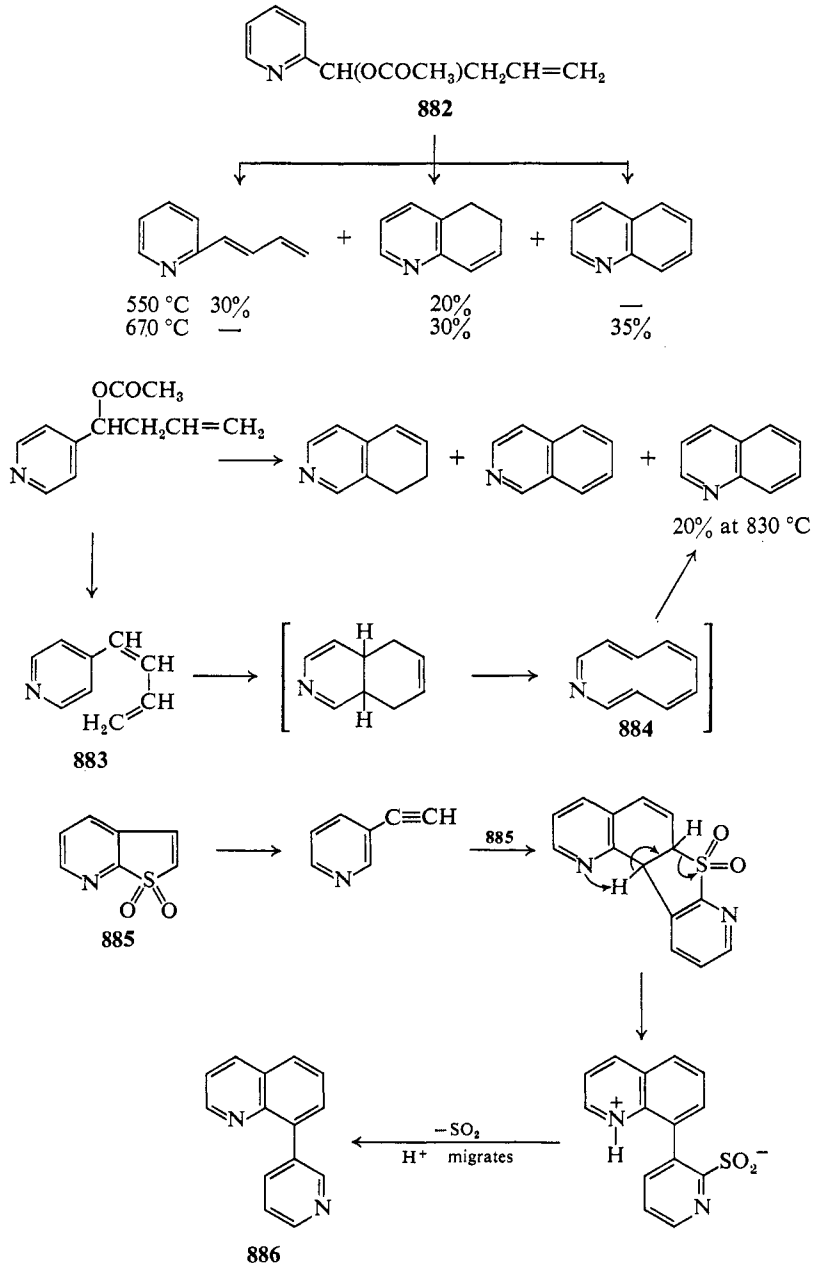
881; 22–50%

i, LiR in furan. ii, *n*-C_4H_9Li in furan.

gave fair yields of bridged dihydroquinolines (**881**) when treated with *n*-butyllithium in furan.

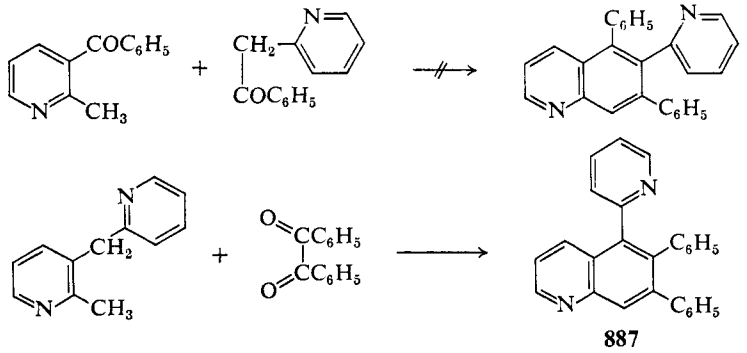
Syntheses using monosubstituted pyridines have been reported.[901, 902] Flash-pyrolysis of the potential 2-(butadienyl)pyridine (**882**) gave increasing amounts of quinoline at increasing temperatures. More interesting from a mechanistic point of view was the observation that 4-(butadienyl)pyridine (**883**) gave some quinoline at high temperatures, possibly through an intermediate monocyclic system (**884**).

Klemm and Merrill found[903] that the sulphone (**885**), when heated, gave 8-(3-pyridyl)quinoline (**886**), presumably by condensation of the first-formed ethynylpyridyne with the sulphone and subsequent loss of sulphur dioxide.



The most obvious routes to quinoline derivatives from 2,3-disubstituted pyridines involve aldol or Claisen condensations. While it was not possible to condense together 3-benzoyl-2-methylpyridine and ω-(2-pyridyl)acetophenone, benzil condensed with 2-methyl-3-(2-pyridylmethyl)pyridine to give the highly substituted

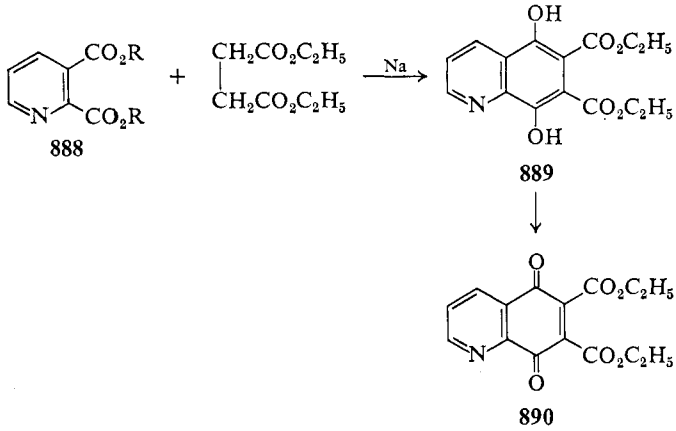
quinoline (**887**) needed for comparison with a degradation product from lobinaline.[904]



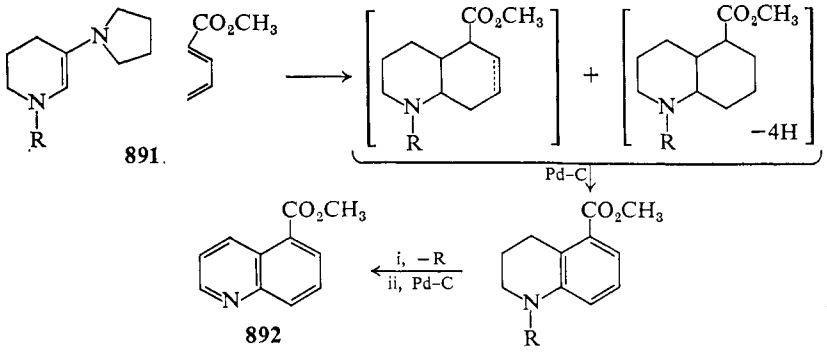
887

Quinolinic esters (**888**) were shown to condense in good yield with diethyl succinates to give 5,8-dihydroxyquinolines (**889**), providing a good route to quinoline-5,8-quinones (**890**).[905]

A route from a tetrahydropyridine, the enamine (**891**), to methyl quinoline-5-carboxylate (**892**) has been described.[906]



888 **889** **890**



891 **892**

VI. Tables

Introduction to Tables

The Tables are included to show the range of substituted quinolines that can be prepared by the most widely used syntheses. In Table 1 quinolines synthesized by the Skraup, Doebner–von Miller, Beyer, and Combes procedures are grouped together this Table is arranged to show the range of aromatic amines which have been used. Since the co-reactants vary considerably these are also shown in Table 1, but not in subsequent Tables. In Table 2, quinolines prepared by the Knorr or the Conrad–Limpach procedures are grouped; the quinolines in Table 2 are hence either 2-quinolones or 4-quinolones. In Table 3 are shown quinoline-4-carboxylic acids (cinchoninic acids) prepared by the Pfitzinger or the Doebner synthesis. In all Tables the quinolines are arranged in main groups as mono-, di-, or multi-substituted; within each main group the simple alkyl- and aryl-quinolines are placed first, followed by halo-, nitro-, hydroxy-, and alkoxy-quinolines, and, finally, other substituents. Such Tables cannot be complete; they are intended only to illustrate the range of substituted quinolines that can be made.

TABLE 1. Selected Quinolines Synthesized by Skraup or Doebner–von Miller Procedure

G = Glycerol; SA ( ) = sulphuric acid (%); As = arsenic acid; NC = a nitro-compound; PPA = polyphosphoric acid; MVK = methyl vinyl ketone.

TABLE 1A. Monosubstituted Quinolines

Aniline substituent	Reagents	Quinoline	Yield (%)	References
None	G, SA (95), NC, $FeSO_4$	Quinoline	84–91	97
None[a]	G, SA (95), NC, $FeSO_4$		90	96
None[b]	G, SA		80	174
None	G, SA, I_2		70–75	169
Alkyl and Aryl Substituents				
None	Paraldehyde, NC, SA	2-Methylquinoline	—	38, 167
	Pyruvic acid, NC, SA		40	120
	Acetaldehyde, conc. HCl, $ZnCl_2$		—	52
	Crotonaldehyde, NC, SA		43	126
	Crotonaldehyde diacetate, As, NC, SA		49	126
	1,3,3-Triethoxybutane		50	907
	1,1,3-Triethoxypentane, HCl	2-Ethylquinoline	50	907
	Pentane-1,2,3-triol, SA, NC		15	128
	Hexane-1,2,3-triol, SA, NC	2-*n*-Propylquinoline	17.5	128
	Isobutyraldehyde, acetaldehyde, HCl	2-Isopropylquinoline	Poor	908
	Heptane-1,2,3-triol, SA, NC	2-*n*-Butylquinoline	—	128
	3-Phenyl-1,1,3-triethoxypropane, HCl	2-Phenylquinoline	50	907
	3-Phenyl-1,1-diethoxypropane-2,3-diol, SA, NC		6	909
	3-Nitrocinnamaldehyde, HCl (140 °C)	2-(*m*-Nitrophenyl)quinoline	—	994
	Dimethoxymethane, propionaldehyde, HCl	3-Methylquinoline (+2-ethyl-3-methylquinoline) (42 : 58)	—	135
	Methacraldehyde, gas phase, catalyst	3-Methylquinoline	—	56

[a] Using acetanilide. [b] Using stannichloride.

TABLE 1A (*Cont.*)

Aniline substituent	Reagents	Quinoline	Yield (%)	References
Alkyl and Aryl Substituents (Contd.)				
None	Methacraldehyde diacetate, NC, SA, As	3-Methylquinoline	49	126, 112
	2,3-Dihalo-2-methylpropionaldehyde, H_3PO_4		—	110
	2-Ethylacrolein diacetate, SA, As	3-Ethylquinoline	54	126
	2,2-Di(hydroxymethyl)pentan-1-ol, SA	3-*n*-Propylquinoline	15	133
	1,3-Diethoxy-2-isobutylpropane, NC, SA, (130–135 °C)	3-Isobutylquinoline	40	910
	1,3-Diethoxy-2-phenylpropan-2-ol, SA, NC, acetic acid	3-Phenylquinoline	12	130
	1,3-Diethoxy-2-benzylpropan-2-ol, SA	3-Benzylquinoline	22	911
None[c]	MVK, $FeCl_3$ (or 4-methoxybutan-2-one, or 1,1,3-trimethoxybutane)	4-Methylquinoline	72	149
	4-Hydroxybutan-2-one, HCl, $ZnCl_2$		36	143, 136, 912
None	4-Diethylaminobutan-2-one, $ZnCl_2$, $FeCl_3$, NC		65	151, 152, 155, 23
	1-Chloropentan-3-one, SA, $SnCl_4$	4-Ethylquinoline	40	913, 143, 147
	1-Chlorohexan-3-one, SA, $SnCl_4$	4-*n*-Propylquinoline	40	913, 139
	1-Chloroheptan-3-one, SA, $SnCl_4$	4-*n*-Butylquinoline	40	913
		4-Phenylquinoline and various 4-(*x*-substituted)phenylquinolines	53	913
2-Methyl	G, SA (80), NC	8-Methylquinoline	70	914, 36 186, 915
	Acrolein diacetate, $FeCl_3$, HCl	8-Methylquinoline	31	113
2-Trifluoromethyl	G, SA, As, ammonium vanadate	8-(Trifluoromethyl)quinoline	—	916
2-Ethyl	G, SA, NC, boric acid	8-Ethylquinoline	36	917, 918
2-*n*-Propyl	G, SA, As	8-*n*-Propylquinoline	35	919
2-Isopropyl	G, SA	8-Isopropylquinoline	—	87
2-Phenyl	G, SA, NC	8-Phenylquinoline	60	920, 98
2-(2-Pyridyl)	G, SA, As	8-(2-Pyridyl)quinoline	38	921
2-(3-Pyridyl)	G, SA, As	8-(3-Pyridyl)quinoline	—	921

2-(4-Pyridyl)	G, SA, As	8-(4-Pyridyl)quinoline	—	921
2-(1-Piperidylmethyl)	G, SA, NC, $FeSO_4$, boric acid	8-(1-Piperidylmethyl)quinoline	—	922
2-(2-Benzimidazolyl)	G, SA, NC	8-(2-Benzimidazolyl)quinoline	50	923
3-Methyl	G, SA (75), NC	7-Methylquinoline	74	78
	G, SA, As, H_3BO_3		—	924
	Acrolein diacetate, $FeCl_3$, HCl		22	94
3-Trifluoromethyl	G, SA, As	5- and 7-(Trifluoromethyl)-quinoline (1 : 3)	56% total	925, 926
3-Ethyl	G, SA, NC, $FeSO_4$, boric acid	7-Ethylquinoline	74	927
3-*n*-Propyl	G, SA, NC, $FeSO_4$, boric acid	7-*n*-Propylquinoline	45	927
3-*n*-Butyl	G, SA, NC, $FeSO_4$, boric acid	7-*n*-Butylquinoline	70	927
3-Phenyl[d]	G, SA, As (140 °C)	7-Phenylquinoline	—	928
3-(*m*-Nitrophenyl)	G, SA, NC	7-(*m*-Nitrophenyl)quinoline	12.5	929
3-(*p*-Nitrophenyl)	G, SA, As (below 135 °C)	7-(*p*-Nitrophenyl)quinoline	28	928
3-(*m*-Aminophenyl)	G, SA, NC (130–140 °C)	7,7- and 5,7-Biquinoline	15+16.5%	929
3-(2-Pyridyl)	G, SA, As	5- and 7-(2-Pyridyl)quinoline	—	921
3-(2,6-Dimethyl-4-pyridyl)	G, SA	5- and 7-(2,6-Dimethyl-4-pyridyl)-quinoline	3 and 25	930
4-Methyl	G, SA, NC, $FeSO_4$, boric acid	6-Methylquinoline	80–84	915, 167, 166, 914
	Acrolein diacetate, $FeCl_3$, HCl		17	113
4-(Trifluoromethyl)	G, SA, As, ammonium vanadate	6-(Trifluoromethyl)quinoline	—	916
4-Ethyl	G, SA, NC	6-Ethylquinoline	82	927
4-*n*-Propyl	G, SA, NC	6-*n*-Propylquinoline	68	927
4-Isopropyl[e]	Conc. HCl	6-Isopropylquinoline and 8-chloro-6-isopropylquinoline	10 and 35	87
4-*n*-Butyl	G, SA, NC	6-*n*-Butylquinoline	82	927
4-*n*-Dodecyl	G, SA, NC	6-*n*-Dodecylquinoline	56	927
4-Phenyl	G, SA, $FeSO_4$	6-Phenylquinoline	42	96, 98, 931
4-Benzhydryl	G, SA, NC	6-Benzhydrylquinoline	—	932
4-(4-Biphenylyl)	G, SA, NC, boric acid	6-(4-Biphenylyl)quinoline	59	933
4-(2-Pyridyl)	G, SA, As	6-(2-Pyridyl)quinoline	—	921
4-(3-Pyridyl)	G, SA, As	6-(3-Pyridyl)quinoline	—	921
4-(4-Pyridyl)	G, SA, As	6-(4-Pyridyl)quinoline	—	921
4-(2,6-Dimethyl-4-pyridyl)	G, SA, As, NC	6-(2,6-Dimethyl-4-pyridyl)quinoline	71	934

[c] Hydrochloride used. [d] As acetyl derivative. [e] Using the nitro-compound, not the aniline.

TABLE 1A (*Cont.*)

Aniline substituent	Reagents	Quinoline	Yield (%)	References
Alkyl and Aryl Substituents (Contd.)				
4-(1-Piperidylmethyl)	G, SA, NC, $FeSO_4$, boric acid	6-(1-Piperidylmethyl)quinoline	—	922
4-(1-Pyrazolyl)	G, SA, As	6-(1-Pyrazolyl)quinoline	25	935
4-(4-Nitro-1-pyrazolyl)	G, SA, As	6-(4-Nitro-1-pyrazolyl)quinoline	—	935
4-(2-Benzimidazolyl)	G, SA, NC	6-(2-Benzimidazolyl)quinoline	40	936
4-(2-Benzothiazolyl)	G, SA, As	6-(2-Benzothiazolyl)quinoline	15	937
4-(2-Quinolyl)	G, SA, NC (180 °C)	2,6-Biquinoline	—	938
Haloquinolines and Nitroquinolines				
2-Fluoro	G, SA, NC, $FeSO_4$, boric acid	8-Fluoroquinoline	72	59
2-Chloro	G, SA (65), NC	8-Chloroquinoline	68	59, 939
2-Bromo	G, SA (75), NC	8-Bromoquinoline	49	59, 88, 940, 941
2-Nitro	G, SA, As	8-Nitroquinoline	72	942, 943, 168, 670, 944
	Acrolein, phosphoric acid (85), As		32	102
3-Fluoro	G, SA, NC	5- and 7-Fluoroquinoline (1 : 3)	73	60
3-Chloro	G, SA, NC, $FeSO_4$, boric acid	5- and 7-Chloroquinoline	79 total	945, 59, 60, 939, 941
3-Bromo	G, SA, NC	5- and 7-Bromoquinoline	61 total	941, 60, 78, 946
3-Iodo	G, SA (70), NC	5- and 7-Iodoquinoline (1 : 1)	69 total	60
3-Nitro	G, SA (70), NC	5- and 7-Nitroquinoline (3.5 : 1)	57	60, 78, 947, 168, 670, 944
4-Fluoro	G, SA, NC, $FeSO_4$, boric acid	6-Fluoroquinoline	98	948, 939
4-Chloro	G, SA (65), NC	6-Chloroquinoline	90	59, 949, 931
4-Bromo	G, SA (75), NC	6-Bromoquinoline	69	59, 931, 941, 102
4-Nitro	G, SA, As	6-Nitroquinoline	67	950, 949, 168, 670, 944, 409

Hydroxy-, Alkoxy-, and Aryloxy-quinoline				
2-Hydroxy	G, SA, acetic acid	8-Hydroxyquinoline	90–98	951, 167, 89, 85, 952, 953, 84, 67, 915, 954, 955
	Acrolein diacetate, HCl		82	114
2-Hydroxy-5-sulphonic acid[f]	G, SA, NC		72	67
2-Methoxy	G, SA, NC	8-Methoxyquinoline	39	956, 957
[g]	G, SA, $FeSO_4$, NC		Good	96
	Acrolein diacetate, $FeCl_3$, acetic acid, HCl		35	112
2-Ethoxy	G, SA, NC, $FeSO_4$	8-Ethoxyquinoline	39	956
3-Hydroxy	G, SA (70), NC	7-Hydroxyquinoline	46	78
3-Methoxy	G, SA, NC	7-Methoxyquinoline (trace of 5-hydroxyquinoline)	46	958, 233, 60, 78
3-Phenoxy	"Skraup reagents"	7-Phenoxyquinoline	—	959
4-Hydroxy	G, SA, NC	6-Hydroxyquinoline	Poor	951, 960
4-Methoxy	G, SA (90), NC	6-Methoxyquinoline	64	961, 962, 963
	G, SA (85), NC, boric acid	6-Methoxyquinoline and 6-hydroxyquinoline	57 7	960
	1,3,3-Triethoxypropane, SA, NC		43	116
4-Ethoxy	G, SA, NC, $FeSO_4$	6-Ethoxyquinoline	50	956, 569, 964
Quinoline-carboxylic and -sulphonic acids				
2-Carboxyl	G, SA, NC	Quinoline-8-carboxylic acid	53	965, 966, 967
3-Carboxyl	G, SA (75), NC	Quinoline-5- and -7-carboxylic acids (5 : 1)	70 total	78, 914
3-Sulphonic acid	G, SA, NC	Quinoline-5- and quinoline-7-sulphonic acid	51 total	78
4-Carboxyl	G, SA, As	Quinoline-6-carboxylic acid	78[h]	968, 123, 966

[f] Sulphonic acid group lost during synthesis. [g] Using the *N*-acetyl derivative. [h] Isolated as ethyl ester.

TABLE 1A (*Cont.*)

Aniline substituent	Reagents	Quinoline	Yield (%)	References
Quinoline-carboxylic and -sulphonic acids (Cont.)				
4-Sulphonic acid	G, SA, NC	Quinoline-6-sulphonic acid	40–55	969, 970, 971
4-Sulphonamido[g]	G, SA	Quinoline-6-sulphonamide	30	972
Miscellaneous Quinolines				
4-Benzoyl	G, SA, As, boric acid (138–140 °C)	6-Benzoylquinoline	57	73, 72, 973
4-Acetyl	G, SA	None	—	72
3-Dimethylamino		5- and 7-Dimethylaminoquinoline (1 : 3)	27 total	60, 168
4-Dimethylamino		6- Dimethylaminoquinoline	66	168, 974

TABLE 1B. Quinolines with Two or More Substituents, Synthesized by Skraup, Doebner–von Miller or Related Routes

Aniline substituent	Reagents	Quinoline	Yield (%)	References
Alkyl- and Aryl-quinolines				
None	2-Methylbut-2-enal, $FeCl_3$, HCl (120 °C)	2,3-Dimethylquinoline	—	975
	3-Chloro-2-methylbut-2-enal, acetic acid		45	236, 237
	Propionaldehyde, HCl	2-Ethyl-3-methylquinoline	25	976, 977
	2-Methyl-3-oxobutanal, $ZnCl_2$	[a]	—	213
	Butyral, HCl	3-Ethyl-2-*n*-propylquinoline	79	978
	3-Chloro-2-methyl-3-phenylacrolein, acetic acid	3-Methyl-2-phenylquinoline	94	236, 237
	Pentane-2,4-dione, then SA	2,4-Dimethylquinoline	Up to 75	979, 980
	Acetaldehyde, acetone, NC (or conc. HCl)		—	206
	4-Hydroxypentan-2-one, SA, NC, $FeSO_4$ (160 °C)		20	981, 982
	Pent-3-en-2-one, $FeCl_3$, HCl, $ZnCl_2$		61	149
	Acetone, propane-1,2-diol, SA, NC (140–150 °C)	2-Ethyl-4-methylquinoline	50	158
	Heptane-3,5-dione, then SA	2,4-Diethylquinoline	—	983
	1-Phenylbutane-1,3-dione, then SA	2-Methyl-4-phenylquinoline	40	227, 979, 156
	1-(3-Pyridyl)butane-1,3-dione, then SA (110 °C)	2-Methyl-4-(3-pyridyl)quinoline	75	984
	1-(4-Pyridyl)butane-1,3-dione, then SA (110 °C)	2-Methyl-4-(4-pyridyl)quinoline	85	984
	1-(5-Nitro-2-furyl)butane-1,3-dione, then SA (120 °C)	2-Methyl-4-(5-nitro-2-furyl)quinoline	—	226
	3-Methylbut-3-en-2-one, $FeCl_3$, acid	3,4-Dimethylquinoline	52	138
	4-Dimethylamino-3-methylbutan-2-one, $ZnCl_2$, $FeCl_3$, HCl		40	151
2-Methyl	Acetaldehyde, HCl, $ZnCl_2$	2,8-Dimethylquinoline	—	981, 985

[a] With some 3-ethyl-4-methylquinoline.

TABLE 1B (*Cont.*)

Aniline substituent	Reagents	Quinoline	Yield (%)	References
Alkyl- and Aryl-quinolines (Contd.)				
2-Methyl	Crotonaldehyde, As, SA	2,8-Dimethylquinoline	—	986
	Sodium, paraldehyde, then HCl[b]		34	987
3-Methyl	Paraldehyde, conc. HCl	2,7-Dimethylquinoline	—	981, 985
	Crotonaldehyde, SA, NC		62	126
	2-Methylacrolein diacetate, SA, As, NC	3,7-Dimethylquinoline (+some 3,5-dimethylquinoline)	65	126
4-Methyl	Acetaldehyde, HCl, $ZnCl_2$	2,6-Dimethylquinoline	50	981
	Crotonaldehyde, SA, NC		49	985
	2-Methylacrolein diacetate, SA, As, NC	3,6-Dimethylquinoline	54	126
	4-Diethylaminobutan-2-one, $ZnCl_2$, $FeCl_3$, HCl, NC	4,6-Dimethylquinoline	50–55	151
2,3-Dimethyl	G, SA, NC, $FeSO_4$	7,8-Dimethylquinoline	50	981
2,4-Dimethyl	G, SA, NC, boric acid	6,8-Dimethylquinoline	70	981, 988
	Paraldehyde, acetone, HCl	2,4,6,8-Tetramethylquinoline	—	989
2,5-Dimethyl	G, SA, NC, boric acid	5,8-Dimethylquinoline	—	981
	Pentane-2,4-dione, SA or acetone, paraldehyde, HCl	2,4,5,8-Tetramethylquinoline	90	227, 990
	3-Methylpent-3-en-2-one, H_3PO_4 (85), As	2,3,4,5,8-Pentamethylquinoline	6	141
3,4-Dimethyl	G, SA, NC, boric acid	6,7-Dimethylquinoline	67	981
	4-Hydroxy-3-methylbutan-2-one, H_3PO_4, As	3,4,6,7-Tetramethylquinoline	14	141
3,5-Dimethyl	G, SA, NC, $FeSO_4$	5,7-Dimethylquinoline	Small	991
Haloquinolines and Nitroquinolines				
None	2,3,3-Trichlorobutanal, $ZnCl_2$, HCl	3-Chloro-2-methylquinoline	7	992
	Methylal, chloroacetone, HCl	3-Chloro-4-methylquinoline	4	993
2-Chloro	Crotonaldehyde, SA, As	8-Chloro-2-methylquinoline	—	986
[c]	Sodium, paraldehyde, then HCl		—	987
	Acetone, formaldehyde, $FeCl_3$ (80–90 °C)	8-Chloro-4-methylquinoline	20	995
	1,3,3-Trimethoxybutane, $FeCl_3$, HCl		23	149
2-Bromo	Crotonaldehyde, HCl, SA	8-Bromo-2-methylquinoline	20	996
3-Fluoro	Paraldehyde, $ZnCl_2$, HCl	7-Fluoro-2-methylquinoline	33	997

3-Chloro	Paraldehyde, NC, SA	5- and 7-Chloro-2-methylquinoline (1 : 3)	60	998
	Crotonaldehyde, SA, NC	7-Chloro-2-methylquinoline	60	126
	1,1,3-Trimethoxybutane, $FeCl_3$, HCl	7-Chloro-2-methylquinoline	30	129
	Acetaldehyde, HCl	7 (or 5)-Chloro-2-methylquinoline	—	999
	Methacraldehyde diacetate, SA, As	7-Chloro-3-methylquinoline	52	126
	1,3,3-Trimethoxybutane, $FeCl_3$, HCl	5- and 7-Chloro-4-methylquinoline (45 : 65)	67	1000
3-Bromo	Paraldehyde, HCl	5(or 7)-Bromo-2-methylquinoline	—	1001
4-Fluoro	Paraldehyde, $ZnCl_2$, HCl	6-Fluoro-2-methylquinoline	32	997
4-Chloro	Crotonaldehyde, $FeCl_3$, $ZnCl_2$, HCl	6-Chloro-2-methylquinoline	79	1002
	Crotonaldehyde, SA, NC		55	126
	Crotonaldehyde, SA, As		—	986
	Acetaldehyde, HCl		—	999
	3-Chlorobutan-2-one	6-Chloro-4-methylquinoline	55	147
	1,3,3-Trimethoxybutane, $FeCl_3$, HCl		55	1003
4-Bromo	Paraldehyde, HCl	6-Bromo-2-methylquinoline	—	1001
	Methacraldehyde	6-Bromo-3-methylquinoline	—	981
4-Iodo	Paraldehyde, HCl, $ZnCl_2$	6-Iodo-2-methylquinoline	20	62, 59
2-Chloro-5-methyl	G, SA, NC	8-Chloro-5-methylquinoline	62	1004, 1005
2-Chloro-3-methyl	Acrolein diacetate, $FeCl_3$, acetic acid, HCl	8-Chloro-7-methylquinoline	16	112
	"Skraup"		—	1006
2-Bromo-4-methyl	G, SA, As	8-Bromo-6-methylquinoline	36	1007
3-Chloro-2-methyl	G, SA, NC	7-Chloro-8-methylquinoline	74	78
3-Bromo-2-methyl		7-Bromo-8-methylquinoline	—	1008
4-Bromo-2-methyl		6-Bromo-8-methylquinoline	95	1009
4-Chloro-3-methyl	"Skraup"	6-Chloro-5-methylquinoline	57	1010
5-Bromo-2-methyl		5-Bromo-8-methylquinoline	7	1008
2-Nitro	Paraldehyde, HCl	2-Methyl-8-nitroquinoline	15–20	1011
	Crotonaldehyde		62	1012
	Methacraldehyde diacetate, SA, As	3-Methyl-8-nitroquinoline	43	1013
	4-Hydroxybutan-2-one, As	4-Methyl-8-nitroquinoline	50	46
	Methyl vinyl ketone		62	1012
3-Nitro	Acetaldehyde, HCl	2-Methyl-5-nitroquinoline	—	1014, 1015

[b] The *N*-formyl derivative was used. [c] On the *N*-formyl derivative.

TABLE 1B (*Cont.*)

Aniline substituent	Reagents	Quinoline	Yield (%)	References
Haloquinolines and Nitroquinolines (Contd.)				
4-Nitro	Paraldehyde, HCl	2-Methyl-6-nitroquinoline	27	1016, 148
	Crotonaldehyde dipropionate, As, SA		30	126
	Methacraldehyde diacetate, SA, As	3-Methyl-6-nitroquinoline	35	126
	4-Chlorobutan-2-one, NC, As	4-Methyl-6-nitroquinoline	20	144, 148, 147
4-Methyl-2-nitro	G, SA, NC	6-Methyl-8-nitroquinoline	81	1017, 999
			60	988
2-Methyl-3-nitro	"Bradford Elliott and Rowe's method" (G, SA, As)	8-Methyl-7-nitroquinoline	—	1018
4-Methyl-3-nitro	G, SA, NC	6-Methyl-5(and 7)-nitroquinoline	53	1019
2-Methyl-4-nitro	G, SA, NC	8-Methyl-6-nitroquinoline	—	1020, 148
3-Methyl-4-nitro	G, SA, As	5-Methyl-6-nitroquinoline	7	148
		7-Methyl-6-nitroquinoline	35	
2-Methyl-5-nitro	G, SA, NC	8-Methyl-5-nitroquinoline	—	988
3-Methyl-6-nitro	G, SA, NC, Boric acid	5-Methyl-8-nitroquinoline	23	981, 1021
4-Fluoro-2-nitro	G, SA (130–160 °C), As	6-Fluoro-8-nitroquinoline	46	948
2-Chloro-5-nitro	G, SA, As (130 °C)	8-Chloro-5-nitroquinoline	63	939, 1022
4-Chloro-3-nitro	G, SA, As (120 °C)	6-Chloro-7-nitroquinoline (+6-chloro-5-nitroquinoline)	—	939
4-Chloro-2-nitro	G, SA, As (to 125 °C)	6-Chloro-8-nitroquinoline	75	1023, 1024
	2,2,3-Tribromopropional, acetic acid	3-Bromo-6-chloro-8-nitroquinoline	—	106
2-Bromo-4-nitro	SA (50–60), G, As	8-Bromo-6-nitroquinoline	65	1025
4-Bromo-2-nitro	2-Bromoacrolein diacetate, SA, As (130 °C)	3,6-Dibromo-8-nitroquinoline	—	108
Hydroxy- and Alkoxy-quinolines				
2-Hydroxy	Paraldehyde, HCl	8-Hydroxy-2-methylquinoline	24	1026
	As, Crotonaldehyde, NC			
	Crotonaldehyde, PPA (90 °C)		20–24	1027
	Methacraldehyde, SA, As, HCl	8-Hydroxy-3-methylquinoline	4	1028
	MVK, HCl	8-Hydroxy-4-methylquinoline	20	1029

2-Methoxy	Paraldehyde, HCl	8-Methoxy-2-methylquinoline	—	1015
	NC, HCl, butylvinylether		25	1030
	1,1,3-Trimethoxybutane, NC, ammonium chloride		55	1031
	Crotonal, HCl, NC		44–49	1032
	MVK, SA, acetic acid (90 °C)	8-Methoxy-4-methylquinoline	19	46
3-Methoxy	1,3-Diphenylpropane-1,3-dione, HCl, acetic acid (0 °C)	7-Methoxy-2,4-diphenylquinoline	80	233
4-Hydroxy	Paraldehyde, HCl	6-Hydroxy-2-methylquinoline	24	1015
4-Methoxy	Crotonal, $FeCl_3$, on hydrochloride	6-Methoxy-2-methylquinoline	45	129
	Paraldehyde, conc. HCl		25	1033, 1034
	MVK, 4-methoxybutan-2-one or 2,2,4-trimethoxybutane + $FeCl_3$ on the hydrochloride	6-Methoxy-4-methylquinoline	52	149, 144, 993
	Acetone, methylal, HCl			
4-Ethoxy	Paraldehyde, acetone, HCl	6-Ethoxy-2,4-dimethylquinoline	—	1035
	Acetone, formaldehyde, HCl	6-Ethoxy-4-methylquinoline	—	1036
2-Hydroxy-3-methyl	G, SA, NC	8-Hydroxy-7-methylquinoline	80	988
2-Hydroxy-5-methyl	G, SA, NC	8-Hydroxy-5-methylquinoline	65	988
2-Methoxy-5-methyl	"Skraup"	8-Methoxy-5-methylquinoline	50	68
4-Methoxy-2-methyl	G, SA, As, $FeSO_4$	6-Methoxy-8-methylquinoline	48	1037

Carboxylic Acids, Sulphonic Acids, Ketones, and Amines

None	Benzoylacrylic acid, NC, HCl	4-Phenylquinoline-2-carboxylic acid	Very small	230
2-Ethoxycarbonyl	4-Chlorobutan-2-one, acid, NC	4-Methylquinoline-8-carboxylic acid	—	144, 147
3-Ethoxycarbonyl	1,3-Diethoxy-2-phenylpropan-2-ol, H_3PO_4 (85) (60–80 °C)	Ethyl 3-phenylquinoline-5-carboxylate	19	132
4-Carboxy	Crotonaldehyde, SA, As, or NC	2-Methylquinoline-6-carboxylic acid	—	986
2-Cyano-4-methyl[d]	G, SA, As	6-Methylquinoline-8-carboxylic acid	70	63, 78
2-Cyano-5-methyl	G, SA, As (140–145 °C)	5-Methylquinoline-8-carboxylic acid	70	64
2-Chloro-5-carboxy	G, SA, As (150–160 °C)	8-Chloroquinoline-5-carboxylic acid	83	968
4-Chloro-3-carboxy	G, SA, As (150–160 °C)	6-Chloroquinoline-5-carboxylic acid	38	1010
2,4-Dichloro-5-carboxy	G, SA, As	6,8-Dichloroquinoline-5-carboxylic acid	24	1010

[d] Using the nitro-compound, not the aniline.

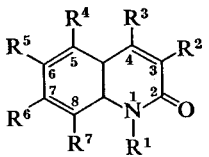
TABLE 1B (*Cont.*)

Aniline substituent	Reagents	Quinoline	Yield (%)	References
Carboxylic Acids, Sulphonic Acids, Ketones, and Amines (Contd.)				
5-Nitro-2-carboxy	G, SA (65), As	5-Nitroquinoline-8-carboxylic acid	70	78
2-Hydroxy-5-methoxy-carbonyl	G, SA, As (140–150 °C)	8-Hydroxyquinoline-5-carboxylic acid	25	1038
2-Hydroxy-4-methoxy-carbonyl	G, SA, As (140–150 °C)	8-Hydroxyquinoline-6-carboxylic acid	60	1038
4-Methoxy-2-carboxy	G, SA, NC	6-Methoxyquinoline-8-carboxylic acid	20	965
4-Sulphonic acid	Benzaldehyde, glycerol, SA, dichromate	2-Phenylquinoline-6-sulphonic acid	—	1039
2-Methyl-4-sulphonic acid	G, SA, NC	8-Methylquinoline-6-sulphonic acid	85	1040, 1020
2-Methyl-5-sulphonic acid	G, SA, NC	8-Methylquinoline-5-sulphonic acid	85	1040
4-Methyl-2-sulphonic acid	G, SA, NC	6-Methylquinoline-8-sulphonic acid	—	970
4-Methyl-3-sulphonic acid	G, SA, NC	6-Methylquinoline-7-sulphonic acid	40	1041
2-Chloro-5-sulphonic acid	G, SA	8-Chloroquinoline-5-sulphonic acid	—	1042
2,5-Dimethyl-4-sulphonic acid	G, SA, NC	5,8-Dimethylquinoline-7-sulphonic acid	—	1043
2,5-Dimethyl-4-sulphonic acid	G, SA, NC	5,8-Dimethylquinoline-6-sulphonic acid	—	1043
3-Amino	Pentane-2,4-dione, SA	5- or 7-Amino-2,4-dimethyl-quinoline	—	1045
4-Amino-2,5-dimethyl	G, SA, NC	6-Amino-5,8-dimethylquinoline	—	1044
3-Amino-2-methyl-5-carboxy	G, SA, NC	7-Amino-8-methylquinoline-5-carboxylic acid	—	1045
	Paraldehyde, HCl	7-Amino-2,8-dimethylquinoline-5-carboxylic acid	—	1045
3-Amino-2-methyl-5-sulphonic acid	G, SA, NC	7-Amino-8-methylquinoline-5-sulphonic acid	—	1045
	Paraldehyde, HCl	7-Amino-2,8-dimethylquinoline-5-sulphonic acid	—	1045
4-Acetyl	Paraldehyde, acid	6-Acetyl-2-methylquinoline	Poor	72
2-Benzoyl	Paraldehyde, SA	8-Benzoyl-2-methylquinoline	—	74
Di-(*p*-tolyl)amine	Pentane-2,4-dione, HCHO, NC, HCl, or $HClO_4$	3-Acetyl-4,6-dimethyl-1-(*p*-tolyl)-quinolinium chloride or perchlorate	—	1046
Di-(*p*-anisyl)amine	Pentane-2,4-dione, HCHO, NC, HCl, or $HClO_4$	3-Acetyl-1-(*p*-anisyl)-6-methoxy-4-methylquinolinium chloride or perchlorate	—	1046

TABLE 2. Quinolones Synthesized by Knorr or Conrad–Limpach Procedures

TABLE 2A. 2-Quinolones Synthesized by the Knorr Procedure

Table 2A is arranged with 2-quinolone and mono-substituted 2-quinolones first. Then follow *x*,*y*-disubstituted 2-quinolones where *x* increases (1, 3, 4); within each group *y* increases also (e.g. 4, 5; 4, 6; etc.). Some more highly substituted quinolones are included with most groups.



R^1	R^2	R^3	R^4	R^5	R^6	R^7	Yield (%)	References
H	H	H	H	H	H	H	100	368, 391
CH_3	H	H	H	H	H	H	73	368, 391
H	CH_3	H	H	H	H	H	82	368, 391, 301
H	C_6H_5	H	H	H	H	H	—	1047
H	H	CH_3	H	H	H	H	86–91	1048, 1049, 1050, 304, 301, 303, 1051, 980
H	H	$BrCH_2$	H	H	H	H	—	385
H	H	C_2H_5	H	H	H	H	37	381
H	H	C_6H_5	H	H	H	H	70	304, 1052, 1053
H	H	2-Furyl	H	H	H	H	—	383
H	H	H	H	CH_3	H	H	100	368, 391
H	H	H	H	Cl	H	H	100	368, 391
H	H	H	H	H	H	CH_3	89	368, 391
H	H	H	H	H	H	Cl	100	368, 391
CH_3 [a]	H	CH_3	H	H	H	H	83	305, 1054
C_6H_5	H	CH_3	H	H	H	H	Quant.	1055, 1056, 375

[a] Also 1-ethyl (83%), 1-*n*-C_3H_7 (58%), 1-*n*-C_4H_9 (72%), 1-*n*-C_5H_{11} (74%), 1-allyl (44%), and 1-benzyl (58%).

TABLE 2A (*Cont.*)

R^1	R^2	R^3	R^4	R^5	R^6	R^7	Yield (%)	References
CH_3	H	$CO_2C_2H_5$	H	H	H	H	53	1054, 389
H	CH_3	CH_3	H	H	H	H	100	393, 371
H	C_2H_5	CH_3	H	H	H	H	99	393, 371
H	*n*-C_3H_7	CH_3	H	H	H	H	76	393, 371
H	*n*-C_4H_9	CH_3	H	H	H	H	89	393, 371
H	$C_6H_5CH_2$[b]	CH_3	H	H	H	H	89	402, 371
H	$C_2H_5OCH_2CH_2$	CH_3	H	H	H	H	50	1057
H	$CH_2(CH_2)_3CH_2$		H	H	H	H	—	398
H	2-Nitro-1-phenylethyl, etc.[c]	CH_3	H	H	H	H	35–54	394
H	Cl	CH_3	H	H	H	H	87	397
H	CH_3[d]	C_6H_5	H	H	H	H	89	372
H	CH_3[d]	*p*-$O_2NC_6H_4$	H	H	H	H	95	372
H	C_6H_5	C_6H_5	H	H	H	H	75	400
H	CH_3	H	H	H	H	CH_3	98	368, 391
H	H	CH_3	CH_3	H	H	CH_3	96	79, 1058, 306
H	H	CH_3	CH_3O	H	H	CH_3O	—	1059
H	H	C_6H_5	C_2H_5O	H	H	C_2H_5O	—	1059
H	H	CH_3	Cl	H	CH_3O	H	60	1060
H	H	CH_3	CH_3O	CH_3O	H	Cl	36	403
H	H	CH_3	Cl	NH_2	H	CH_3	—	1058
H	H	CH_3	Br	CH_3O	CH_3O	H	60	69
H	H	CH_3	CH_3O	CH_3O	CH_3O	H	80	1061
H	H	CH_3	CH_3O	CH_3O	H	NO_2	—	69
H	H	CH_3	H	CH_3	H	H	99	306, 378, 1062, 1063, 374, 376
H	H	CH_3	H	$NCCH_2$	H	H	—	376
H	H	CH_3	H	CH_3	H	CH_3	92	306
H	H	CH_3	H	CH_3	H	NO_2	—	376
H	H	CH_3	H	CH_3	NH_2	H	80	1064
H	H	CH_3	H	C_6H_5	H	H	—	377
H	H	CH_3	H	CH_3	Cl	H	90	1065
H	H	CH_3	H	CH_3	H	Cl	6–7	1065
H	H	CH_3	H	*p*-XC_6H_4	H	H	—	327

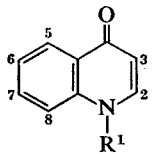
H	H	C_2H_5	H	CH_3	H	H	99	1066
H	H	CH_3	H	Cl	H	H	70	1067, 374
H	H	CH_3	H	Cl	H	Cl	35	99
H	H	CH_3	H	Cl	NH_2	H	81	1064
H	H	CH_3	H	Br	H	H	—	374
H	H	CH_3	H	NO_2	H	H	—	374
H	H	CH_3	H	CH_3O	H	H	100	1068, 1069, 1070, 374, 306
H	H	CH_3	H	CH_3O	CH_3O	H	70	1071, 735, 1072
H	H	CH_3	H	CH_3O	CH_3O	NO_2	—	1071
H	H	CH_3	H	NH_2	H	H	—	382
H	H	CH_3	H	SO_2NH_2	H	H	—	408
H	H	CH_3	H	SO_2NH_2	CH_3	H	—	408
H	H	CH_3	H	SO_2NH_2	H	CH_3	—	408
H	H	CH_2CO_2H	H	CH_3	H	H	58	388
H	H	CH_2CO_2H	H	Cl	H	H	54	388
H	H	CH_2CO_2H	H	Br	H	H	59	388
H	H	C_6H_5	H	Cl	H	H	62	1073
H	H	C_6H_5	H	CH_3O	H	H	30	381
H	H	C_6H_5	H	C_2H_5O	H	H	69	381
H	H	2-Furyl	H	CH_3	H	H	—	383
H	H	CH_3	H	H	CH_3	H	85	1062, 374, 1063
H	H	CH_3	H	H	Cl	H	—	1074
H	H	CH_3	H	H	Br	H	—	374
H	H	CH_3	H	H	CH_3O	H	—	374, 958
H	H	CH_3	H	H	C_2H_5O	H	100	380
H	H	CH_3	H	H	CH_3O	CH_3O	80	1061
H	H	CH_3	H	H	NH_2	H	92	1064, 409, 382, 1075
H	H	C_2H_5	H	H	CH_3	H	24	1066
H	H	C_6H_5	H	H	CH_3O	H	64	381

[b] Also 3-(4-nitrobenzyl) (81), phenethyl (25%), and other alkyl substituents.
[c] Variously substituted phenylethyl derivatives, with other substituents also in the benzenoid ring.
[d] Also 3-ethyl, n-C_3H_7, iso-C_3H_7, and $C_6H_5CH_2$ (only with p-$O_2NC_6H_4$).

TABLE 2A (*Cont.*)

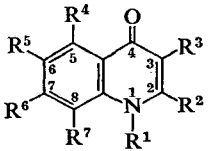
R^1	R^2	R^3	R^4	R^5	R^6	R^7	Yield (%)	References
H	H	C_6H_5	H	H	C_2H_5O	H	84	381
H	H	CH_2CO_2H	H	H	CH_3	H	50	388
H	H	CH_2CO_2H	H	H	Cl	H	58	388
H	H	CH_2CO_2H	H	H	Br	H	69	388
H	H	CH_3	H	H	H	CH_3	99	306, 1050, 304, 1063, 378, 374, 1076
H	H	CH_3	H	H	H	Cl	90	1077, 1078, 1079, 1065
H	H	CH_3	H	H	H	CH_3O	70	380
H	H	C_2H_5	H	H	H	CH_3	73	1066
H	H	CH_2CO_2H	H	H	H	CH_3	43	388
H	H	CH_2CO_2H	H	H	H	Cl	50	388
H	H	CH_2CO_2H	H	H	H	Br	62	388
H	H	C_6H_5	H	H	H	CH_3	50	304
H	H	C_6H_5	H	H	H	CH_3O	47	381
H	H	C_6H_5	H	H	H	C_2H_5O	57	381
H	H	C_6H_5	H	H	H	C_6H_5	—	1059
H	H	2-Furyl	H	H	H	CH_3	—	383
H	H	$CO_2C_2H_5$	H	H	NH_2	H	—	318

TABLE 2B. 4-Quinolones with a Single Substituent (including some Camps Syntheses)
C.L. = Conrad–Limpach. Ca = Camps

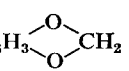


Substituent	Route (C.L. or Ca)	Yield (%)	References
None	C.L.	—	332
	Ca	68	587
2-Methyl	C.L.	90	302, 1080, 539, 310, 324
2-(Trichloromethyl)	C.L.	66	1081
2-Isopropyl	Ca	—	1082
2-*n*-Pentyl	C.L.	20	1083
2-*n*-Heptyl	C.L.	—	1084
2-*n*-Tridecyl	C.L.	35	1085
2-Phenyl	C.L.	55	1086, 1087
	Ca	—	1082
2-Methoxycarbonyl	C.L.	—	1088
2-Methoxycarbonyl	C.L.	70	339, 337, 1089, 1090
	Ca	Poor	587
3-Phenyl	C.L.	—	563
3-(*o*-Bromophenyl)	C.L.	—	563
3-Nitro	C.L.	80	339
3-Ethoxycarbonyl	C.L.	95	1091, 1092
	Ca	90 (crude)	587

TABLE 2C. Conrad–Limpach Syntheses of 4-Quinolones with Two Substituents



R^1	R^2	R^3	R^4	R^5	R^6	R^7	Yield (%)	References
CH_3	H	CO_2H	H	H	H	H	88	364
C_2H_5	H	CO_2H	H	H	H	H	96	364
C_2H_5	H	$CO_2C_2H_5$	H	H	H	H	—	1093
n-C_4H_9	H	CO_2H	H	H	H	H	78	364
H	CH_3	CH_3	H	H	H	H	40	1094
H	CH_3	C_2H_5	H	H	H	H	—	1094
H	CH_3	n-C_3H_7 [a]	H	H	H	H	—	1095
H	CH_3	Allyl	H	H	H	H	—	1095
H	CH_3	n-C_7H_{15}	H	H	H	H	30	1096
H	$CH_2CH_2CH_2$		H	H	H	H	—	589
H	CH_3	$CH{=}CCl_2$	H	H	H	H	83	1097
H	CH_3	$CO_2C_2H_5$	H	H	H	H	42	1098
H	CH_3	C_6H_5CO	H	H	H	H	48	1099
H	C_6H_5	C_2H_5	H	H	H	H	—	1100
H	C_6H_5	$CO_2C_2H_5$	H	H	H	H	27	1101, 1102, 338
H	C_6H_5	$CONH_2$	H	H	H	H	—	1087, 1103, 1104
H	p-ClC_6H_4	$CO_2C_2H_5$	H	H	H	H	40	1105
H	p-$O_2NC_6H_4$	$CO_2C_2H_5$	H	H	H	H	38	1105
H	o-$CH_3C_6H_4$ [b]	$CO_2C_2H_5$	H	H	H	H	—	1106
H	3,4-C_6H_3(O)(O)CH_2	$CO_2C_2H_5$	H	H	H	H	—	1107
H	C_6H_5	CH_3CO	H	H	H	H	60–80	1108, 1109

H	*o*-$CH_3C_6H_4$	CH_3CO	H	H	H	H	60–80	1108
H	*p*-$CH_3C_6H_4$	CH_3CO	H	H	H	H	70–90	1110
H	$CO_2C_2H_5$	CH_3	H	H	H	H	85	1112
H	CO_2R	Allyl [c]	H	H	H	H	85	348
H	$CO_2C_2H_5$	4-Cyclohexylbutyl	H	H	H	H	49	346
H	CH_3	H	H	CH_3	H	H	79	406, 1113
H	CH_3	H	H	$CH_2CO_2C_2H_5$	H	H	96	327
H	CCl_3	H	H	CH_3	H	H	44	1081
H	CH_3	H	H	Cl	H	H	70	304, 406, 349, 1114
H	CCl_3	H	H	Cl	H	H	69	1081
H	CH_3	H	H	Br	H	H	60–70	1114, 1115
H	CCl_3	H	H	Br	H	H	63	1081
H	CH_3	H	H	C_2H_5O	H	H	30	406, 358
H	CH_3	H	H	CH_3CO	H	H	82	73
H	CH_3	H	H	CH_3CONH	H	H	96	1116, 319, 1113
H	$CH_2CO_2C_2H_5$	H	H	CH_3	H	H	—	1117
H	C_6H_5	H	H	CH_3	H	H	50	329
H	C_6H_5	H	H	Cl	H	H	41	329
H	C_6H_5	H	H	Br	H	H	58	1086
H	C_6H_5	H	H	CH_3O	H	H	50	329, 1118
H	3,4- 	H	H	CH_3O	H	H	—	1119
H	2-Furyl	H	H	CH_3 [d]	H	H	—	383
H	*p*-$CH_3OC_6H_4$	H	H	CH_3CONH	H	H	92	320
H	$CO_2C_2H_5$	H	H	*n*-C_7H_{15}	H	H	—	1120
H	$CO_2C_2H_5$	H	H	$C_6H_5CH_2$	H	H	41	973
H	$CO_2C_2H_5$	H	H	$(C_6H_5)_3C$	H	H	80	973

[a] Also *n*-C_4H_9, *i*-C_4H_9, and higher alkyl groups.
[b] Also *m*- and *p*-$CH_3C_6H_4$, *m*- and *p*-BrC_6H_4, *m*-$CH_3OC_6H_4$, and 1-naphthyl substituents.
[c] Also 1- and 2-methylallyl.
[d] Also 6-Cl, 6-Br, 6-CH_3O, and 6-C_2H_5O substituents.

TABLE 2C (*Cont.*)

R^1	R^2	R^2	R^4	R^5	R^6	R^7	Yield (%)	References
H	$CO_2C_2H_5$	H	H	Cl	H	H	—	1088
H	$CO_2C_2H_5$	H	H	Br	H	H	50	343
H	$CO_2C_2H_5$	H	H	NO_2	H	H	40	343
H	$CO_2C_2H_5$	H	H	CH_3CO	H	H	—	1121
H	$CO_2C_2H_5$	H	H	C_6H_5CO	H	H	82	973
H	$CO_2C_2H_5$	H	H	CH_3O	H	H	85	1089, 1122, 735, 1123, 349
H	$CO_2C_2H_5$	H	H	CH_3CONH	H	H	—	1124
H	CH_3	H	H	H	CH_3 [e]	H	76	406, 998, 1125
H	CH_3	H	H	H	Cl [f]	H	72	332, 998, 406, 1126
H	CH_3	H	H	H	CH_3O	H	50	1127, 958
H	CH_3	H	H	H	NH_2	H	60	318
H	CF_3	H	H	H	CH_3O	H	—	330
H	$CH_2CO_2C_2H_5$	H	H	H	CH_3	H	—	1117
H	$CH_2CO_2C_2H_5$	H	H	H	Cl	H	—	1117
H	$CH_2CO_2C_2H_5$	H	H	H	Br	H	—	1117
H	C_6H_5	H	H	H	Cl [g]	H	—	1128
H	C_6H_5	H	H	H	OH [g]	H	—	314
H	C_6H_5	H	H	H	OCH_3	H	90	314
H	$CO_2C_2H_5$	H	H	H	Cl [g]	H	72	1129, 1130, 1131
H	$CO_2C_2H_5$	H	H	H	Br [g]	H	—	1129
H	$CO_2C_2H_5$	H	H	H	I [g]	H	—	1129
H	$CO_2C_2H_5$	H	H	H	C_6H_5O	H	—	1132
H	CH_3	H	H	H	H	CH_3	72	406, 304, 1133, 1117
H	CH_3	H	H	H	H	Cl	67	406, 1114, 1078
H	CH_3	H	H	H	H	CH_3O	72	406
H	CH_3	H	H	H	H	C_2H_5O	49	406
H	CH_3	H	H	H	H	CH_3CONH	—	321
H	CCl_3	H	H	H	H	Cl	43	1081
H	CCl_3	H	H	H	H	Br	63	1081

H	$CH_2CO_2C_2H_5$	H	H	H	H	CH_3	—	1117
H	$CH_2CO_2C_2H_5$	H	H	H	H	Cl	—	1117
H	$CH_2CO_2C_2H_5$	H	H	H	H	Br	—	1117
H	C_6H_5	H	H	H	H	CH_3	38	304, 1108
H	2-Furyl	H	H	H	H	CH_3	—	383
H	2-Furyl	H	H	H	H	CH_3O	—	383
H	$CO_2C_2H_5$	H	H	H	H	NO_2	47	1134
H	$CO_2C_2H_5$	H	H	H	H	CH_3O	95	1135, 1136, 1137, 1138
H	CO_2CH_3	H	H	H	H	CO_2CH_3	73	342
H	CO_2CH_3	H	H	H	H	$CO_2C_2H_5$	—	350
H	H	$CO_2C_2H_5$	CH_3 [h]	H	H	H	—	1141
H	H	$CO_2C_2H_5$	Cl [h]	H	H	H	—	1141
H	H	$CO_2C_2H_5$	CN	H	H	H	—	1140
H	H	CH_3CO	H	CH_3	H	H	36	1141
H	H	CH_3CO	H	Cl	H	H	52	1141
H	H	CH_3CO	H	Br	H	H	50	1142
H	H	CH_3CO	H	NO_2	H	H	—	1141, 1142
H	H	CH_3CO	H	CH_3O	H	H	28	1141
H	H	CH_3CO	H	C_2H_5O	H	H	65	1141
H	H	CH_3CO	H	6-(*m*-Nitro-anilino)	H	H	93	1141
H	H	$CO_2C_2H_5$	H	CH_3	H	H	55	1092, 356
H	H	$CO_2C_2H_5$	H	n-C_7H_{15}	H	H	[i]	1120
H	H	$CO_2C_2H_5$	H	p-$O_2NC_6H_4$	H	H	88	1144
H	H	$CO_2C_2H_5$	H	F	H	H	—	1145
H	H	$CO_2C_2H_5$	H	Cl	H	H	80	1091, 1092, 1146, 356
H	H	$CO_2C_2H_5$	H	Br	H	H	99	1147
H	H	$CO_2C_2H_5$	H	NO_2	H	H	90	1091, 1148

[e] Mixed with the 5-substituted isomer.
[f] Sometimes mixed with 5-chloro-isomer.
[g] With some 5-chloro-isomer.
[h] Orientation said to depend on cyclization medium.
[i] 46 g of starting material were said to give 50 g of product (>100%).

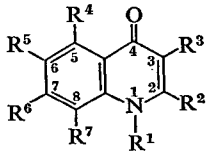
TABLE 2C (*Cont.*)

R^1	R^2	R^3	R^4	R^5	R^6	R^7	Yield (%)	References
H	H	$CO_2C_2H_5$	H	CH_3O	H	H	65	1149, 1145, 1150, 1151, 1152
H	H	$CO_2C_2H_5$	H	C_2H_5O	H	H	56	1153
H	H	$CO_2C_2H_5$	H	C_6H_5O	H	H	71	1091
H	H	$CO_2C_2H_5$	H	CO_2H	H	H	—	1154
H	H	$CO_2C_2H_5$	H	CH_3CONH	H	H	70	1091, 1092
H	H	$CO_2C_2H_5$	H	$(CH_3)_2N$	H	H	50	1091
H	H	$CO_2C_2H_5$	H	C_6H_5NH	H	H	—	1148
H	H	$CO_2C_2H_5$	H	Thiazole-2-sulphonamido	H	H	93	1155
H	H	$CO_2C_2H_5$	H	Phenylazo	H	H	81	1156, 1157
H	H	$CO_2C_2H_5$	H	p-$RC_6H_4N=N$[j]	H	H	—	1157
H	H	CH_3	H	H	Cl[k]	H	65–75	332
H	H	C_6H_5	H	H	Cl[k]	H	36	1158, 1159, 353
H	H	CH_3CO	H	H	Cl	H	90	1159, 353, 1142
H	H	CH_3CO	H	H	NO_2	H	—	1142
H	H	CN	H	H	CF_3	H	50	1159, 353
H	H	CN	H	H	Cl	H	90	1159, 353, 352
H	H	m-ClC_6H_4-NHCO	H	H	Cl	H	50	1159, 353, 352
H	H	$CO_2C_2H_5$	H	H	CH_3	H	83–97[k]	356, 1141
H	H	$CO_2C_2H_5$	H	H	CF_3	H	84	1145, 347
H	H	$CO_2C_2H_5$	H	H	F	H	—	1145
H	H	$CO_2C_2H_5$	H	H	Cl	H	85–90	1160, 1161, 1145, 356, 1092, 1162 1163, 1164, 355, 1165, 1166
H	H	$CO_2C_2H_5$	H	H	Br	H	44	1167

H	H	$CO_2C_2H_5$	H	H	I	H	45	1167
H	H	$CO_2C_2H_5$	H	H	CH_3O	H	90	1166
H	H	$CO_2C_2H_5$	H	H	C_2H_5O	H	53	1168
H	H	$CO_2C_2H_5$	H	H	CF_3O	H	—	1169
H	H	$CO_2C_2H_5$	H	H	n-$C_6H_{13}O$	H	41	1168
H	H	$CO_2C_2H_5$	H	H	C_6H_5O	H	45	1091
H	H	CH_3CO	H	H	H	C_2H_5	—	1141
H	H	CH_3CO	H	H	H	Cl	60	1141
H	H	CH_3CO	H	H	H	NO_2	—	1141, 1142
H	H	CH_3CO	H	H	H	CH_3O	39	1141
H	H	CH_3CO	H	H	H	C_2H_5O	82	1141
H	H	$CO_2C_2H_5$	H	H	H	CH_3	77	1092, 1168, 1108, 356
H	H	$CO_2C_2H_5$	H	H	H	CF_3	—	1170
H	H	$CO_2C_2H_5$	H	H	H	p-$O_2NC_6H_4$	82	1171
H	H	$CO_2C_2H_5$	H	H	H	Cl	63	1141, 356, 1146, 1172
H	H	$CO_2C_2H_5$	H	H	H	NO_2	80	1091
H	H	$CO_2C_2H_5$	H	H	H	OH	—	1173
H	H	$CO_2C_2H_5$	H	H	H	CH_3O	80	1166
H	H	$CO_2C_2H_5$	H	H	H	CF_3O	—	1174
H	H	$CO_2C_2H_5$	H	H	H	C_2H_5O	15	1141
H	H	$CO_2C_2H_5$	H	H	H	CO_2CH_3	35	1175
H	H	$CO_2C_2H_5$	H	H	H	p-ClC_6H_4NH	50	1148

[j] R = $HOCH_2CH_2N(C_2H_5)$. [k] Plus some 5-isomer.

TABLE 2D. Selected Trisubstituted 4-Quinolones



R^1	R^2	R^3	R^4	R^5	R^6	R^7	Yield (%)	References
CH_3	H	CO_2H	H	H	H	CH_3	85	364
H	$CH_2CH_2CH_2CH_2$		H	CH_3 [a]	H	H	—	1115
H	CH_3	3-Chlorobut-2-enyl	H	$CO_2C_2H_5$	H	H	—	1097
H	CH_3	3,3-Dichloroallyl	H	CH_3CONH	H	H	—	1176
H	CH_3	$CO_2C_2H_5$	H	CH_3	H	H	40	1098
H	C_6H_5	CH_3CO	H	CH_3	H	H	—	1108, 1109
H	C_6H_5	CH_3CO	H	CH_3O	H	H	—	1108
H	p-$CH_3C_6H_4$	CH_3CO	H	CH_3	H	H	70–90	1110
H	p-$CH_3OC_6H_4$	CH_3CO	H	CH_3O	H	H	70–90	1110
H	C_6H_5	$CO_2C_2H_5$	H	CH_3	H	H	28	1101, 1111, 1105
H	C_6H_5	$CO_2C_2H_5$	H	Cl	H	H	30	1105, 1101
H	C_6H_5	$CO_2C_2H_5$	H	NO_2	H	H	35	1105
H	C_6H_5	$CO_2C_2H_5$	H	CH_3O	H	H	38	1128
H	p-$CH_3OC_6H_4$	$CO_2C_2H_5$	H	CH_3O [b]	H	H	—	358
H	3,4-C_6H_3(O)(O)CH_2	$CO_2C_2H_5$	H	CH_3O	H	H	—	1118
H	C_6H_5	$CONH_2$	H	CH_3	H	H	—	1087, 1104
H	$CO_2C_2H_5$	CH_3	H	CH_3	H	H	92	1112
H	$CO_2C_2H_5$	CH_3	H	F	H	H	89	345
H	$CO_2C_2H_5$	CH_3	H	Cl	H	H	95	1112, 1177
H	$CO_2C_2H_5$	CH_3	H	Br	H	H	77	1112

H	$CO_2C_2H_5$	CH_3	H	I	H	H	82	1178
H	$CO_2C_2H_5$	CH_3	H	NO_2	H	H	Poor	1179
H	$CO_2C_2H_5$	CH_3	H	CH_3O	H	H	97	1112, 349
H	$CO_2C_2H_5$	CH_3	H	C_2H_5O	H	H	95	1112
H	CH_3	CH_3	H	H	Cl [c]	H	—	346
H	CH_3	CH_3	H	H	CH_3O	H	17	1127
H	CH_3	n-C_7H_{15}	H	H	CH_3O	H	40	335
H	CH_3	C_6H_5CO	H	H	Cl [c]	—	—	1099
H	C_6H_5	$CO_2C_2H_5$	H	H	CH_3 [c]	H	—	1111, 1105
H	C_6H_5	$CO_2C_2H_5$	H	H	Cl [c]	H	—	1105, 1128
H	C_6H_5	$CO_2C_2H_5$	H	H	CH_3O	H	35	1128
H	$CO_2C_2H_5$	CH_3	H	H	CH_3	H	43 [h]	344
H	$CO_2C_2H_5$	CH_3	H	H	CF_3 [d]	H	46	347
H	$CO_2C_2H_5$	CH_3	H	H	F [e]	H	53	345
H	$CO_2C_2H_5$	CH_3	H	H	Cl [f]	H	50	1180
H	$CO_2C_2H_5$	CH_3	H	H	Br [g]	H	53	1180
H	$CO_2C_2H_5$	CH_3	H	H	I	H	60	1178
H	$CO_2C_2H_5$	CH_3	H	H	CH_3O	H	24	1177
H	$CO_2C_2H_5$	CH_3	H	H	C_2H_5O	H	69	344
H	$CH_2CH_2CH_2CH_2$		H	H	H	CH_3	—	1115
H	$CH_2CH_2CH_2CH_2$		H	H	H	CH_3O	—	1115
H	$CH_2CH_2CH_2CH_2$		H	H	H	C_2H_5O	—	1115
H	CH_3	CH_3CO	H	H	H	CH_3	30	1099
H	C_6H_5	CH_3CO	H	H	H	CH_3	—	1108
H	C_6H_5	$CO_2C_2H_5$	H	H	H	CH_3	26	1101, 1111, 1105
H	C_6H_5	$CO_2C_2H_5$	H	H	H	Cl	32	1105
H	p-$CH_3OC_6H_4$	$CO_2C_2H_5$	H	H	H	C_2H_5O	—	358
H	$CO_2C_2H_5$	CH_3	H	H	H	CH_3	87	1181
H	$CO_2C_2H_5$	CH_3	H	H	H	F	80	345
H	$CO_2C_2H_5$	CH_3	H	H	H	Cl	68	1177
H	$CO_2C_2H_5$	CH_3	H	H	H	Br	59	1181
H	$CO_2C_2H_5$	CH_3	H	H	H	I	89	1178

[a] Also 6-chloro-, 6-bromo-, 6-nitro-, 6-methoxy-, and 6-ethoxy-derivatives. [b] Also 6-ethoxy-derivative.
[c] With 5-isomer. [d] With 11% of 5-isomer. [e] With 45% of 5-fluoro-compound. [f] With 47% of 5-chloro-isomer. [g] With 45% of 5-bromo-isomer. [h] With 37% of 5-methyl isomer.

TABLE 2D (*Cont.*)

R^1	R^2	R^3	R^4	R^5	R^6	R^7	Yield (%)	References
H	$CO_2C_2H_5$	CH_3	H	H	H	CH_3O	85	1181
H	$CO_2C_2H_5$	CH_3	H	H	H	C_2H_5O	73	1181
H	CH_3	H	Cl	H	H	OH	40	1060
H	CF_3	H	CH_3O	H	H	Cl	95	330
H	$CO_2C_2H_5$	H	Cl	H	Cl	H	55	1129
H	$CO_2C_2H_5$	H	Cl	H	H	Cl	50	1129, 1182
H	$CO_2C_2H_5$	H	Br	H	H	Br	70	1129
H	CO_2CH_3	H	NO_2	H	H	CO_2CH_3	60	342
H	$CO_2C_2H_5$	H	CH_3O	H	H	CH_3O	86	1183, 735, 1184
H	$CO_2C_2H_5$	H	H	Cl	Cl [i]	H	—	1182
H	$CO_2C_2H_5$	H	H	CH_3O	Br [i]	H	—	1182, 1185
H	$CO_2C_2H_5$	H	H	CH_3O	CH_3O [i]	H	—	1186
H	CH_3	H	H	CH_3	H	CH_3	49	406, 1133
H	CH_3	H	H	Cl	H	Cl	—	1115, 1187
H	CO_2CH_3	H	H	CH_3	H	CO_2CH_3	82	342
H	CO_2CH_3	H	H	Cl	H	CO_2CH_3	70	342
H	CO_2CH_3	H	H	Br	H	CO_2CH_3	71	342
H	CO_2CH_3	H	H	I	H	CO_2CH_3	70	342
H	$CO_2C_2H_5$	H	H	Cl	H	CO_2CH_3	65	342
H	$CO_2C_2H_5$	H	H	H	CH_3O	CH_3O	—	1188
H	H	$CO_2C_2H_5$	CH_3	H	CH_3	H	51	1168
H	H	$CO_2C_2H_5$	CH_3	H	H	CH_3	59	1168
H	H	$CO_2C_2H_5$	CH_3	H	H	CH_3O	45	1168
H	H	$CO_2C_2H_5$	Cl	H	H	CH_3O	6	1168
H	H	$CO_2C_2H_5$	CH_3O	H	Cl	H	—	1145
H	H	$CO_2C_2H_5$	CH_3O	H	H	CH_3O	86	1183
H	H	CH_3CO	H	CH_3	H	CH_3	65	1141
H	H	CN	H	CH_3O [j]	CH_3O [j]	H	—	1164, 1189, 354
H	H	$CO_2C_2H_5$	H	CH_3	Cl	H	—	1190
H	H	$CO_2C_2H_5$	H	CH_3O	Cl	H	—	1163, 1145
H	H	$CO_2C_2H_5$	H	CH_3O [j]	CH_3O [j]	H	82	735, 1091, 1191

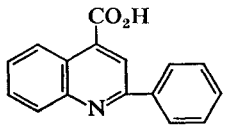
H	H	$CO_2C_2H_5$	H	C_2H_5O	C_2H_5O	H	85	1189, 1191, 1192, 1194, 735
H	H	$CO_2C_2H_5$	H	iso-C_4H_9O	iso-C_4H_9O	H	92	1189, 316, 1191–1193, 1195, 1196
H	H	$CO_2C_2H_5$	H	C_6H_5S	Cl	H	89	1091
H	H	$CO_2C_2H_5$	H	CH_3	H	CH_3	82	1168
H	H	$CO_2C_2H_5$	H	O—CH_2—O		H	78	1197
H	H	$CO_2C_2H_5$	H	O-$CH_2(CH_2)_nCH_2O$ [k]		H	—	1198
H	H	$CO_2C_2H_5$	H	CH_3O	H	NO_2	85	1091, 1148
H	H	$CO_2C_2H_5$	H	CH_3O	H	CH_3O	60	1172, 735
H	H	$CO_2C_2H_5$	H	p-$CH_3C_6H_4N_2$	H	CH_3	—	1156
H	H	$CO_2C_2H_5$	H	H	CH_3	CH_3	—	1199
H	H	$CO_2C_2H_5$	H	H	CH_3	Cl	73	1177

[i] With some 5,6-disubstituted isomer.
[j] Numerous other 6,7-dialkoxy-derivatives were also reported.
[k] $n = 1$ or 2.

TABLE 3. Quinoline-4-Carboxylic Acids Prepared by the Pfitzinger or Doebner Syntheses

Table 3 has three major sub-divisions. In Table 3A are listed many quinoline-4-carboxylic acids which have as the only other substituent a phenyl or substituted phenyl group at position 2. In Table 3B are quinoline-4-carboxylic acids with other aromatic or heterocyclic substituents at position 2. In Table 3C a range of substituted quinoline-4-carboxylic acids is shown, emphasizing in turn the positions 2–8. The synthesis used for each compound is shown as P or D (Pfitzinger or Doebner).

TABLE 3A. 2-Phenylquinoline-4-carboxylic Acids with No Other Substituent on the Quinoline Ring



Phenyl substituents	Route (D or P)	Yield (%)	References
Unsubstituted or Monosubstituted			
None	D	53	239, 241, 243, 267, 244, 1200
None	P	72	1201, 612, 1202[a]
o-Methyl	D	—	240
m-Methyl	P	—	1203
m-(Trifluoromethyl)	P	—	1204
p-Methyl	P	—	1203, 1205
	D	—	240
p-Cyclopentyl	P	—	1206
p-Phenethyl	P	—	1209
p-Phenyl	P	Quant.	1207, 1208, 1202
p-(*p*-Tolyl)	P	—	1210
p-(*p*-Ethylphenyl)	P	—	1210
p-(*p*-*n*-Propylphenyl)	P	76	1211
p-(*p*-Anisyl)	P	—	1212
p-(3-Bromo-4-methoxyphenyl)	P	60	1213
p-(2-Chloro-3-methoxyphenyl)	P	65	1214
p-(3-Chloro-4-methoxyphenyl)	P	80–90	1215
o-Fluoro	P	63	1216

o-Chloro	P	95	1216, 648, 1205
o-Bromo	P	67	648
m-Chloro	P	95	1216, 1205
p-Chloro	P	65	1216, 1205
p-Bromo	P	85	1217, 1216
p-Iodo	P and D	—	1218
o-Nitro	D	—	1219
m-Nitro	D	47	262, 1220
p-Nitro	D	6	1220, 1219
o-Amino	P	Quant.	1221
m-Amino	P	—	671
p-Acetylamino	D	80	123
p-Amino	P	92	123, 1222
p-Dimethylamino	D	—	1223
p-Diethylamino	D	35	1216
p-(Di-2-chloroethyl)amino	D	50	1224
o-Hydroxy	D	—	1225
p-(D-Glucopyranosyl)	D	75	1226, 1205
m-Hydroxy	P	90	1227
p-Hydroxy	D	—	1228
	P	Quant.	1228, 1205
p-Methoxy	D	—	1223
	P [b]	—	1229
p-(Anisyloxy)	P	70	1230
p-(Methylthio)	P	—	1231
p-Acetyl	P	46	1232
p-Carboxy	P	—	1232
Multisubstituted			
2,4-Dimethyl	P	—	1205, 1233
2,5-Dimethyl	P	95	1216, 1205, 1233
3,4-Dimethyl	P	—	1216, 1233, 1203
2-Fluoro-5-methyl	P	—	1234
4-Fluoro-2-methyl	P	—	1234
2,4-Dichloro	P	90	1216

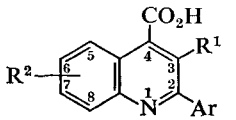
[a] Gave the amide. [b] And other 4-alkoxy-substituents.

TABLE 3A (*Cont.*)

Phenyl substituents	Route (D or P)	Yield (%)	References
2,5-Dichloro	P	90	1216
3,4-Dichloro	P	82	1216, 254
2-Chloro-3-methoxy	P	65	1214
3-Chloro-4-methoxy	P	—	1235
3-Fluoro-6-methoxy	P	—	1236
3-Bromo-4-methoxy	P	—	1235
5-Hydroxy-2-iodo	P	83	1237
4-Methoxy-2-methyl	P	—	1238
4-Methoxy-3-methyl [c]	P	—	1238
5-*tert*-Butyl-2-methoxy	P	—	1239
2-Methoxy-5-phenyl	P	82	1240
2,4-Dihydroxy	P	—	244
2,4-Dimethoxy	P	—	1239
2,5-Dimethoxy	P	—	1239
3,4-Dimethoxy	D	32	1241
	P	—	1239
3,4-(Dialkylmethylenedioxy)	P	75–85	1242
3-Carboxy-4-hydroxy	P	—	1243
2-Fluoro-4-(methylthio)	P	—	1204
3-Fluoro-4-(methylthio)	P	—	1204
2,4,5-Trimethyl	P	70	638, 1205
3,4,5-Trimethyl	P	90	1245
4-*tert*-Butyl-2,6-dimethyl	P	—	638
2-Methoxy-4,5-dimethyl [d]	P	—	1246
2-*tert*-Butyl-4-methoxy-6-methyl	P	—	638
4-Hydroxy-2-isopropyl-6-methyl	P	—	1247
2-Hydroxy-5-isopropyl-6-methyl	P	—	1248
3-Chloro-2-methoxy-5-phenyl	P	65	1214
2,3,4-Trimethoxy	P	—	1239
2-Hydroxy-3,4-dimethoxy	P	—	1241
2-Hydroxy-3,5-di-iodo	P	83	1237
2,3,4,5-Tetramethyl	P	—	1244

[c] And 4-ethoxy-, 4-propoxy-, and 4-butoxy-analogues. [d] And other similar trisubstituted ethers.

TABLE 3B. Quinoline-4-carboxylic Acids having a Polycyclic or Heterocyclic Group in Position 2



Aryl group	R^1	R^2	Route	Yield (%)	References
Polycyclic Substituents					
1-Naphthyl	H	H	P	79	691, 1216, 1249
	OH	H	P	—	653
4-Fluoro-1-naphthyl	H	H	P	—	1250
4-Fluoro-1-naphthyl	CH_3[a]	6-Br [a]	P	—	1250
2-Methoxy-6-*n*-propyl-1-naphthyl	H	H	P	60	1251
2-Methoxy-6-*n*-propyl-1-naphthyl			D	15	1251
2-Methyl-1-naphthyl	H	H	P	100	638
2-Methoxy-1-naphthyl	H	H	P	90	638
4-Methyl-1-naphthyl	H	H	P	Quant.	638
4,5-Dimethoxy-1-naphthyl	H	H	P	75	1252
4-Ethyl-3-methoxy-1-naphthyl	H	H	P	—	1253
3,6-Dimethoxy-1-naphthyl	H	H	P	—	1254
2,5-Dimethoxy-1-naphthyl	H	H	P	—	1254
2-Naphthyl	H	H	P	90	691, 1216, 1249, 641
	CH_3	H	P	90	638
	C_2H_5	H	P	90	638
	n-C_3H_7[b]	H	P	—	641
5,6,7,8-Tetrahydro-2-naphthyl	H	H	P	80	1255
	H	7-Br	P	—	1256
	p-Tolyl	H	P	—	1257
2,3-Dimethyl-2-naphthyl	C_6H_5	H	P	82	1258

[a] Other substituents also.
[b] And *n*-C_4H_9, *n*-C_5H_{11}, *n*-C_6H_{13}, *n*-C_7H_{15}, *n*-C_9H_{19}, *n*-$C_{11}H_{23}$.

TABLE 3B (*Cont.*)

Aryl group	R^1	R^2	Route	Yield (%)	References
7-*tert*-Butyl-2-naphthyl	H	H	P	—	1259
	H	6-CH_3	P	90	1259
	H	6-Br	P	80	1259
7-(Methylthio)-2-naphthyl	H	H	P	—	1259
	H	6-CH_3 [c]	P	—	615
	CH_3	6-CH_3 [c]	P	—	615
1-Hydroxy-2-naphthyl	H	H	P	—	1260
5-Bromo-6-methoxy-2-naphthyl	H	H [d]	P	—	1261
3,6-Dimethoxy-2-naphthyl	H	H	P	—	1254
6,7-Dimethoxy-2-naphthyl	H	H	P	—	1262
	CH_3	H	P	—	1262
2-Fluorenyl	H	H	P	95	638
	CH_3	H	P	90	638
	C_2H_5	H	P	40	638
5-Acenaphthenyl	CH_3	H	P	—	638, 1249
	C_2H_5	H	P	—	638, 1249
2-Biphenylyl	H	H	P	77	1263
2-Anthracenyl	H	H	P	—	1249, 1264
3-Phenanthryl	C_2H_5	H	P	—	638
1,2,3,4-Tetrahydro-9-phenanthryl	H	H	P	Quant.	1265
3-Pyrenyl	H	H	P	—	1249
2-Chrysenyl	H	H	P	—	1249
3-Retenyl	H	H	P	—	1266
Heterocyclic 2-Substituents					
2-Furyl	H	H	P	—	1267
	H	H	D	10	240, 1268
	CH_3	H	P	—	1269
	H	8-Cl	P	—	1270
5-Methyl-2-furyl	H	H	P	—	1269
	CH_3	H	P	—	1269
5-Nitro-2-furyl	H	8-Cl	P	—	1270
2-benzo[*b*]furyl	H	H	P	—	1271
	H	6-CH_3	P	—	1272
	CH_3	H	P	—	1272

	CH_3	6-CH_3	P	—	1272
	CH_3	6-Br	P	—	1272
	C_2H_5	H	P	—	1272
2,3-Dihydro-5-benzo[*b*]furyl	H	H	P	—	1273
2,3-Dimethyl-6-benzo[*b*]furyl	H	H	P	80	1274
7-Benzyl-2-benzo[*b*]furyl	H	H	P	—	1275
5-Chloro-2-benzo[*b*]furyl	H	H	P	—	1271
7-Methoxy-2-benzo[*b*]furyl	H	H	P	—	1271
2-Dibenzofuryl	H	H	P	75	1276
	CH_3 [e]	H	P	—	1276
8-Bromo-2-dibenzofuryl	H	H	P	—	1276
8-Ethyl-2-dibenzofuryl [f]	H	H	P	—	1277
	CH_3	H	P	—	1277
2-Methoxy-3-dibenzofuryl	H	H	P	10	1278
	CH_3	H	P	40	1278
2-Naphtho[1,2-*b*]furyl	H	H	P	—	1271
2,3-Dihydro-9-naphtho[2,1-*b*]furyl	H	H	P	—	1279
2-Thienyl	H	H	P	—	1280, 1281, 1208
	H	6-CH_3	P	—	1281, 1282
	CH_3 [g]	H	P	—	1282
	CH_3 [g]	6-CH_3	P	—	1282
	n-C_4H_9 [h]	6-CH_3	P	—	1283
	H	8-Cl	P	—	1270
3-Methyl-2-thienyl	H	H	P	—	1284
	CH_3	H	P	—	1285
4-Methyl-2-thienyl	H	H	P	—	1285
	H	6-CH_3	P	—	1285
5-Methyl-2-thienyl	H	H	P	65	1208, 1286
5-Ethyl-2-thienyl	H	6-Br	P	—	1287
	CH_3	6-Br	P	—	1287
4-*tert*-Butyl-2-thienyl	H	H	P	90	1288

[c] Also 6-Chloro-, and 6-bromo-derivatives.
[d] Also 6-methyl, 6-bromo-, and 6,8-dichloro-derivatives.
[e] Also 3-ethyl, or 3-phenyl. [f] Also 8-*n*-propyl, 8-heptyl-, or 8-octyl.
[g] Also C_2H_5, C_3H_7, or C_6H_5. [h] Also n-C_5H_{11} to n-$C_{10}H_{21}$.

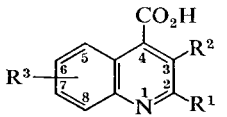
TABLE 3B (*Cont.*)

Aryl group	R^1	R^2	Route	Yield (%)	References
5-*tert*-Butyl-2-thienyl	H	6-Br	P	—	1289
	CH_3	H	P	—	1289
5-Phenyl-2-thienyl	H	H	P	50	1290
5-*p*-Tolyl-2-thienyl	H	H	P	—	1291
	CH_3	H	P	—	1291
5-*p*-Chlorophenyl-2-thienyl	H	H	P	—	1291
	CH_3	H	P	—	1291
2-(5,5′-Bithienyl)	C_6H_5	H	P	—	1291
	H	H	P	—	1290
5-Nitro-2-thienyl	H	6-F	P	—	1281
	H	8-CH_3	P	—	1281
2,5-Dimethyl-3-thienyl	H	H	P	60	1208, 1286
2-Benzo[*b*]thienyl	H	H	P	—	1248
4,5,6,7-Tetrahydro-2-benzo[*b*]-thienyl	H	H	P	—	1293, 1294
	H	6-CH_3	P	—	1293, 1294
	H	6-Cl	P	—	1294
3-Benzo[*b*]thienyl	H	H	P	80	1295, 1248
	H	6-CH_3	P	—	638
3-Ethyl-2-benzo[*b*]thienyl	H	H	P	—	1248
2,3-Dimethyl-6-benzo[*b*]thienyl	H	6-CH_3	P	—	1296
2,3,5-Trimethyl-6-benzo[*b*]thienyl	H	6-CH_3	P	—	1296
2-Dibenzothienyl	C_6H_5	H	P	50	1297, 1276
3-Dibenzothienyl	CH_3	H	P	90	638
5,6,7,8-Tetrahydro-2-dibenzothienyl	H	6-CH_3	P	Quant.	1298
2-Thianthrenyl	H	H	P	58	1299
2-Pyrryl	H	H	P	—	1267
3-Indolyl	H	8-Cl	P	—	1270
9-Ethyl-3-carbazolyl	H	6-Br	P	Quant.	1300
	CH_3	H	P	55	1300
	CH_3	6-Br	P	55	1300
6-Chloro-9-ethyl-3-carbazolyl	H	H	P	80	1300
	H	6-Br	P	Quant.	1300
2,3-Dimethyl-1-phenylpyrazin-5-on-4-yl	H	H	D	—	1301
	OH	H	P	—	653

2-Methyl-1-phenylpyrazin-5-on-4-yl	H	H	P	—	1302
1-Phenyl-2-(3-carboxy-4-hydroxyphenyl)-5-oxo-Δ^3-(1,2,3)-triazin-4-yl)[i]	H	H	P	—	1303
2-Methyl-1-phenylbenzimidazol-5-yl	H	H	P	79	1304
2-Pyridyl	H	6-CH_3	P	55	1305
	H	8-Cl	P	—	1270
	H	6,8-Cl_2	P	87	1306
3-Pyridyl	H	6-CH_3	P	62	1305, 1307
3-Pyridyl (1-oxide)	H	H	P	—	1308
4-Pyridyl	H	6-CH_3	P	80	1305
4-Methyl-3-pyridyl	H	H	P	—	1307
2-Methyl-4-pyridyl	H	H	P	—	653
2-Quinolyl	H	H	P	80	1309
4-Phenyl-2-quinolyl	H	H	P	36	1310
2-Phenyl-4-quinolyl	H	H	P	—	653
6-Methoxy-4-quinolyl	H	H	P	—	653
2-Phenoxathiinyl	H	H	P	80	1311
	CH_3	H	P	—	1311

[i] Also the 4-(3-carboxy-4-hydroxyphenyl) derivative.

TABLE 3c. Selected Quinoline-4-carboxylic Acids Showing a Range of Nuclear Substituents [a]



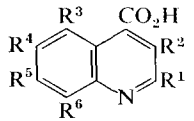
R^1	R^2	R^3	Route	Yield (%)	References
(i) *Substituents at position 2 and/or 3*					
CH_3	H	H	D	—	240, 239, 1312
			P	80	1313, 612, 1201
C_2H_5	H	H	D	12	1314, 239, 140
			P	—	980, 610, 1201, 612
n-C_3H_7	H	H	P	40	1315
iso-C_3H_7	H	H	D	10	239, 240, 259
iso-Propenyl	H	H	D	10	1316
iso-C_3H_7	C_6H_5	H	P	—	529
iso-C_4H_9	H	H	D	10	239, 240
			P	50	1315
tert-C_4H_9	H	H	D	15	259
3-Pentyl	H	8-CH_3O	D	26	1317
Penta-1,3-dienyl	H	H	D	10	1316
n-C_6H_{13}	H	H	P	90	1315, 694
Cyclohexyl	H	H	D	—	1318
	H	H	P	66	1221, 1319, 259
Cyclohex-3-enyl	H	H	P	—	1320
n-C_7H_{15}	H	H [b]	P	—	1321
Hepta-1,3,5-trienyl	H	H	D	10	1316
1-Vinylpent-4-enyl	H	H	D	5	1322
Benzyl	C_6H_5	H	P	85	1323
Phenethyl	H	H	P	—	1324
2-Cyclohexylethyl	H [c]	H	P	48	1325
	CH_3 [d]	H	P	50	1325
1-Theobrominylmethyl	H	H	D	—	1326

Styryl	H	H	D	8	1327
	H	H	P	—	1328
Variously substituted styryl	H	H	P	—	1328
n-$C_{11}H_{23}$	H	6-CH_3	P	—	1321
	H	6-Br	P	—	1321
n-$C_{15}H_{31}$	H	H	P	—	1321
	H	6-CH_3	P	—	1321
n-$C_{17}H_{35}$	H	H	P	—	1321
	H	6-CH_3	P	—	1321
2-Methoxyethyl	H	H	P	60	664
	CH_3	H	P	74	664
Diethoxymethyl	C_2H_5	H	P	—	694
5-(Carboxymethyl)-2,2-dimethyl-cyclobutyl	H	H	P	—	1330, 1331
2-(Tetrahydro-2,2-dimethyl-5-oxo-3-furyl)ethyl	H	H	P	81	1330
Carboxy	H	6-CH_3O	P	—	680
	H	6-Cl [e]	P	62	681
	H	5-Cl	P	30	683
	H	7-Cl	P	84	683
	C_6H_5	H	P	75	530
	C_6H_5	6-CH_3	P	75–80	530
	$C_6H_5CH_2$	H	P	90	530
H	CH_3	H	P	70	632
H	*n*-C_5H_{11}	H	P	25	1332
H	*n*-C_8H_{17}	H	P	25	1332
C_6H_5	*p*-(Methylthio)phenethyl	H	P	50	1333
H	2-Thienylmethyl	6-CH_3	P	Small	1334
H	(2-Thienyl)ethyl	6-CH_3	P	Good	1334
p-Substituted phenyl	Carboxymethyl	H	P	53–66	692

[a] For 2-aryl and 2-heteroaryl see Tables 3A and 3B.
[b] Also 6-methyl and 6-bromo-derivatives.
[c] Plus trace of 2-(cyclohexylmethyl)-3-methyl isomer.
[d] Also 3-ethyl (43%), 3-*n*-propyl (42%), 3-*n*-butyl (35%), and 3-isobutyl (25%) derivatives.
[e] Also 8-chloro- and 6,8-dichloro-compounds.

TABLE 3C (*Cont.*)

R^1	R^2	R^3	Route	Yield (%)	References
CH_3	2-Carboxyethyl	H	P	62	693
CH_3	3-Chlorobut-2-en-yl	6-CH_3	P	—	1335
CH_3	Acetonyl	H	P	—	636
CH_3	Acetyl	H	P	—	636
CH_3	Propionyl	H	P	—	636
C_6H_5	Benzoyl	H	P	—	636
H	OH	H	P	71	652
CH_3	OH	H	P	—	622
CH_3	OH	6-C_6H_5	P	—	622
CH_3	OH	6,8-Cl_2	P	—	622
C_6H_5	OH	H	P	38	651
C_6H_5	CH_3O	H	P	Quant.	661
CH_3	C_2H_5O	H	P	44	662
C_2H_5	C_2H_5O	H	P	92	662
C_2H_5	C_2H_5O	6-CH_3	P	56	662
C_2H_5 [f]	n-C_3H_7O	H	P	20	663
CH_3	C_6H_5O [g]	H	P	81	656
CH_3	o-Tolyloxy [h]	H	P	67	658
CH_3	o-Tolyloxy [h]	6-CH_3	P	73	658
C_6H_5	C_6H_5O	H	P	80	659
p-Anisyl	C_6H_5O	H	P	80	659
C_6H_5	p-Carboxyphenyl	H	P	80	659
CH_3	Phenylthio	H	P	62	666
CH_3	Phenylthio	6-CH_3	P	60	666
C_6H_5	Phenylthio	H	P	66	668
C_6H_5	Cyclohexylamino	H	P	70	672
C_6H_5	Phthalimido	H	P	—	678
C_6H_5	2-Naphthylamino [i]	H	P	90	1336, 674
p-Tolyl	o-Toluidino [i]	H	P	—	1337
CH_3	CO_2H	H	P	—	689
C_6H_5	CO_2H	H	P	—	689
CH_3	CN	H	P	50	690
C_6H_5	CN	H	P	Small	548
p-Tolyl	CN	H	P	Small	548
H	NO_2	H	P	—	670



R^1	R^2	R^3	R^4	R^5	R^6	Route	Yield (%)	References
(ii) *Substituents at positions* 5-, 6-, 7-, *and/or* 8								
CO_2H	H	Cl	H	H	H	P	30	683
p-ClC_6H_4	H	Cl	H	H	H	P	71	254
4-Cl-2$CH_3C_6H_3$	H	Cl	H	H	H	P	76	254
C_6H_5	H	Cl	H	H	Cl	P	65	254
Styryl	H	Cl	Br	H	H	P	—	1328
CO_2H	H	Cl	H	H	CH_3O	P	—	686
CO_2H	C_6H_5	Cl	H	H	H	P	—	1338
C_6H_5	H	OH [j]	H	H	H	P	52	1339
C_6H_5	H	CO_2H	H	H	H	P	—	627
C_6H_5	H	TsNH [k]	H	H	CH_3	D	Small	244
CH_3	H	H	CH_3	H	CH_3	P	—	1340
CH_3	2-Thienyl	H	CH_3	H	H	P	—	1341
p-ClC_6H_4	H	H	CH_3	H	CH_3	D	35	254
C_6H_5	H	H	CH_3	NH_2	H	D	85	244
C_6H_5	H	H	CH_3	TsNH	H	D	51	244
C_6H_5	H	H	CH_3	H	H	D, P	35	1342, 1343, 1344
Vanillyl	H	H	CH_3	H	H	D	—	1343
Piperonyl	H	H	CH_3	H	H	D	—	1343
C_6H_5	H	H	CH_3	H	CH_3	D	—	1344, 1345
p-Tolyl	H	H	CH_3	H	CH_3	D	—	1345
2-Furyl	H	H	CH_3	H	H	P	—	1346

[f] And *n*-C_3H_7 (42%), *n*-C_4H_9 (41%), iso-C_5H_{11} (53%), *n*-C_5H_{11} (32%), iso-C_4H_9 (50%), and C_6H_5 (59%).
[g] And 1-naphthyloxy (68%) or thymyloxy (33%).
[h] And *m*-tolyloxy, *p*-tolyloxy, 1-naphthyloxy, or 2-naphthyloxy.
[i] And numerous other arylamino-substituents.
[j] Starting from isatin-4-sulphonic acid; isolated as internal lactone.
[k] Ts = *p*-$CH_3C_6H_4SO_2$.

TABLE 3C (*Cont.*)

R^1	R^2	R^3	R^4	R^5	R^6	Route	Yield (%)	References
C_6H_5	H	H	2-Pyridyl	H	H	D	—	1347
C_6H_5	H	H	3-Pyridyl	H	H	D	—	1347
CH_3	H	H	F	H	H	P	—	614
C_6H_5	H	H	F	H	H	P	—	614
p-FC_6H_4	H	H	F	H	H	P	—	614
$CH_2CH_2CH_2CH_2$		H	F	F	H	P	—	614
p-Tolyl	C_6H_5	H	Cl	H	H	P	—	617
H	OH	H	Cl	H	Cl	P	85	652
CO_2H	H	H	Cl	H	H	P	78	684, 682
CH_3	H	H	Cl	H	Br	P	—	1348
n-C_3H_7	H	H	Cl	H	Br	P	—	1348
C_6H_5	OH	H	Cl	H	H	P	35	651
C_6H_5 [l]	H	H	Cl	H	Br	P	90–97	1348
H	OH	H	Br	H	H	P	40	652
C_6H_5	H	H	Br	H	H	P	—	1217
p-BrC_6H_4	H	H	Br	H	H	P	—	1217
3-HO-4-$HO_2CC_6H_3$	H	H	Br	H	H	P	—	1243
p-NCC_6H_4	H	H	Br	H	H	P	—	1349
4-(*m*-Terphenyl)	CH_3	H	Br	H	H	P	—	1350
Styryl [m]	H	H	Br	H	H	P	—	1328
Styryl	H	H	Br	H	Br	P	—	1328
p-IC_6H_4	H	H	Br	H	Br	P	—	1351
p-*n*-$C_4H_9)OC_6H_4$	CH_3	H	Br	H	H	P	—	1352
6-Methoxy-2-naphthyl	H	H	Br	H	H	P	—	1353
6-Methoxy-2-naphthyl	CH_3 [n]	H	Br	H	H	P	—	1353
CH_3	CO_2H	H	Br	H	Br	P	—	685
CO_2H	H	H	Br	H	Br	P	—	685
p-IC_6H_4	H	H	Br	H	H	P	—	1354
C_6H_5	OH	H	Br	H	H	P	15	651
p-BrC_6H_4	OH	H	Br	H	H	P	—	651
H	OH	H	I	H	H	P	32	652
CH_3	H	H	I	H	H	P	90	763
Cyclohexyl	H	H	I	H	H	P	—	1221
C_6H_5	H	H	I	H	H	P	83	620

p-HOC_6H_4	H	H	I	H	H	P	—	620
p-IC_6H_4	H	H	I	H	H	P	—	1355
m-$NH_2C_6H_4$	H	H	I	H	H	P	—	619
2-CH_3-4-HO-6-iso-$C_3H_7C_6H_2$	H	H	I	H	H	P	—	1247
p-BrC_6H_4	H	H	I	H	H	P	—	1354
p-IC_6H_4	H	H	I	H	H	P	—	1354
Styryl	H	H	I	H	H	P	—	1328
C_6H_5 [o]	OH	H	I	H	H	P	15	651
CH_3	H	H	CH_3O	H	H	D	—	680
C_6H_5	H	H	OH	H	H	D	—	1356
C_6H_5	H	H	CH_3O	H	H	D	—	680, 1357
C_6H_5	H	H	CH_3O	H	H	P	—	625
C_6H_5	H	H	C_2H_5O	H	H	D	—	1356
2-Furyl	H	H	CH_3O	H	H	P	—	680
C_6H_5	C_6H_5	H	CH_3O	H	H	P	—	680
CO_2H	H	H	CH_3O	H	H	P	—	680
CO_2H	CO_2H	H	CH_3O	H	H	P	—	680
C_6H_5	H	H	CH_3O	CH_3O	H	D	—	256
C_6H_5	H	H	CH_3O	CH_3O	CH_3O	D	—	1358
C_6H_5	H	H	CO_2H	H	H	P	—	626
C_6H_5	H	H	$CO_2C_2H_5$	H	H	D	10	1359
C_6H_5	H	H	$SONH_2$	H	H	D	Small	1360
C_6H_5	H	H	2-Pyridyl-$NHSO_2$	H	H	D	—	1360
CH_3	CH_3	H	NO_2	H	H	P	—	1361
C_6H_5	H	H	NO_2	H	H	D	Poor	623
C_6H_5 [p]	H	H	NO_2	H	H	P		623
p-$O_2NC_6H_4$ [q]	H	H	NO_2	H	H	P	—	624
p-$O_2NC_6H_4$ [q]	H	H	NO_2	H	NO_2	P	—	624

[l] Also other aryl substituents.
[m] Also *p*-$Me_2NC_6H_4CH{=}CH$.
[n] Also 3-ethyl and 3-phenyl derivatives.
[o] Also various substituted phenyl derivatives.
[p] Using ammonia as base (the 4-carboxamide was obtained).
[q] Also with various other substituted phenyl groups.

TABLE 3C (*Cont.*)

R^1	R^2	R^3	R^4	R^5	R^6	Route	Yield (%)	References
C_6H_5	H	H	NH_2	H	H	D	—	1223
CH_3	H	H	NH_2	H	H	D	—	1362
C_6H_5	H	H	CH_3CONH	H	CH_3	P	—	628
C_6H_5	H	H	H	CH_3	H	D	—	1345
p-ClC_6H_4	H	H	H	CH_3	H	D	50	254
C_6H_5	H	H	H	Cl	H	D, P	35, 45	616
CO_2H	H	H	H	Cl	H	P	84	683, 684
CO_2H	C_6H_5	H	H	Cl	H	P	—	1338
p-ClC_6H_4	H	H	H	Cl	H	D	22	254
p-FC_6H_4	H	H	H	Cl	H	D	24	254
4,5-Cl_2-2-$CH_3C_6H_2$	H	H	H	Cl	H	P	45	254
C_6H_5	H	H	H	Cl	CH_3	D	24	254
n-C_3H_7	H	H	H	OH	H	D	33	402
CH_3	C_6H_5	H	H	OH	H	D	—	402
C_6H_5	C_6H_5	H	H	OH	H	D	20	402
CH_3	H	H	H	CH_3O	H	D	40	402
C_6H_5	H	H	H	CH_3O	H	D	—	402
C_6H_5	H	H	H	OH	H	D	—	1228
3,4-$(CH_3O)_2C_6H_3$	H	H	H	OH	H	D	—	255
3,4-$(CH_3O)_2C_6H_3$	H	H	H	CH_3O	H	D	—	255
2-Furyl	H	H	H	OH	H	D	50	253
C_6H_5	H	H	H	$(CH_3)_2N$	H	D	—	1363
4-$CH_3OC_6H_4$ [r]	H	H	H	$(CH_3)_2N$	H	D	—	255, 1364
C_6H_5	H	H	H	H	CH_3	D	20	1342
C_6H_5	H	H	H	H	C_6H_5	D	22	1342
C_6H_5	H	H	H	H	CH_3O	D	27	616
3,4-$(CH_3O)_2C_6H_3$	H	H	H	H	CH_3O	D	—	255
2-Furyl [s]	H	H	H	H	Cl	P	—	1270
C_6H_5	H	H	H	H	CO_2H	P	—	626
C_6H_5	H	H	H	H	NO_2	D	34	258

[r] Also other phenyl substituents. [s] Also other heterocyclic radicals.

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CHAPTER 3

Haloquinolines

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I. Introduction

All possible monohaloquinolines are known, as are the majority of the dichloro- and dibromo-derivatives. In addition, a large number of trihaloquinolines, mainly trichloro- and tribromo-, have been characterized. Recent interest in the synthesis and properties of polyhalo-compounds has resulted in the preparation and characterization of perfluoro- and perchloro-quinoline.

The monofluoroquinolines are liquids at room temperature, as are many of the monofluoroalkylquinolines. The remainder of the monohaloquinolines, with the exception of 3-chloro-, 3-bromo-, 8-chloro-, 8-bromo-, and 7-iodo-quinoline, are colourless, low-melting, (<100 °C) and, in general, steam-volatile solids. Haloquinolines are stable compounds although 4-fluoroquinoline shows a pronounced tendency towards self-quaternization and difficulty has been encountered in its isolation and characterization.

Almost all the monobromoquinolines are available by direct halogenation procedures, i.e. processes involving molecular bromine, whereas of the monochloro- and monoiodo-quinolines only the 5-, 6-, and 8-substituted derivatives are accessible by this method. Fluoroquinolines are prepared almost exclusively from diazonium salts by the familiar Balz–Schiemann reaction. Surprisingly, however, the diazonium route to chloro-, bromo-, and iodo-quinolines has been relatively unexploited, possibly because of the somewhat limited availability of the appropriate aminoquinolines.

Many indirect halogenation procedures have been explored and sulphuryl halides, *N*-halosuccinimides, iodine monochloride, and various chlorates and hypochlorites have been employed with varying degrees of success.

By far the most popular method of preparing 2- and 4-chloroquinolines involves heating 2- or 4-quinolones with phosphorus tri- or penta-chloride, in most cases in combination with phosphorus oxychloride. Very few failures using this method have been documented. 2-Bromo- and 4-bromo-quinolines are also available if the corresponding phosphorus bromides are employed. However, on isolated occasions bromoquinoline formation is accompanied by extraneous nuclear bromination and the method has been utilized far less than the chlorination procedure.

Many haloquinolines, particularly 2- and 4-halo, have been synthesized by halogen–halogen exchange reactions, and the advent of new solvent systems, e.g. dimethylformamide, *N*-methylpyrrolidone, dimethyl sulphoxide etc., has enhanced the preparative potential of this type of reaction. The displacement of other substituent groups, e.g. SO_2OH, by halogen, constitutes an early preparative route to haloquinolines and has some value as a synthetic method.

Halo-substituted quinolones, and haloquinolinecarboxylic acids are readily available by classical quinoline syntheses, and many examples of their preparation by Conrad–Limpach, Knorr, and Pfitzinger reactions will be found in the following sections. In addition the Skraup quinoline synthesis, and related reactions, have been used extensively for the preparation of a wide variety of substituted haloquinolines.

Without doubt the most exploited, documented, and mechanistically investigated aspect of haloquinoline chemistry is the reactivity shown by 2- and 4-haloquinolines towards nucleophilic displacement of the halo-substituent, and many examples involving a host of different nucleophiles have been recorded. Of particular interest are reactions involving amines, since many of the aminoquinolines so formed have proven value as antimalarial agents. In fact, the tremendous upsurge during the war and immediate post-war years in the number of publications involving the synthesis and reactivity of haloquinolines arises from the blood-sucking activities of *Anopheles maculipennis* Meigen, the malaria-carrying mosquito. It is worth noting that the

emergence of resistant malarial strains has again awakened research interest in quinoline chemistry.

Of current interest is the structure and mode of formation of the many halogen–quinoline molecular complexes. Such complexes have long been known in the chemical literature, but it is only comparatively recently that their participation during the direct halogenation (particularly bromination) of quinoline, under all but strongly acidic conditions, has become suspected.

The majority of reported (haloalkyl)quinolines have the substituent at the 2- and 4-position of the quinoline nucleus. Alkyl groups at these positions are "activated", at the α-carbon atom towards electrophilic substitution, by the ring nitrogen, and halogenation occurs readily. Various direct chlorination and bromination procedures have been developed, and, as expected, indirect halogenation of the alkyl side chain is efficiently brought about by *N*-halosuccinimides.

Few (iodoalkyl)quinolines are known and as far as the author is aware (monofluoroalkyl)quinolines have yet to be prepared. (Trifluoromethyl)quinolines are, however, well documented and, in general, are prepared by classical quinoline syntheses using the appropriate (trifluoromethyl)-substituted β-keto-ester, aniline, etc.

The (monohaloalkyl)quinolines show a tendency towards self-quaternization and are best stored as their hydrochlorides. The di- and tri-(haloalkyl)quinolines are much more stable and find use in the synthesis of quinoline aldehydes and carboxylic acids. Hydrolysis is generally brought about under either acidic or basic conditions, although much use has been made of silver nitrate in aqueous ethanol.

As expected, (haloalkyl)quinolines resemble in their chemistry the alkyl halides, and enter into a wide range of nucleophilic displacement reactions. Several of the (monohaloalkyl)derivatives are vigorous skin-irritants and should be handled with care.

II. Nuclear Halogen Derivatives

1. Preparation

A. Direct Halogenation

a. INTRODUCTION. Various methods have been employed to effect the direct chlorination, bromination, and iodination of quinoline. On the other hand, direct fluorination processes are unknown.* The bulk of investigations into the halogenation of quinoline have been concerned with bromination procedures, whereas chlorination and iodination methods have received only relatively scant attention from both a preparative and a mechanistic viewpoint.

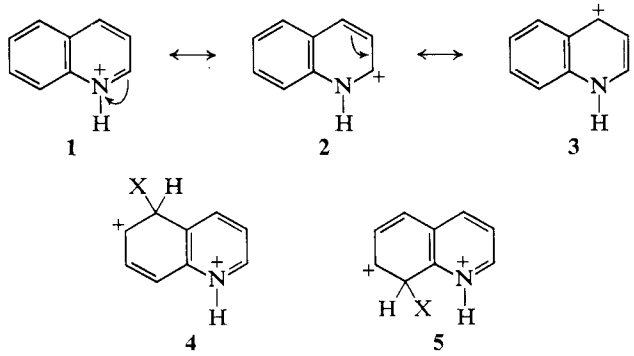
Quinoline reacts slowly with both bromine and iodine at room temperature but the exact nature of the reaction is little understood. As expected, quinolines possessing an activating (i.e. electron-donating) substituent are readily halogenated under mild conditions, and the orientation of the products is that expected from a knowledge of benzene chemistry.

Halogenation of quinoline is a complex process, more so than with either benzene or pyridine in that a larger range of isomeric products is possible. Some indication of the degree of complexity can be gathered from the fact that, with the exception of the 7-bromo-isomer, every monobromoquinoline together with several di- and tribromo-derivatives, is obtainable by direct bromination procedures.

* See, however, Addenda, p. 674.

In general, halogenation of quinoline under neutral or weakly acidic conditions occurs initially at the pyridine ring (position 3), while in acid solution substitution occurs at the 5- and 8-positions. It may be that in neutral media halogenation proceeds via formation of some type of halogen–nitrogen complex. Alternatively an addition–elimination mechanism may be involved. The position is, however, further complicated in that the orientation of the products is dependent on reaction temperature. In general, vapour-phase halogenation at temperatures of around 300 °C yields mainly 3-haloquinoline, whereas at high temperatures (> 300 °C) only 2-substitution is observed. A radical mechanism is probable in the latter case.

In strongly acidic media the species undergoing halogenation is the quinolinium ion (**1**). Mesomeric contributions of type (**2**) and (**3**) decrease the tendency towards



1 **2** **3**

4 **5**

electrophilic substitution at the pyridine ring, and consideration of the relative stabilities of the expected transition states, e.g. (**4**) and (**5**), indicates that the 5- and 8-positions are favoured towards electrophilic attack. Early theoretical considerations[1] of the localization energies for the quinolinium ion predicted a reactivity of $8 > 5 > 6 = 3 > 7 \gg 4 \gg 2$ towards electrophilic substitution.

Experimentally it is found that nitration yields roughly equal amounts of the 5- and 8-nitro-isomers, and halogenation studies under strongly acidic conditions reveal a similar isomer distribution. In both reactions the amount of 8-substituted quinoline produced is less than that predicted on the basis of localization energies. However, as the authors[1] point out substitution at the 8-position necessitates an unfavourable close approach by the attacking electrophile to the adjacent positively charged nitrogen centre, a factor which seriously hinders the substitution process.

b. Mechanistic Aspects. As stated in the introductory section halogenation of quinoline is a complicated process and much research is still required to unravel the nature of the seemingly various mechanisms involved. Most of the understanding so far has come from a study of bromination processes, and it is now possible, by judicious choice of reaction conditions and halogenating agent, to synthesize a whole range of mono-, di-, and tri-bromoquinolines. Most of these reactions have been known for many years but it is only recently that the underlying processes involved have begun to emerge.

Jansen and Wibaut[2] studied the vapour-phase bromination of quinoline and other heterocycles. They found that at temperatures between 300 and 500 °C bromination occurs only at the pyridine ring of the quinoline molecule, and that the site of bromination varies with the reaction temperature. At 300 °C, 3-bromoquinoline is the main product, while at 450 °C 2-bromoquinoline (24%) is formed

together with only a small amount of 3-bromo-isomer. Higher yields (53%) of 2-bromo-compound are obtained when the bromination is carried out at 500 °C. The authors offer no mechanistic explanation of their results but it appears likely that at the higher temperature bromination involves a radical process, while at 300 °C some form of electrophilic substitution is taking place possibly at a halogen–quinoline complex. On the other hand, as Eisch[3] has suggested, the absence of 3-bromoquinoline in the high-temperature reaction may be a consequence of the thermal instability of the 3-bromo-compound (see Section II.2.J) rather than of a fundamental change in reaction mechanism or attacking species. A highly speculative mechanism involving homolytic attack by bromine on a 1,2-dihydroquinoline–bromine complex has been proposed[4] to account for the formation of 3-bromoquinoline under low-temperature conditions.

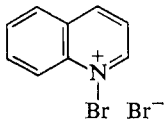
Bromination of quinoline in concentrated sulphuric acid in the presence of silver sulphate (Derbyshire and Waters' method[5]) yields a mixture of 5-bromo-, 8-bromo-, and 5,8-dibromo-quinoline.[6] The isomer distribution is found to be almost identical with that observed for the nitration of quinoline in strongly acidic solution and is in accord with the substitution pattern expected from calculated localization energies[1] for the quinolinium ion. The results appear to indicate an electrophilic attack on the protonated quinoline nucleus by a bromine cation, either free (i.e. Br^+) or as a bromine–sulphuric acid complex ($Br.H_2SO_4^+$ or $BrSO_3^+$).[7] Under these conditions the absence of products arising from bromination at the 2-, 3-, and 4-positions of the quinoline nucleus is not surprising since protonation will seriously deactivate the pyridinoid ring towards electrophilic substitution, as indicated previously (Section II.1.A.a). A more detailed study[7] of bromination in sulphuric acid reveals that with an excess of quinoline the ratio of 5- to 8-bromo-quinoline remains essentially constant, whereas the total yield of brominated product decreases as the acid concentration decreases. The reaction fails at around an acid concentration of 87%. In all the brominations studied the major product is 5,8-dibromoquinoline and in explanation it is suggested[8] that the conjugate acids of 5- and 8-bromo-quinoline are stronger than the conjugate acid of quinoline. Hence bromination of the initially formed monobromoquinolines, present to an appreciable extent as free base, takes place at a faster rate than monobromination of quinoline which is present as quinolinium ion. Under these conditions the position taken up by the second bromine substituent is determined by the nature of the substituent already present in the system rather than by the nitrogen function of the quinoline ring.

However, the situation is not so straightforward as the above argument suggests. de la Mare, Kiamud-din, and Ridd[7] have shown by use of isotopic dilution techniques that not only is the rate of monobromination at the 5- and 8-positions the same, but that 5- and 8-bromoquinoline undergo further bromination at essentially the same rate. In explanation of this it is suggested that the presence of a 5- or 8-bromo-substituent must somehow be increasing the partial rate factor for substitution at the other position. The authors further argue that, if dibromination is occurring at the free base rather than at a cationoid species, then the proportion of dibromo-compound should increase with decreasing acid strength of the reaction medium; i.e. as the amount of free base increases. In fact, experiment reveals that the ratio of dibromo- to monobromo-quinoline remains constant as the acid strength of the brominating medium decreases, although the total yield of brominated product decreases. The authors conclude that both mono- and di-bromination are occurring at some form of common quinoline–conjugate acid species.

Similar yields and isomer distribution to those observed above were obtained by Gordon and Pearson[9] employing the so-called "swamping catalyst effect". This technique involves brominating a quinoline–aluminium chloride complex in the

presence of an excess of aluminium chloride. Bromination is thought to occur initially at the 5-position, followed by further bromination to give 5,8-dibromoquinoline. With an excess of bromine 5,6,8-tribromoquinoline is produced. These results are in full agreement with a process involving attack on a quinolinium–aluminium chloride complex by a bromonium ion species. Formation of the 5,6,8-tribromo-compound is expected on the basis of the theoretical calculations of Dewar and Maitlis.[1]

It has long been known[10] that quinoline and bromine at low temperatures form a complex which on thermal decomposition yields mainly 3-bromoquinoline. Many reactions of this type are known and may be viewed as bromination of the neutral quinoline molecule rather than, as has so far been discussed, the quinolinium component. [The synthetic implications of these reactions are discussed in Section II.1.B.c(i).] The mechanism of these decompositions is still somewhat obscure, but recent investigations by Eisch and by Ridd have gone some way towards explaining the bromination processes involved. Eisch[3] found that bromine and quinoline react in dry carbon tetrachloride to give a complex of molecular formula $C_9H_7NBr_2$. This complex differed from the dibromide reported earlier by Lubavin,[11] and from the tetrabromide, $C_9H_7NBr_4$, obtained by Grimaux.[12] On the basis of ultraviolet and infrared spectral data Eisch[13] considered the dibromide to be either a charge-transfer complex or *N*-bromoquinolinium bromide (**6**). Later studies[14] involving more detailed spectroscopic measurements and the correlation of stability constants of various quinoline–bromine complexes, favour an *n*-donor complex of type (**7**).



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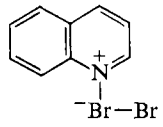

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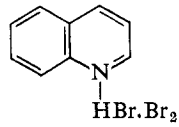

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Decomposition of this complex in boiling carbon tetrachloride gives a mixture of 3-bromoquinoline and the quinolinium perbromide* (**8**).[13] However, decomposition of the complex in carbon tetrachloride containing one equivalent of pyridine, which serves to remove the hydrogen bromide formed in the reaction, yields 3-bromoquinoline (90%) together with 3,6-dibromoquinoline (ca. 2%), and lesser amounts of 3,8-dibromo-, and 3,6,8-tribromo-quinoline. Careful investigation of the decomposition of complex (**7**) in a range of solvents (e.g. chloroform, acetic acid) and in the molten state reveals that (a) the 3-position is most readily brominated under all conditions; (b) decomposition in glacial acetic acid promotes polybromination in contrast to decomposition in chloroform, carbon tetrachloride, or in the molten state, whereupon selective bromination at the 3-position is observed; and (c) in the advent of polybromination only the 3-, 6-, and 8-positions are substituted. Eisch argues convincingly for the involvement of a polar rather than a radical bromination process and considers that the quinoline–bromine complex (**7**) could well be the source of the electrophilic brominating species.[13, 14] On this basis bromination of the neutral quinoline molecule may be written as in reaction 1.

$$C_9H_7NBr^{\delta+}\cdots Br^{\delta-} + C_9H_7N \longrightarrow C_9H_6NBr + C_9H_7\overset{+}{N}H\overset{-}{Br} \qquad (1)$$

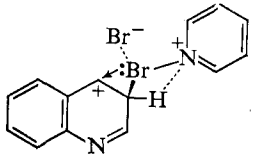
* See footnote to Table 5, p. 375.

Eisch further argues that in acetic acid hydrogen-bonding between quinoline and the acid brings about dissociation of the quinoline–bromine complex with concomitant formation of molecular bromine (reaction 2).

$$C_9H_7NBr_2 + AcOH \longrightarrow C_9H_7\overset{\delta+}{N}H\cdots\overset{\delta-}{O}Ac + Br_2 \qquad (2)$$

9

Polybromination in acetic acid is reconciled, therefore, on two main points. Firstly, that the molecular bromine produced will be more reactive and hence less selective than complex (**7**) in its attack on the quinoline nucleus. Secondly, the introduction of a bromo-substituent onto the quinoline nucleus causes a decrease in the basicity of the quinoline system, so that the initially formed monobromoquinoline will hydrogen bond less firmly with the solvent, i.e. acetic acid. As a consequence 3-bromoquinoline is present as a neutral species and undergoes further bromination more rapidly than the quinoline–acetic acid system (**9**) which behaves as a deactivated quinolinium species. However, the fact that polybromination occurs at the 6- and 8-positions rather than at the 5- and 8-positions, as observed previously, strongly indicates that the actual species undergoing halogenation is not the quinolinium ion. In fact these results are in agreement with some molecular-orbital calculations[15] for the neutral quinoline molecule which predict an π-electron-density order of $C_8 > C_6 > C_3 > C_5 > C_7$, significantly different from the localization-energy values mentioned previously.[1] * The anomalously low yield of the 8-substituted compound can be explained on the basis of *peri*-type interactions between the 1- and the 8-position. However, the predominant formation of 3-bromoquinoline under both aprotic and weakly acidic conditions still remains to be answered satisfactorily. Eisch[13] has proposed a mechanism to explain 3-bromoquinoline formation under aprotic conditions which involves attack by the complex (**7**) on a neutral quinoline molecule, and formation of the bridged bromonium ion transition state (**10**).



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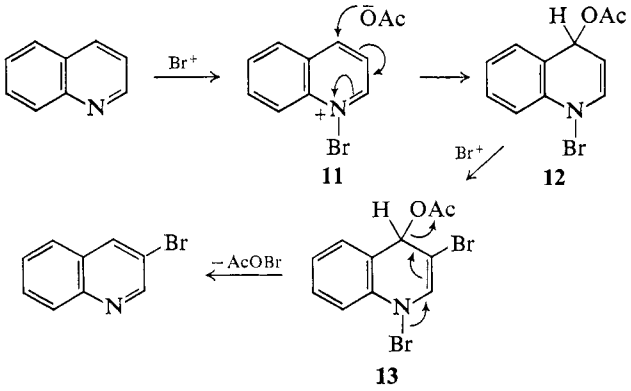
Brown and Harcourt[4] found that the predominance of 3-substitution could not be reconciled with their theoretically derived π-electron-density values for quinoline. Nor do the earlier calculations and ideas of 1,2-addition, propounded by Dewar and Maitlis[16] to explain nitration of quinoline, coincide with the observed orientation during halogenation. Brown and Harcourt therefore (in order to explain the formation of 3-bromoquinoline in acetic acid), proposed a reaction mechanism involving 1,4-addition of bromine to the quinoline ring. Initial formation of the quinoline–bromonium ion complex (**11**) is followed by addition of acetate ion at the 4-position as indicated in Scheme 1. The resulting 1,4-dihydroquinoline (**12**) then undergoes electrophilic substitution at the 3-position which theoretical considerations show has the greatest π-electron density. Elimination of bromonium acetate from the 1,4-dihydroquinoline (**13**) yields 3-bromoquinoline. In further support of their ideas

* For a more comprehensive account of π-electron-density calculations on the quinoline nucleus see Chapter 1, p. 3.



SCHEME 1

Brown and his co-workers[17] have shown by means of VESCF (variable electronegativity self-consistent field[18]) molecular-orbital methods that, of the two possible addition products (1,2- or 1,4-), only the latter exhibits the greatest charge density at position 3. Thus participation of a 1,2-adduct in the bromination process is criticized by Brown and Harcourt in that substitution of such an adduct should proceed preferentially at the carbocyclic ring rather than at the 3-position.

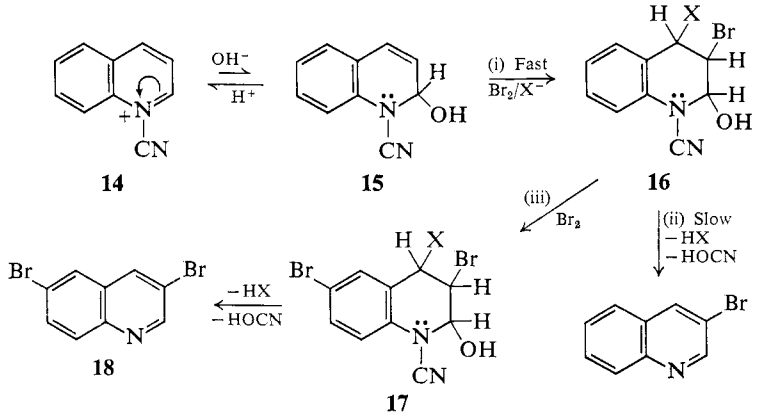
de la Mare, Johnson, and Ridd,[19] however, have shown that 1-cyano-1,2-dihydro-2-hydroxyquinoline (**15**), a stable 1,2-adduct of quinoline, with one equivalent of bromine in hydrochloric acid gives 3-bromoquinoline. An excess (2–3 mol) of bromine yields a mixture of 3,6-dibromo- and 3,6,8-tribromo-quinoline. The mechanism of these reactions has been fully investigated by Johnson and Ridd;[20, 21] they have shown that at low acidities the *N*-cyanoquinolinium ion (**14**) readily forms a pseudo-base (**15**) that reacts with bromine in a variety of buffered solutions to yield a series of 3,4-adducts (**16**; X = OH, OAc, Br, or Cl, depending on the solvent system used).

Presumably *N*-cyano-compound (**15**) suffers an initial electrophilic attack by bromine at the 3-position followed by addition of a nucleophile at the 4-position.

That bromine enters the 3-position is demonstrated by the fact that, on treatment of the adducts (**16**; X as before) with strong acid, 3-bromoquinoline is formed in 30–72% yield. In the presence of an excess of bromine rapid attack to give adduct (**16**; X = Br) is followed by a slower substitution at the benzene ring to give brominated adduct (**17**). The position taken up in the adduct by the second bromine substituent is determined by the directive influence of the tertiary amino-function, and hence substitution at the 6- and 8-positions is observed. In fact, when an aqueous-ethanolic solution of pseudo-base (**15**) is treated with a large excess of bromine and then with concentrated acid, 3,6,8-tribromoquinoline is formed. Johnson and Ridd summarize their results by means of Scheme 2.

They argue that reaction (i) is fast, whereas reaction (ii) is comparatively slow, i.e. the tetrahydroquinoline is more stable in acid solution than cyano-compound (**15**). Thus the concentration of bromo-adduct (**16**) can build up until it exceeds that of pseudo-base (**15**), at which point further bromination, i.e. reaction (iii), although slow, can compete with reaction (ii). Hence dibromination to yield ultimately dibromo-compound (**18**) occurs to an appreciable extent. The final yield of 3,6-dibromo-compound depends, of course, on the amount of brominated adduct (**17**) formed in the reaction. These concepts were extended by Johnson and Ridd to

explain the bromination of quinoline at low acidities. They argue that under these conditions the equivalent of the *N*-cyano-compound (**14**) is the quinoline–bromonium ion complex (**11**), which should behave in a like manner to that outlined in Scheme 2.



SCHEME 2

The effect of substituents on the equilibrium between *N*-substituted quinolines and their pseudo-bases (e.g. **14**⇌**15**) has been discussed in detail by Cooksey and Johnson.[22]

To summarize, it appears that:

(*a*) Bromination of quinoline in the vapour phase yields mainly 2- or 3-bromoquinoline depending on the temperature of the reaction.

(*b*) Bromination of quinoline in strongly acidic media, or as an aluminium chloride complex, involves a bromonium ion and gives initially 5- and 8-bromoquinoline.

(*c*) Bromination of quinoline at low temperature in an aprotic solvent leads to the formation of a 1 : 1 quinoline–bromine adduct which when heated yields mainly 3-bromoquinoline.

(*d*) Decomposition of the adduct in dilute acid solution, or direct bromination of quinoline in dilute acid media, yields a mixture of 3-bromo-, 3,6-dibromo-, 3,8-dibromo-, and 3,6,8-tribromo-quinoline. Under these conditions either a 1,2- or a 1,4-adduct is involved which is brominated rapidly at the 3-position, possibly via a 3,4-addition product, and which is also brominated, albeit more slowly, at the 6- and the 8-position.

Johnson and Ridd[21] emphasize that the interest in these reactions lies not so much in the initial addition but in the nature of the acid-catalysed eliminations undergone by the tetrahydroquinoline (**17**).

Chalvet, Daudel, and McKillop[23] have applied a delocalized transition-state model approach to the electrophilic substitution of quinoline and the quinolinium ion. Their results for substitution in strong acid solution tally with previous workers, i.e. substitution is predicted to occur at the 5- and 8-positions. However, for brominations in weak acid they conclude that the observed order of reactivity towards electrophilic substitution (i.e. $3 > 6 \geqslant 8$) is not explicable on the delocalized transition-state model and certainly involves some type of addition–elimination mechanism, probably of the type discussed above.

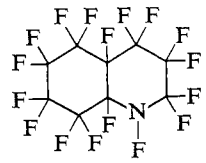
de la Mare, Kiamud-din, and Ridd[24] have isolated a bromine diquinoline perchlorate, $(C_9H_7N)_2Br^+ClO_4^-$ from the reaction of a perchloric acid solution of quinoline with hypobromous acid. The complex is potentially a bromonium salt, similar to the now well-established nitronium salts, and as such should behave as a brominating agent. The authors found, however, that the complex dissociates in aqueous solution, as shown in reaction 3, to give ultimately a low yield (15%) of a mixture of brominated quinolines from which only 5-bromoquinoline (identified as its picrate) has been isolated and characterized.

$$(C_9H_7NBr)_2{}^+ClO_4^- \rightleftharpoons C_9H_7NBr^+ClO_4^- + C_9H_7N \xrightarrow{H_2O} C_9H_7N + HOBr + HClO_4 \qquad (3)$$

The kinetics of the reaction between bromine and quinoline in carbon tetrachloride solution have been measured.[25] The results indicate that at comparable bromine and quinoline concentrations the reaction is second-order in quinoline and first-order in bromine. With an excess of quinoline, however, the reaction becomes both very fast and first-order in each reactant.

Several articles on the halogenation of aromatic and heteroaromatic systems are available.[26, 27] A review by Eisch[28] summarizes the position regarding the halogenation of heterocyclic systems, and in it he makes obvious the paucity of knowledge in this surprisingly neglected corner of heterocyclic chemistry.

c. FLUORINATION.* The reaction between fluorine and quinoline, or substituted quinolines, does not appear to have been investigated. However, heptadecafluorodecahydroquinoline (**19**) is obtained[29] in 2% yield when quinoline vapour is passed over cobalt trifluoride at 400 °C. Fluorination is accompanied by extensive fragmentation of the heterocyclic ring and other products including perfluorocyclohexane, perfluoromethylcyclohexane, and perfluoro(*n*-propyl)cyclohexane can be isolated from the reaction mixture. Perfluorodecahydroquinoline (**19**), despite the presence of the N—F bond, is stable towards aqueous alkali, mineral acid, oxidation (potassium permanganate), reduction (zinc–ethanol), and ultraviolet light.



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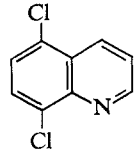
d. CHLORINATION.* (*i*) *Of Quinoline and Alkyl- and Halo-substituted Quinolines.* Relatively little work has been done on the direct chlorination of quinoline. In fact, other than an early paper[30] on the exhaustive chlorination of quinoline over antimony pentachloride, no further report appears in the chemical literature until the past decade. In the early work quinoline was treated with antimony pentachloride in a sealed tube at 170 °C, initially for 5 hours, then successively at 280, 320, and finally 400 °C for further periods of 5 hours (periodic release of hydrogen chloride evolved during the reaction is essential). Eventually this drastic treatment yielded

* See also Addenda, p. 674.

only perchlorinated fragmentation products (e.g. perchlorobenzene and hexachloroethane) rather than the chlorinated heterocycle. More recently,[31, 32] quinoline has been successfully chlorinated by the method of Derbyshire and Waters;[5] this process, which involves passing dry chlorine at room temperature through a solution of quinoline in concentrated sulphuric acid containing silver sulphate, yields a mixture of 5-chloroquinoline (17%), 8-chloroquinoline (21%), and 5,8-dichloroquinoline (**20**) (32%). Under the reaction conditions the effective halogenating agent is thought to be chloronium ion (Cl^+) which attacks the quinoline nucleus, here present as quinolinium ion, at the 5- and 8-positions. Further investigation[32] showed that the 5,8-dichloro-compound (**20**) is produced by chlorination of the initially



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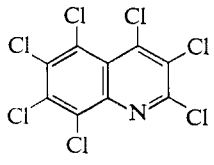
formed monochloroquinolines, and its formation is suppressed if an excess of quinoline is used. Prolonged treatment (2 hours) with chlorine results in sole formation of the dichloro-compound. The ratio of products remains essentially constant, although the total yield decreases as the concentration of sulphuric acid decreases. The reaction fails in dilute sulphuric acid (<70%), in oleum, and in concentrated sulphuric acid in the absence of silver sulphate. Chlorination is not observed in acetic, nitric, or hydrochloric acid solution, while in chloroform at room temperature quinoline and chlorine react to form a "heavy precipitate" about which the authors volunteer no information; presumably, in view of the bromination studies mentioned earlier (Section II.1.A.b), this precipitate is a quinoline–chlorine complex.

Quinoline has also been chlorinated[9, 33] under conditions employing the so-called "swamping catalyst effect".[34] This process involves treating a molten mixture of quinoline (1 mol) and aluminium chloride (2 mol) with chlorine. Under these conditions quinoline is fully complexed through the nitrogen atom and a substrate resembling a quinolinium ion is formed. An excess of aluminium chloride is necessary for reaction to take place as it serves to polarize the halogen molecule and hence aid generation of an active halogenating species, i.e. chloronium ion. Since the species undergoing chlorination is quinolinium ion the pyridine ring is deactivated and substitution at the 5- and 8-positions is observed. The position at which chlorination of substituted quinolines takes place is influenced by the nature of the substituent already present and by the reaction temperature. Thus at 111 °C and with chlorine for 6 hours quinoline–aluminium chloride complex yields 5,8-dichloroquinoline (**20**) (73%),[33] whereas at 150 °C the aluminium chloride complex of 5,8-dichloroquinoline on treatment with chlorine for 4 hours yields 5,6,7,8-tetrachloroquinoline (91%).[9] Under similar conditions bromination appears to be a more selective process since mainly (78%) 5,6,8-tribromoquinoline is formed. By using careful temperature control several chloroquinolines have been prepared; for example, 6-chloroquinoline and aluminium chloride react at 100 °C with chlorine to yield 5,6-dichloroquinoline (85%), whereas at 125 °C 5,6,8-trichloroquinoline (80%) is obtained.[33]

Chlorination of quinoline–aluminium chloride complex with a large excess of chlorine over 48 hours at 190 °C yields a mixture of penta- and tetra-chloroquinoline, the former in greater yield;[35, 36] at 140–160 °C, however, the major product is the tetrahydroquinoline.

Heptachloroquinoline (**21**) has been prepared by a rather complicated process which uses as starting material *N*-(*n*-propyl)-aniline (**22**).[37-40] The amine is condensed with phosgene in toluene solution to give the *N*-chlorocarbonyl derivative (**23**), which is chlorinated in chloroform solution in the dark at 60 °C, and then further chlorinated in trichlorobenzene solution at 200 °C in the presence of ultraviolet radiation; finally after removal of solvent, the residue is heated with chlorine at 200 °C for 8 hours in the presence of ferric chloride, whereupon heptachloroquinoline (**21**) is obtained.



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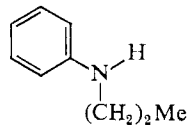

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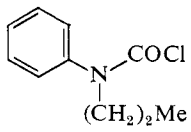

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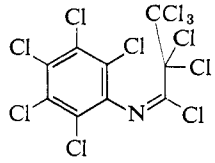

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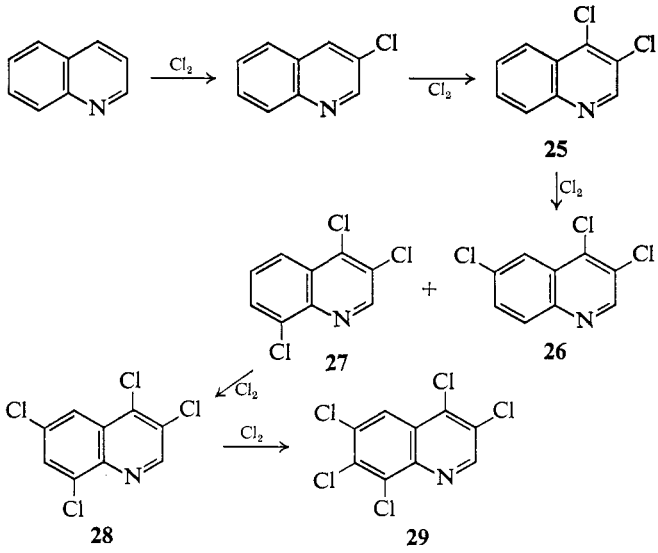
The reaction probably proceeds via an intermediate of type (**24**) which is known[41] to yield perchloroquinoline when heated for several hours at 400 °C. High-temperature chlorinations of the above type have been shown to be of great utility in the preparation of a wide range of perchloro-compounds and excellent reviews of the subject by Holtschmidt and his co-workers[42, 43] are available. 1,2,3,4-Tetrahydroquinoline undergoes high-temperature chlorination to give heptachloroquinoline in moderate yield.[44]

Tong[45] has carried out a careful investigation of the direct uncatalysed chlorination of quinoline at 160–190 °C. Gas–liquid chromatographic analysis of the reaction products reveals a mixture of at least ten components, of which the five chloroquinolines (**25–29**) are the main constituents. The percentages of the total mixture represented by these compounds are 14.9, 9.7, 18.9, 17.1, and 14.8%, respectively. Identification of the chloroquinolines was achieved by a combination of mass, infrared, and nuclear magnetic resonance spectroscopy. In the case of polychloro-compounds (**26**), (**27**), and (**28**) identity was confirmed by unambiguous synthesis.

If the chlorination is carried out at 100 °C over a short time (10 minutes) only a low yield of 3-chloroquinoline is realized. On the basis of this result Tong proposes the reaction Scheme 3 to account for the formation of the main chlorination products (**25–29**) (see p. 336).

Chlorination at the 4-position is somewhat unusual and differs from bromination processes which normally proceed at the 3-, 6-, and 8-positions of the quinoline ring. In explanation Tong suggests an addition–elimination mechanism similar to that proposed by Eisch and Jaselskis[14] to account for the formation of 4-bromoquinoline.

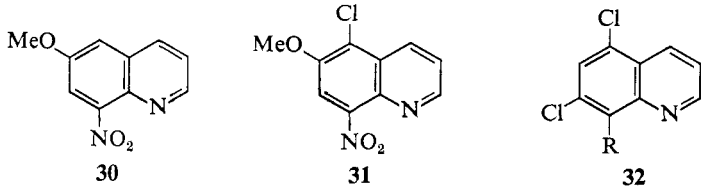
A patent, describing the high-temperature chlorination of quinoline, has appeared.[46] At 440 °C, and using a flow rate of 11.2 mol of chlorine per hour, a mixture of tri-, tetra-, and penta-chloroquinolines is produced. These chloroquinolines may be separated by fractional distillation at 0.7 mm and have boiling



SCHEME 3

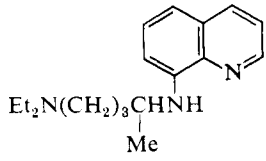
point ranges of 130–135, 146–150, and 180–184 °C, respectively. At higher temperatures (610 °C) and with a faster chlorine flow rate (23 mol per hour) heptachloroquinoline is obtained. Heptachloroquinoline can also be prepared by treating decahydroquinoline with chlorine at 580 °C.[47]

(*ii*) *Chlorination of Other Substituted Quinolines.* No report on the direct chlorination of quinolines bearing only electron-withdrawing substituents has appeared. As expected, quinolines having both electron-withdrawing and electron-donating substituents undergo chlorination at positions determined by the directing influence of the latter groups. Thus 6-methoxy-8-nitroquinoline (**30**) yields the 5-chloro-compound (**31**) when treated with chlorine in acetic acid.[48]



Chlorine in acetic acid has been widely used for the chlorination of quinolines bearing activating groups. For example, 8-aminoquinoline yields 8-amino-5,7-dichloroquinoline (**32**; R = NH_2);[49] demethoxylated "Plasmochin" (**33**) is monochlorinated at the 5-position;[50] and the *p*-tosyl derivative of 8-aminoquinoline undergoes dichlorination at 45 °C to yield 5,7-dichloro-8-(*p*-toluenesulphonamido)-quinoline (**32**; R = *p*-$CH_3C_6H_4SO_2NH$).[51]

Under similar conditions 8-acetamido-6-methoxyquinoline is reported[52, 53] to give the 5-chloro-derivative. Treatment of 8-amino-4,7-dichloroquinoline in dioxan solution with chlorine yields 8-amino-4,5,7-trichloroquinoline (35%).[54]



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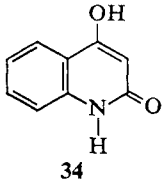
The chlorination of quinolones and hydroxyquinolines has been studied in some detail. 2-Quinolone reacts in acetic acid solution with an equimolar proportion of chlorine to give as major product a dichlorohydroxyquinoline, which on treatment with phosphorus oxychloride yields a trichloro-derivative.[55] An unambiguous synthesis showed the product to be 2,3,6-trichloroquinoline, indicating that the original halogenation had taken place at the 3- and 6-positions. 2,6-Dichloroquinoline was also obtained from the reaction mixture, but attempts to increase the yield of monochloro-2-quinolone by decreasing the reaction temperature failed. Monochlorination is suppressed when the reaction is carried out for 2 hours at 100 °C. 3,6-Dichloro-2-quinolone is also obtained in high yield by chlorinating 6-chloro-2-quinolone in acetic acid.[55] 3-Hydroxyquinoline yields 4-chloro-3-hydroxyquinoline (65%) when treated with chlorine in ethanol at 20 °C.[56]

Chlorination of 4-hydroxy-2-quinolone (**34**) has been studied in some detail by Ziegler and his co-workers.[57] Reaction of the quinolone (**34**) with chlorine in dioxan



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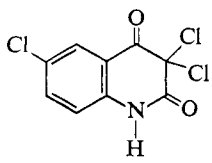

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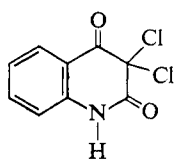

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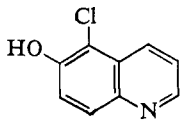
solution for 15 minutes at 80 °C yields 3,3,6-trichloro-1,2,3,4-tetrahydro-2,4-dioxoquinoline (**35**), whereas at 100 °C in a mixture of dioxan and hydrochloric acid the 3,3-dichloro-compound (**36**) (91%) is formed.

Somewhat surprisingly, chlorination of 8-methoxy-4-quinolone in acetic acid is reported[58] to yield only 3-chloro-8-methoxy-4-quinolone.

Zincke[59] has shown that whereas 6-hydroxyquinoline is chlorinated in cold acetic acid to give 5-chloro-6-hydroxyquinoline (**37**), at higher temperatures the tetrachlorotetrahydroquinolone (**38**) is produced: the latter result has been confirmed by Bullock and Tweedie.[60]

Tetrachloro-compound (**38**) can also be prepared by chlorinating 5-chloro-6-hydroxyquinoline under similar conditions,[59] whereas 5,7-dichloro-6-hydroxyquinoline (**39**) yields the tetrachlorodihydroquinolone (**40**).[61] 5-Chloro-6-hydroxyquinoline is reported[62] to yield 5,5-dichloro-5,6-dihydro-6-oxoquinoline (**41**) on treatment with chlorine in aqueous solution. Chlorination of 5-amino-6-hydroxyquinoline in acetic acid is accompanied by oxidation and *o*-quinone (**42**) is obtained in 80% yield.[60, 63] *p*-Quinone (**43**) under similar conditions yields the *gem*-dichloro-compound (**44**).[61]

The chlorination of 8-hydroxyquinoline has been rigorously investigated since dihalo-8-hydroxyquinolines have long been known to possess antiamoebic activity in man. The subject has been extensively reviewed.[64–66] In general chlorination is carried out in acetic acid solution,[67–70] although formic acid,[71] hydrochloric acid,[70]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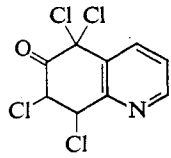
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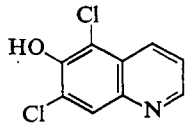
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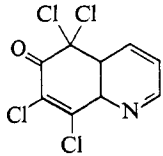
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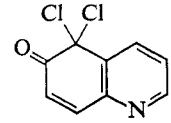
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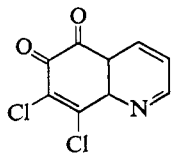
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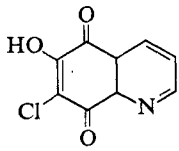
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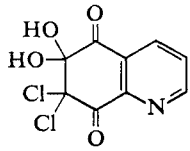
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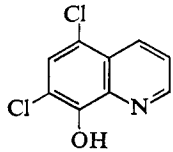
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chloroform,[72] carbon tetrachloride,[73] and ethanol[71, 74] have also been employed as the reaction solvent. Under most conditions 5,7-dichloro-8-hydroxy-quinoline (**45**) is the major product. However, in cold acetic acid a mixture of 5-chloro- and 5,7-dichloro-8-hydroxyquinoline is formed.[75, 76] At room temperature formation of the dichloro-compound is favoured. The yield of dichloro-compound is reported[77] to be increased (52 → 74%) if chlorination is carried out in the presence of antimony trichloride. A mixture of 5-chloro- and 5,7-dichloro-8-hydroxyquinoline is also produced on boiling a concentrated hydrochloric acid solution of 8-hydroxyquinoline for 2 hours in the presence of ferric chloride.[78] High yields (90%) of 5-chloro-8-hydroxyquinoline, reportedly free from the dichloro-compound, have been obtained by chlorinating 8-hydroxyquinoline at −4 °C in concentrated sulphuric acid.[79]

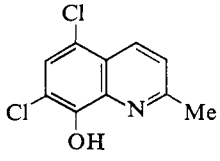
The reported[74] chlorination of 8-hydroxy-5-iodoquinoline in cold chloroform to give the 7-chloro-derivative appears to be in error. This reaction is discussed in Section II.1.A.f(ii).

The chlorination of various metal chelates of 8-hydroxyquinoline has been studied in some detail.[80] The aluminium(III), chromium(III), cupric, and ferric complexes at 0 °C undergo dichlorination at the 5- and 7-positions when treated with chlorine (two equivalents/mol). The aluminium(III) complex, however, reacts with chlorine (three equivalents/mol) to yield a 5,6,7-trichloro-8-hydroxyquinoline–aluminium chelate. From their results the authors conclude that chelation has little or no effect on the orientation and yield of halogenated product. More recently[81] the chlorination of 8-hydroxyquinoline and its copper(II) chelate has been reinvestigated; the results confirm the early work and demonstrate that the rate of chlorination of the chelate is greater than that of the free ligand.

8-Hydroxy-2-methylquinoline is monochlorinated at the 5-position with chlorine in 20% hydrochloric acid,[70] while in acetic acid,[82] formic acid,[83–85] and chloroform[72] the 5,7-dichloro-compound (**46**) is formed.

Chlorination of 6-chloro-8-hydroxyquinoline in ethanol at room temperature yields 5,6,7-trichloro-8-hydroxyquinoline.[86] This trichloro-compound can also be

obtained[75] by chlorinating 5,7,7-trichloro-7,8-dihydro-8-oxoquinoline (**47**)* (prepared by treating 5,7-dichloro-8-hydroxyquinoline with chlorine in chloroform) in boiling acetic acid.



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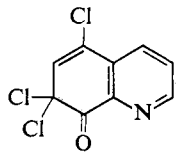

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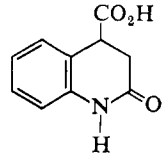

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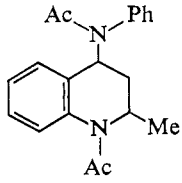
1,2,3,4-Tetrahydroquinolines chlorinate as expected at the 6- and/or 8-positions. For example, 1,2,3,4-tetrahydro-2-oxoquinoline-4-carboxylic acid (**48**) reacts with chlorine in acetic acid to yield the 6,8-dichloro-derivative,[87] whereas the diacetyl compound (**49**), with chlorine in carbon tetrachloride, yields only the 6-chloro-compound (**50**).[88]



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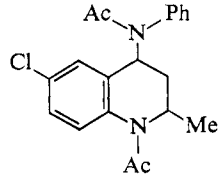

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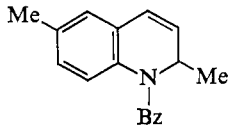

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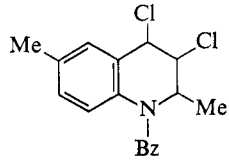

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In contrast the 1,2-dihydroquinoline (**51**) under similar conditions undergoes 3,4-addition of chlorine, to give dichloro-compound (**52**).[89] These and other details are collected in Table 1.

TABLE 1. Chloroquinolines by Direct Chlorination

Chloroquinoline†	Method of preparation (yield)	References
3-Chloro-8-methoxy-4-quinolone	8-MeO-4-Q'one; Cl_2/AcOH at room temp. for 12 h (25%)	58
4-Chloro-3-hydroxy-	3-HO-Q; (i) HCl/15% H_2O_2 at 60–70 °C for 1 h (66%); (ii) Cl_2/EtOH at 20 °C for 1–2 h (65%)	56

* For this compound and the isomeric 5,5,7-trichloro-5,8-dihydro-8-oxoquinoline, see ref. 2026.

† In this and similar Tables the name of the product is obtained by adding "quinoline" to the substituent name(s) listed, except where a "quinolone" is specified.

TABLE 1 (*cont.*)

Chloroquinoline*	Method of preparation (yield)	References
5-CHLORO-		
5-Chloro-	Cl_2 for 1 h through mixture of Q/Ag_2SO_4 and 98% H_2SO_4	31, 32
8-Acetamido-5-chloro-6-methoxy-	8-AcNH-6-MeO-Q; Cl_2/AcOH at 0 °C	52
8-Amino-5-chloro-6-methoxy-	8-AcNH-6-MeO-Q; Cl_2/AcOH at 0 °C then HCl hydrolysis (65%)	53
5-Chloro-6-hydroxy-	6-HO-Q; Cl_2/AcOH cold	59
5-Chloro-6-methoxy-	6-MeO-Q; Cl_2/AcOH (71%)	90
5-Chloro-6-methoxy-8-nitro-	6-MeO-8-NO_2-Q; Cl_2/AcOH	48
5-Chloro-8-hydroxy-	8-HO-Q; Cl_2/conc. H_2SO_4 at −4 °C for 1 h (90.5%)	79
5-Chloro-8-hydroxy-2-methyl-	Cl_2/20% HCl (73%)	70
5-Chloro-8-(4-diethylamino-1-methylbutylamino)-	8-[$Et_2N(CH_2)_3CH(Me)NH$]-Q; Cl_2/AcOH at 0 °C	50
6- and 8-CHLORO-		
1-Acetyl-4-(*N*-acetylanilino)-6-chloro-1,2,3,4-tetrahydro-2-methyl-	1-Ac-4-[PhN(Ac)]-2-Me-1,2,3,4-tetraH-Q; Cl_2/CCl_4 for 1 h (40%)	88
6-Chloro-2-quinolone	2-Q'one; Cl_2/AcOH for 3 h	55
8-Chloro-	Cl_2 for 1 h through mixture of Q/Ag_2SO_4 and 98% H_2SO_4	31, 32
DICHLORO-		
3,3-Dichloro-1,2,3,4-tetrahydro-2,4,-dioxo-	4-HO-2-Q'one; Cl_2/conc. HCl/dioxan at 100 °C (91%)	57
3,4-Dichloro-	Q/Cl_2 at 160–190 °C for 10 h (14.9%)	45
1-Benzoyl-3,4,-dichloro-1,2,3,4-tetrahydro-2,6-dimethyl-	1-Bz-2,6-diMe-1,2-diH-Q; Cl_2/CCl_4	89
3,6-Dichloro-2-quinolone	2-Q'one; excess of Cl_2/AcOH at 100 °C for 2 h (81.4%)	55
5,5-Dichloro-5,6-dihydro-6-oxo-	6-HO- or 5-Cl-6-HO-Q; Cl_2/aq. HCl	62
5,6-Dichloro-	6-Cl-Q/$AlCl_3$ complex at 100 °C with Cl_2 for 2 h (85%)	33
8-Amino-5,7-dichloro-	8-NH_2-Q; Cl_2/AcOH at room temp. (31%)	49
5,7-Dichloro-8-hydroxy-	8-HO-Q; Cl_2/$CHCl_3$ at 25 °C for 3 h with I_2 catalyst; Cl_2/CCl_4 (79%); Cl_2/EtOH at 0 °C; Cl_2/AcOH (85%); conc. HCl/$FeCl_3$ boil for 2 h	67, 69, 71, 72, 73, 74, 75, 78
5,7-Dichloro-8-hydroxy-2-methyl-	8-HO-2-Me-Q; Cl_2/AcOH; Cl_2/HCO_2H; Cl_2/$CHCl_3$ at 25 °C for 3 h with I_2 catalyst (94%)	72, 82, 83, 85
5,7-Dichloro-8-hydroxy-2-methyl-4-carboxylic acid	8-HO-2-Me-Q-4-CO_2H; Cl_2/AcOH at 30 °C	82

* In this and similar Tables the name of the product is obtained by adding "quinoline" to the substituent name(s) listed, except where a "quinolone" is specified.

TABLE 1 (*cont.*)

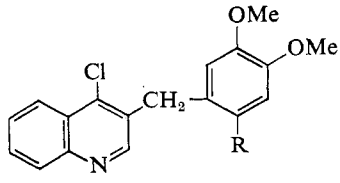
Chloroquinoline*	Method of preparation (yield)	References
5,7-Dichloro-8-(*p*-toluenesulphonamido)-	8-(*p*-Tosyl)NH-Q; Cl_2/AcOH at 45 °C for 2 h (37.4%)	51
5,8-Dichloro-	(i) Q; 5-Cl- or 8-Cl-Q in Ag_2SO_4/98% H_2SO_4 with Cl_2 for 1 h; (ii) Q/$AlCl_3$ complex at 100 °C with Cl_2 for 2 h (73%)	32, 33
6,8-Dichloro-1,2,3,4-tetrahydro-2-oxoquinoline-4-carboxylic acid	1,2,3,4-tetraH-2-oxo-Q-4-CO_2H; Cl_2/AcOH	87
7,8-Dichloro-5,6-dihydro-5,6-dioxo-	5-NH_2-6-HO-Q; Cl_2/AcOH (80%)	60, 63
POLYCHLORO-		
3,4,6,7,8-Pentachloro-	Q/Cl_2 at 160–190 °C for 10 h (14.8%)	45
x,*x*,*x*,*x*,*x*-Pentachloro-	Q/$AlCl_3$ complex; excess of Cl_2 at 110–190 °C for 48 h (79%)	35, 36
3,5,6,7,8-Pentachloro-2,4-dimethyl-	6,8- or 5,8-diCl-2,4-diMe-Q; Cl_2/AcOH at 60° C	91
3,4,6,8-Tetrachloro-	Q/Cl_2 at 160–190 °C for 10 h (17.1%)	45
x,*x*,*x*,*x*-Tetrachloro-	Q/$AlCl_3$ complex; excess of Cl_2 for 48 h at 140–160 °C (87%)	35, 36
5,5,7,8-Tetrachloro-5,6-dihydro-6-oxo-	5,7-diCl-6-HO-Q; Cl_2/AcOH cold (95%)	59, 61
5,5,7,8-Tetrachloro-5,6,7,8-tetrahydro-6-oxo-	6-HO-Q; Cl_2/AcOH for 2 days (90%)	59, 60, 61
5,6,7,8-Tetrachloro-	5,8-diCl-Q/$AlCl_3$ complex at 150 °C with Cl_2 for 4 h	9
5,6,*x*,*x*-Tetrachloro-2,4-dimethyl-	5,6-diCl-2,4-diMe-Q; Cl_2/AcOH at 60 °C	91
6,*x*,*x*,*x*-Tetrachloro-2,4-dimethyl-	6-Cl-2,4-diMe-Q; as above	91
8,*x*,*x*,*x*-Tetrachloro-2,4-dimethyl-	8-Cl-2,4-diMe-Q; as above	91
3,3,6-Trichloro-1,2,3,4-tetrahydro-2,4-dioxo-	4-HO-2-Q'one; Cl_2/dioxan at 80 °C for 15 min (96%)	57
3,4,6-Trichloro-	Q/Cl_2 at 160–190 °C for 10 h	45
3,4,8-Trichloro-	As above (18.9%)	45
8-Amino-4,5,7-trichloro-	8-NH_2-4,7-diCl-Q; Cl_2/dioxan (35%)	54
5,5,7-Trichloro-5,8-dihydro-8-oxo-	—	2026
5,6,7-Trichloro-8-hydroxy-	6-Cl-8-HO-Q; Cl_2/EtOH at room temp. for 12 h (96%)	86
5,6,8-Trichloro-	6-Cl-Q/$AlCl_3$ complex at 125 °C with Cl_2 for 2 h	33
5,7,7-Trichloro-7,8-dihydro-8-oxo-	5,7-diCl-8-HO-Q; Cl_2/$CHCl_3$	75, 2026
7,*x*,*x*-Trichloro-2,4-dimethyl-	7-Cl-2,4-diMe-Q; Cl_2/AcOH at 60 °C	91

e. BROMINATION.* (*i*) *Of Quinoline and Alkyl- and Halo-substituted Quinolines.* Although it is only recently that the nature of quinoline–bromine complexes and their decomposition products have begun to be understood, such complexes have long been used as a preparative route to bromoquinolines [see Section II.1.B.c(i)]. The early workers tended to use far too vigorous conditions to effect bromination with the result that, in general, mixtures of mono-, di-, and tri-bromoquinolines were obtained. It is only recently that bromination of quinoline under mild conditions has been realized, and in many instances the quinoline–bromine complex is isolable (see Table 35, p. 618).

An early report[92] indicates that quinoline with bromine in carbon disulphide solution yields a resinous mixture from which an uncharacterized tetrabromoquinoline, m.p. 119 °C, and quinoline hydrobromide were isolated. Under similar conditions 2-ethyl-3,6-dimethylquinoline yields an unidentified dibromo-compound.[93] 3-Bromoquinoline hydrochloride with bromine in aqueous solution at 130 °C in a sealed tube, or with bromine in boiling acetic acid, reacts to give a mixture of 3,6-dibromo-, 3,6,8-tribromo- (main product), and 3,5,6,8-tetrabromoquinoline.[94–96] In an earlier paper[97] on the bromination of quinoline hydrochloride under aqueous conditions (180 °C in a sealed tube) 3-bromo- and 3,6-dibromoquinoline are reported as the main products; other products were isolated but not identified. 3,6,8-Tribromoquinoline is also obtained on boiling a chloroform solution of 6,8-dibromoquinoline with bromine.[96] Bromination of 6-methylquinoline in 50% oleum yields an unidentified dibromo-6-methylquinoline[98] (probably the 5,8-dibromo derivative).

Ukai[99] has successfully prepared a number of monobromomethylquinolines by treating the mercuriacetate or mercurichloride derivatives of the alkylquinoline with bromine. These reactions are discussed in more detail in Section II.1.H.d.

Bromination of the (dimethoxybenzyl)quinoline (**53**; R = H) with bromine in chloroform results, not unexpectedly, in monobromination of the dimethoxyphenyl ring, rather than the quinoline nucleus, to give bromo-compound (**53**: R = Br).[100]



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The gaseous-phase bromination of quinoline has been investigated by Jansen and Wibaut.[2] When quinoline and bromine are passed through a pumice-filled tube at 300 °C, 3-bromoquinoline (25%) is obtained plus a small amount of a dibromoquinoline tentatively identified as either 3,4- or 3,5-dibromoquinoline. Repetition of the reaction at 450 °C yields 2-bromoquinoline as the main product (24%), accompanied by a small amount of the 3-bromo-isomer. However, if the bromination is carried out in an empty tube at 500 °C with nitrogen as a diluent, 2-bromoquinoline (53%) is obtained, together with a dibromoquinoline, m.p. 171 °C (possibly 2,6-dibromoquinoline—see Table 48); no 3-bromoquinoline is formed under these conditions.

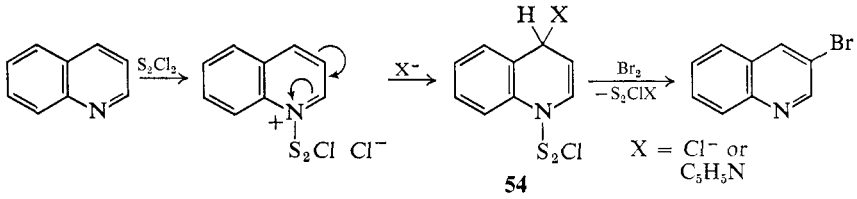
Bromination of quinoline in concentrated sulphuric acid in the presence of silver sulphate yields a mixture of 5-bromo-, 8-bromo-, and 5,8-dibromo-quinoline.[6]

* See also Addenda, p. 675.

Optimum yields are obtained in 100% sulphuric acid.[7] 5,8-Dibromoquinoline is separated from the reaction mixture by precipitation at pH 2. Subsequent adjustment of the reaction mixture to pH 3 causes precipitation of the 5- and 8-bromoquinoline which may be separated by fractional crystallization of their oxalates. Quinoline fails to react with bromine and silver acetate in acetic acid, or with silver nitrate in nitric acid. However, when a hydrochloric acid solution of quinoline is heated under reflux with bromine in chloroform for 24 hours a mixture of 3,6-dibromo- and 3,6,8-tribromo-quinoline is obtained.[7] 3,5-Dibromo- and 3,5,8-tribromo-quinoline can also be prepared by treating a concentrated sulphuric acid solution of 3-bromo-quinoline, containing silver sulphate, with bromine. Similarly prepared are 5,8-dibromo- and 5,6,8-tribromo-quinoline from 5- and 8-bromoquinoline, and 6-bromoquinoline, respectively.

Quinoline in the presence of an excess of aluminium chloride reacts with bromine to yield a mixture of 5-bromo-, 5,6-dibromo-, 5,8-dibromo-, and 5,6,8-tribromo-quinoline.[9] The composition of the reaction mixture is found to depend on the method of bromine introduction. For example, dropwise addition of bromine leads to the formation of a mixture of mono-, di-, and tri-brominated products regardless of the amount of bromine used. However, by using the appropriate amount of gaseous bromine mono-, di-, and tri-bromoquinolines may be selectively synthesized. Reaction of the quinoline–aluminium chloride complex with bromine at 80 °C for 6 hours yields 5,8-dibromoquinoline (86%). In a like manner 5,6,8-tribromoquinoline and 5,6,7,8-tetrabromoquinoline have been prepared in good yield, and the method has been employed[33] also for the preparation of 5,6-dibromo-, 5-bromo-6-chloro-, and 5,8-dibromo-6-ethylquinoline from 6-bromo-, 6-chloro-, and 6-ethyl-quinoline, respectively.

Hunsberger and his co-workers[101] have described a method for the selective bromination of quinoline at the 3-position. The process, which involves treating a mixture of quinoline, sulphur monochloride, and pyridine with a molar excess of bromine, results in the formation of 3-bromoquinoline in 65% yield. The proposed mechanism for the reaction envisages initial quaternization of quinoline by sulphur monochloride (Scheme 4) followed by nucleophilic attack by either pyridine or chloride ion at the 4-position of the quinoline nucleus to yield the vinylamine (**54**).



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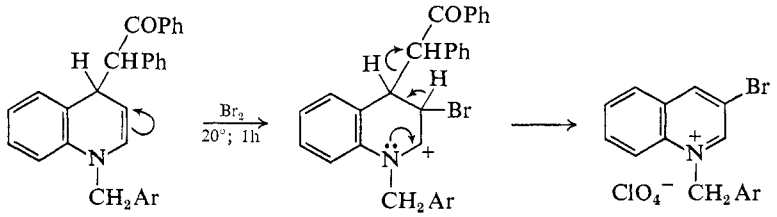
SCHEME 4

Subsequent bromination of the amine at the 3-position and then 1,4-elimination of the appropriate substituents leads to the formation of 3-bromoquinoline.

A similar reaction scheme has been put forward by Kröhnke and Vögt[102] to explain the reaction of the 1-benzylquinolinium–deoxybenzoin adduct (**55**) with bromine (Scheme 5; Ar = 2,6-dichlorophenyl).

The 3-bromoquinoline (**56**) was isolated as the perchlorate and its structure was confirmed by unambiguous synthesis from 3-bromoquinoline and 2,6-dichlorobenzyl bromide.



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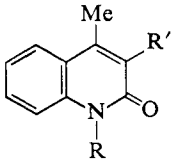
SCHEME 5

(*ii*) *Bromination of Quinolines Bearing Electron-withdrawing Groups.* As with chlorination, little work has been published on the direct bromination of quinolines bearing electron-withdrawing (deactivating) substituents. 8-Nitroquinoline is reported[103, 104] to yield 5,7-dibromo-8-nitroquinoline when heated with aqueous bromine at 130–135 °C in a sealed tube. Under similar conditions 6-methyl-8-nitroquinoline yields what is thought to be the 5-bromo-derivative.[103] The orientation of these products, however, is difficult to believe in the light of both current mechanistic theory, and similar reactions[95-97] on quinoline itself, in which bromination proceeds at the 3- and 6-positions, as theory predicts (see Section II.1.A.b). In fact, the so-called 5,7-dibromo-8-nitroquinoline (m.p. 180 °C) is probably 3,6-dibromo-8-nitroquinoline, which has been prepared unambiguously[105] and which has a melting point of 179–180 °C. More reasonable is the formation of 3-bromo-8-nitroquinoline from the reaction of 8-nitroquinoline with bromine in boiling *o*-dichlorobenzene solution.[106] The yield (55%) of the bromonitroquinoline, which was required in order to investigate the effect of 3-substituents on the antimalarial activity of "Plasmochin", was found to be drastically lowered (29%) on scaling up (× 5) the reaction. Attempts to carry out the bromination in chloroacetic acid, which has been used successfully[107] as a solvent for the bromination of 8-methyl-6-nitroquinoline, gave only impure products. The product from the bromination of 8-methyl-6-nitroquinoline is assumed by the authors to be 3-bromo-8-methyl-6-nitroquinoline on account of the non-reactivity of the bromine substituent towards nucleophilic displacement. Attempts to brominate 8-methyl-6-nitroquinoline in chloroform solution failed.

6-Nitroquinoline is readily brominated[108, 109] at the 3-position under the conditions formulated by Eisch,[13] i.e. bromine in carbon tetrachloride in the presence of pyridine.

(*iii*) *Bromination of Hydroxyquinolines, Quinolones, and their Derivatives.* Hydroxyquinolines and quinolones undergo bromination in a wide variety of solvents. Not unexpectedly the position taken up in the nucleus by the incoming bromine substituent is determined by the position of the resident hydroxyl group.

Early work[110] indicates that 2-quinolone reacts with both bromine vapour and aqueous bromine to give a mixture of mono- and poly-brominated products, none of which was separated and identified. On the other hand, 2-methoxyquinoline with bromine vapour gives a single product which is thought to be 4-bromo-2-methoxyquinoline.[110] More recent work[55] has shown that 2-quinolone is brominated in high yield in acetic acid solution at the 6-position. Bromination of 4-methyl-2-quinolone (**57**; R = R′ = H) and its 1-methyl derivative (**57**; R = Me, R′ = H) in aqueous or acetic acid solution, however, yields the corresponding 3-bromo-derivatives (**57**; R′ = Br, R = H and Me, respectively).[111-113] In a like manner the 3-bromo-derivatives of a whole range of substituted 4-methyl-2-quinolones have been prepared.[114] 4-(Bromomethyl)-2-quinolone in acetic acid solution readily yields the dibromo-compound (**58**).[114]



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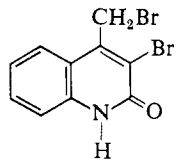

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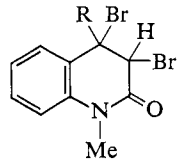

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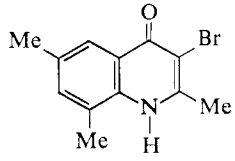
In contrast Daniels and his co-workers[115] report that 1-methyl- and 1,4-dimethyl-2-quinolone with bromine in chloroform undergo 3,4-bromine addition, rather than substitution, to give dibromo-derivatives (**59**; R = H and Me, respectively). The structures of the dibromo-derivatives were confirmed by dehydrobromination to the known 3-bromo-1-methyl-2-quinolones.

In acetic acid at 70–80 °C, 3-hydroxyquinoline is brominated in high yield (78%) to give 4-bromo-3-hydroxyquinoline.[56]

4-Quinolones are brominated at the 3-position (if vacant) regardless of the nature of other substituent groups present in the nucleus. Thus 8-nitro-4-quinolone in acetic acid yields 3-bromo-8-nitro-4-quinolone,[116] and 2,6,8-trimethyl-4-quinolone under similar conditions yields what is thought to be the 3-bromo-derivative (**60**).[117] 4-Quinolone itself in hot glacial acetic acid gives an almost quantitative yield of 3-bromo-4-quinolone.[118] Similar yields of the 3-bromo-derivatives of 2-amino-[119] and 2-amino-7-methyl-4-quinolone[120] have also been realized. 4-Quinolone-2-carboxylic acid (**61**; R = H) and its ethyl ester (**61**; R = Et) can be brominated in



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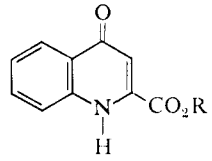

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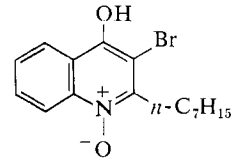

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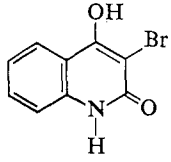
potassium hydroxide solution,[121] and in acetic acid in the presence of iodine,[122] respectively, to yield their 3-bromo-derivatives. Halo-substituted 4-quinolone-2-carboxylic esters behave similarly.[122] 2-(*n*-Heptyl)-4-hydroxyquinoline *N*-oxide on treatment with bromine in chloroform yields what is thought to be the 3-bromo-derivative (**62**).[123]

1-Substituted 4-quinolones are also brominated readily at the 3-position. For example, 1-ethyl-4-quinolone with bromine in acetic acid yields 3-bromo-1-ethyl-4-quinolone.[124, 125] It has been reported,[126] however, that 1-methyl-4-quinolone with bromine in chloroform gives only impure products.

Some confusion exists regarding the bromination products of 4-hydroxy-2-quinolone. Meyer and Heimann[127] report that 4-hydroxy-2-quinolone in cold 100% formic acid, with an equivalent of bromine yields a monobromo-derivative, m.p. 199 °C, whereas in warm formic acid, or with an excess of bromine in the cold, a compound, m.p. 281 °C, formulated as 3-bromo-4-hydroxy-2-quinolone (**63**), is obtained; if, however, the bromination is carried out in boiling benzene in the absence of catalysts a monobromoquinolone, m.p. 241 °C, different from either of the two previous monobromo-derivatives is formed. Other workers,[119] however, find that 4-hydroxy-2-quinolone on treatment with bromine in either boiling acetic or formic acid yields a monobromo-derivative, m.p. 233 °C, which is thought to be the

3-bromo-compound (**63**), as well as an unidentified dibromo-compound, m.p. 278 °C. In neither of the above cases, however, did the authors rigorously confirm the structure of their "3-bromo derivative", and the large discrepancy in the reported melting point of the so-called monobromo-derivative (**63**) (i.e. 233 and 281 °C) warrants further investigation of these reactions.



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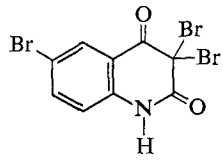

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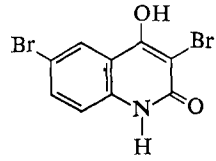

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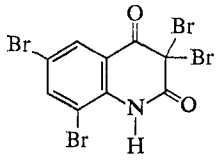
Ziegler and his co-workers,[128] using a different brominating system, have obtained a variety of bromination products from 4-hydroxy-2-quinolone, none of which correspond to those discussed above. Thus, 4-hydroxy-2-quinolone with bromine in boiling aqueous dioxan yields 3,3,6-tribromo-1,2,3,4-tetrahydro-2,4-dioxoquinoline (**64**), whereas with bromine in a mixture of dioxan and hydrobromic acid 3,6-dibromo-4-hydroxy-2-quinolone (**65**) is obtained. Dibromo-compound (**65**) readily gives the tribromo-derivative (**64**) on further treatment with bromine in dioxan. Bromination of 4-hydroxy-2-quinolone in a mixture of dioxan, concentrated hydrochloric acid, and water unexpectedly yields 6-bromo-3-chloro-4-hydroxy-2-quinolone (90%), while bromination of 6,8-dibromo-4-hydroxy-2-quinolone in dioxan at 35 °C gives tetrabromo-compound (**66**) in high yield.

3-Benzyl-4-hydroxy-2-quinolone (**67**; R = H) and its 1-methyl derivative (**67**; R = Me) on treatment with bromine in ethanol, and aqueous dioxan solution,



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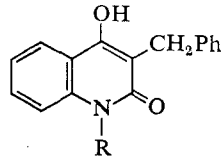

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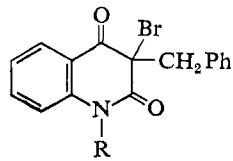

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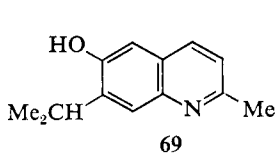
respectively, yield the 3-bromo-derivatives (**68**; R = H and Me).[128] Similarly 4-hydroxy-1,3-dimethyl-2-quinolone is brominated at the 3-position in benzene solution in the presence of ultraviolet light.[129]

Bromination of 5-hydroxyquinoline in acetic acid solution gives a mixture of 8-bromo-5-hydroxy- and 6,8-dibromo-5-hydroxy-quinoline.[130] The latter compound can also be prepared by brominating 8-bromo-5-hydroxyquinoline under similar conditions.

6-Hydroxyquinolines appear to be brominated mainly at the 5- and 7-positions, and occasionally at the 8-position. An early report[131] indicates that 6-hydroxyquinoline with an excess of bromine gives either 3,5,7- or 3,5,8-tribromo-6-hydroxyquinoline. The same product is obtained on heating 5-bromo-6-hydroxyquinoline with two equivalents of bromine at 250 °C in a sealed tube. 5-Bromo-6-hydroxyquinoline can be prepared by treating 6-hydroxyquinoline with bromine in ethanol,[132] acetic acid,[133] or chloroform[133] solution. 6-Hydroxy-7-isopropyl-2-methylquinoline (**69**) is brominated in acetic acid solution at the 5-position in high yield.[134] 6-Methoxy-8-nitroquinoline is reported[48] to be brominated under similar conditions to give

5-bromo-6-methoxy-8-nitroquinoline (**70**); however, later studies by Elderfield and his co-workers[135, 136] have shown that the product is in fact the bromoquinolinium dibromide (**71**) and that the required bromo-nitro-compound (**70**) may be liberated by treating the dibromide with cyclohexene. Under optimum conditions bromo-compound (**70**) is obtained in 85% yield.[136]



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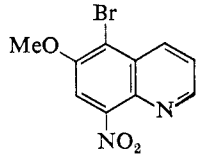

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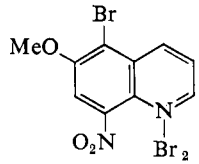

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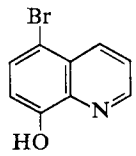
7-Hydroxyquinoline in acetic acid solution is brominated at the 8-position in high yield (78–86%).[132, 137, 138]

Much work has been published on the bromination of 8-hydroxyquinoline and short reviews are available.[64, 65] 8-Hydroxyquinoline undergoes bromination at the 5- and 7-positions and the main product in many cases is the 5,7-dibromo-compound. Skraup,[132] and Claus and Howitz,[133] were the first to brominate 8-hydroxyquinoline and they obtained a mixture of the 5-bromo- and 5,7-dibromo-derivatives. Conditions necessary for the formation of 5-bromo-8-hydroxyquinoline (**72**) in optimum yield have been determined.[139, 140] In 94% sulphuric acid at −5 °C the monobromo-derivative is obtained in 57% yield. An increase in reaction temperature of 15° causes the formation of the 5,7-dibromo-compound, while at −10 °C a mixture of 5-bromo- (52%) and 5,7-dibromo-8-hydroxyquinoline (19%) is formed. Decreasing the acid concentration to 70% also increases the proportion of dibromo-compound (40% at −5 °C) and decreases the yield of 5-bromo-compound (16% at −5 °C).

8-Acetoxyquinoline is reported[141] to give a good yield (71.4%) of the 5-bromo-derivative on treatment with bromine in chloroform solution at room temperature. In a similar manner a large number of esters derived from 8-hydroxyquinoline undergo bromination to give the 5-bromo-derivatives.[141]



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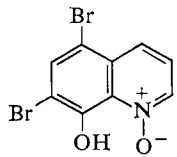

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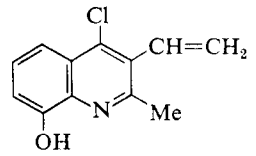

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5,7-Dibromo-8-hydroxyquinoline may be prepared by the action of bromine on 8-hydroxyquinoline in a variety of solvents; e.g. ethanol,[132] water,[142] dilute sulphuric acid,[69] and dilute hydrochloric acid.[71, 143] Similarly, dibromination of 8-hydroxy-2-methylquinolines and their esters[141] can be carried out in formic acid,[83, 84] acetic acid,[141] and chloroform[141, 144] solution. 8-Hydroxyquinoline *N*-oxide yields the 5,7-dibromo-derivative (**73**) on treatment with bromine in acetic acid.[145]

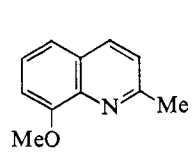
Bromination studies on a variety of 8-hydroxyquinoline–metal chelates have been published.[80, 81] For a variety of metals it is found that the chelate and the free ligand behave in a like manner towards electrophilic substitution, and with bromine in chloroform at 0 °C yield 5,7-dibromo-8-hydroxyquinoline. However, competitive

bromination studies[146] on a mixture of 8-hydroxyquinoline and its iron(III), chromium(III), or cobalt(III) chelate reveal that the chelate is brominated some 35 times faster than the free ligand.

Numerous reports concerning the bromination of 5-substituted 8-hydroxyquinolines have appeared. As expected, bromination always occurs at the 7-position regardless of the directive influence of the 5-substituent. Thus bromination of 5-nitro-,[147-149] 5-chloro-,[150, 151] 5-bromo-,[131, 152] 5-iodo-,[69] 5-alkoxymethyl-,[153, 154] 5-formyl-,[155] and 5-alkyl-8-hydroxyquinoline[156, 157] and of 8-hydroxyquinoline-5-sulphonic acid[158] in a variety of solvents yields the corresponding 7-bromo-derivatives. Similarly 7-formyl-,[159, 160] 7-aminoalkyl-,[161, 162] 7-alkyl-,[157, 163] 7-carboxy-,[164] and 7-halo-8-hydroxy-quinolines[163, 165] on bromination yield the corresponding 5-bromo-derivatives. It is of interest that the 8-hydroxy-3-vinylquinoline (**74**) with 1 mol of bromine in acetic acid undergoes bromination at the 5-position rather than bromine addition to the vinyl side chain.[166]

Pearson and his co-workers[167] have developed a convenient procedure for the selective bromination of phenols at the *ortho*-position, and application of the method to 8-hydroxyquinoline constitutes the only reported example of the monobromination of this compound at the 7-position. Practically, the process consists of treating 8-hydroxyquinoline with a toluene solution of bromine at −70 °C in the presence of *tert*-butylamine; 7-bromo-8-hydroxyquinoline is obtained in 92% yield and an examination of the product by thin-layer chromatography showed the absence of any isomeric product.

8-Ethoxyquinoline yields the 5-bromo-derivative when treated with bromine in boiling acetic acid.[168] However, more recent results[169] indicate that the bromination of 8-methoxy-2-methylquinoline (**75**) is more complex. At 80 °C the methoxy-compound reacts with bromine to form a tetrabromo-derivative which, from the



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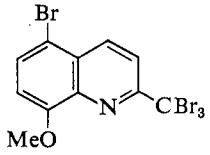

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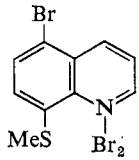

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results of hydrolysis reactions, appears to contain a (tribromomethyl) group; unambiguous synthesis shows that the tetrabromo-compound is in fact 5-bromo-8-methoxy-2-(tribromomethyl)quinoline (**76**).

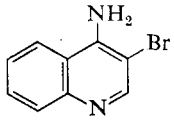
Careful bromination of the methoxyquinaldine (**75**) at room temperature yields 5-bromo-8-methoxy-2-methylquinoline, which on further bromination at 100 °C in acetic acid is converted into the (tribromomethyl) derivative (**76**).

8-(Methylthio)quinoline reacts with bromine in acetic acid to give initially the bromo-dibromide (**77**) which in boiling acetone loses a molecule of bromine to yield 5-bromo-8-(methylthio)quinoline.[170] Bromination of a variety of other quinoline-8-thioethers under similar conditions is also reported.

(*iv*) *Bromination of Aminoquinolines and Hydroquinolines.* Aminoquinolines, as expected, are brominated readily at positions *ortho* and *para* to the amino-function. Thus 4-aminoquinoline yields 4-amino-3-bromoquinoline (**78**) on treatment with bromine in chloroform[171] or acetic acid.[171-173] There is, however, a large discrepancy (156 °C [171] and 203 °C [172]) in the reported melting points of the bromo-amine (**78**).

4-Aminoquinoline *N*-oxide also is brominated at the 3-position.[174] 5-Amino- and 5-acetamidoquinoline in acetic acid give the 6,8-dibromo- and 8-bromo-derivative,

respectively.[175] 6-Aminoquinoline under similar conditions yields 6-amino-5-bromoquinoline (**79**; R = H)[176] and not, as previously reported,[177] the 7-bromo-isomer. Further bromination of the 5-bromoquinoline (**79**; R = H) or its *N*-acetyl



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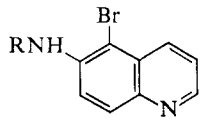

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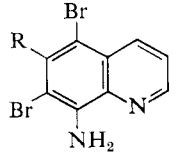
derivative (**79**; R = Ac) in acetic acid yields in each case a dibromo-compound of undetermined structure.[177] 8-Aminoquinoline undergoes dibromination, at the 5- and 7-positions,[49, 175] while 8-acetamidoquinoline[175, 178] and 8-(*p*-toluenesulphonamido)-quinoline[51] are monobrominated, solely at the 5-position. Quinolines bearing a secondary or tertiary amino-group at the 8-position also undergo monobromination at the 5-position with bromine in acetic acid.[50, 179] 8-Amino-5-bromo- and 8-amino-7-bromo-6-methoxyquinoline under similar conditions yield the 5,7-dibromo-derivative (**80**; R = MeO),[180] while 8-amino-6-chloro- and 8-amino-6-bromo-quinoline yield the dibromo- (**80**; R = Cl) and tribromo-derivative (**80**; R = Br), respectively.[181]

1,2,3,4-Tetrahydroquinoline yields a variety of bromination products depending on the conditions used. For instance, with one equivalent of bromine in chloroform 6-bromo-1,2,3,4-tetrahydroquinoline is formed,[182] together with a dibromo-compound, possibly the 6,8-dibromo-derivative;[104] with two equivalents of bromine the dibromo-compound is the sole product,[103, 104, 182] while with a large excess of bromine in either hot acetic acid[103] or chloroform[182] oxidation of the tetrahydroquinoline is observed and 3,6,8-tribromoquinoline (**81**) is obtained in good yield. The



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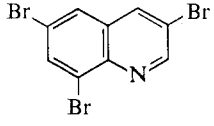

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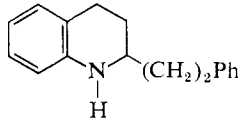

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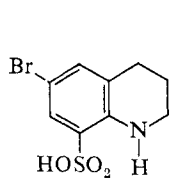
tribromoquinoline is also formed, together with an unidentified tetrabromo-compound, when 1,2,3,4-tetrahydroquinoline is allowed to react with bromine vapour.[183]

1,2,3,4-Tetrahydro-2-methyl-[184] and 1,2,3,4-tetrahydro-2-phenethyl-quinoline (**82**)[185] yield their respective 6-bromo-derivatives on treatment with bromine in chloroform, as do 1-alkyl-tetrahydroquinolines.[186] 1-Acetyl-1,2,3,4-tetrahydroquinoline reacts[187] with 2 mol of bromine in warm acetic acid to yield what is probably the 6-bromo-derivative, whereas with an excess of bromine 3,6,8-tribromoquinoline results.[103]

8-Ethoxy-1,2,3,4-tetrahydroquinoline and its 1-ethyl derivative yield unidentified monobromo-derivatives when treated with a cold solution of bromine in chloroform;[188] the bromo-derivative of the former is reported to decompose explosively at 150 °C. 1,2,3,4-Tetrahydroquinoline-8-sulphonic acid, however, under the same conditions gives a quantitative yield of 6-bromo-1,2,3,4-tetrahydroquinoline-8-sulphonic acid (**83**), which on further treatment with aqueous bromine yields 3,6,8-tribromoquinoline.[189] Bromination in sulphuric acid yields the same product, whereas

in aqueous solution a complex mixture of dibromo- (probably 6,8-dibromo-), tribromo- (main product), and tetrabromo-quinoline, together with 8-bromoquinoline, quinoline-8-sulphonic acid, and an unidentified bromoquinoline-8-sulphonic acid, is produced.

The bromination of 1-acyl-4-amino-1,2,3,4-tetrahydroquinolines has been investigated in some detail. The diacetyl (**84**; R = R′ = Ac)[190] and dibenzoyl- (**84**; R = R′ = Bz)[191] compounds are brominated in cold chloroform to yield the 6-bromo-derivatives (**85**; R = R′ = Ac and Bz, respectively), while the monoacetyl



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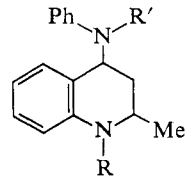

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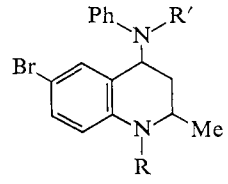

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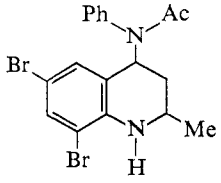

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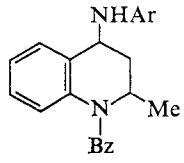

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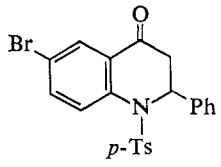
derivative (**84**; R = H, R′ = Ac) gives only the 6,8-dibromotetrahydroquinoline (**86**).[192] Obviously in the latter case the quinoline ring is far more activated (by the free secondary amino-group) towards electrophilic attack than in the former case, in which the amine function is present as a secondary amide. In the case of the monobenzoyl derivative (**84**; R = Bz, R′ = H) the phenyl ring of the secondary amino-substituent is more activated towards attack by electrophilic bromine than the quinoline nucleus and hence, in this case, bromination is observed solely at the phenyl ring of the 4-anilino-substituent, resulting in the formation of the dibromo-derivative (**87**; Ar = 2,4-dibromophenyl).[88, 192]

de Diesbach and Kramer[193] brominated 1,2,3,4-tetrahydro-4-oxo-2-phenyl-1-*p*-tosylquinoline and obtained a product which they assigned as the 6-bromo-derivative (**88**). Recently, however, this monobromo-derivative has been shown[194] by proton magnetic resonance measurements to be the 3-bromo-derivative (**89**; R = Ph).

Under identical conditions 1,2,3,4-tetrahydro-4-oxo-1-*p*-tosylquinoline yields the 3-bromo-derivative (**89**; R = H) together with a dibromo-compound thought to be the 3,3-dibromotetrahydro-4-oxoquinoline (**90**).[193] In contrast, 1,2,3,4-tetrahydro-4-oxo-2-phenyl-4-quinoline with one equivalent of bromine in chloroform gives the 6-bromo-derivative, while with an excess of bromine (four equivalents) the 3,6,8-tribromotetrahydro-4-oxoquinoline (**91**) is obtained together with a small amount of the 6,8-dibromo compound.[194] Similarly 1,2,3,4-tetrahydro-2-oxoquinoline (**92**; R = H)[195] and its 3-acetamido-derivative (**92**; R = NHAc)[196] on bromination give a mixture of the respective 6-bromo- and 6,8-dibromotetrahydro-2-oxoquinolines.

7-Acetamido-1,2,3,4-tetrahydro-2-oxoquinoline[197] and the tetrahydro-2-oxoquinoline-4-carboxylic acid (**93**)[87] yield their respective 6,8-dibromo-derivatives on bromination with bromine (two equivalents) in acetic acid. What is thought to be the 6-bromo-derivative of the 2-oxoquinoline (**93**) has also been prepared.[198] However,



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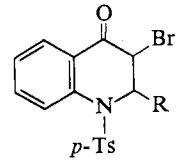

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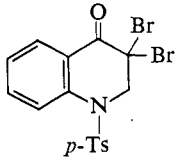

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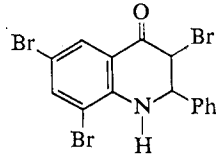

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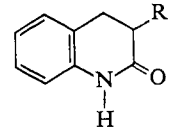

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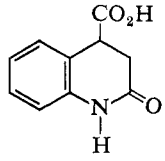

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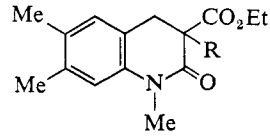

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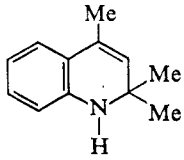
ethyl 1,2,3,4-tetrahydro-1,6,7-trimethyl-2-oxoquinoline-3-carboxylate (**94**; R = H) is brominated at the 3-position to give monobromo-derivative (**94**; R = Br) and an unidentified "dibromide".[199] A hexahydroquinoline of unknown constitution is reported[200] to yield an equally unidentifiable monobromo-derivative on treatment with bromine in chloroform.

The bromination of dihydroquinolines has received considerable attention. The so-called "acetone-anil" first prepared by Knoevenagel and Jäger[201] has been shown[202] to be 1,2-dihydro-2,2,4-trimethylquinoline (**95**). On bromination in methanol this trimethyl compound undergoes both substitution and bromine addition to yield 3,4,6,8-tetrabromo-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline (**96**).



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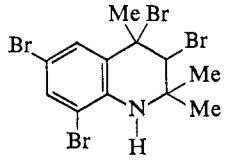

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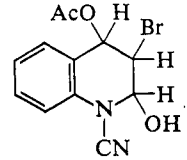

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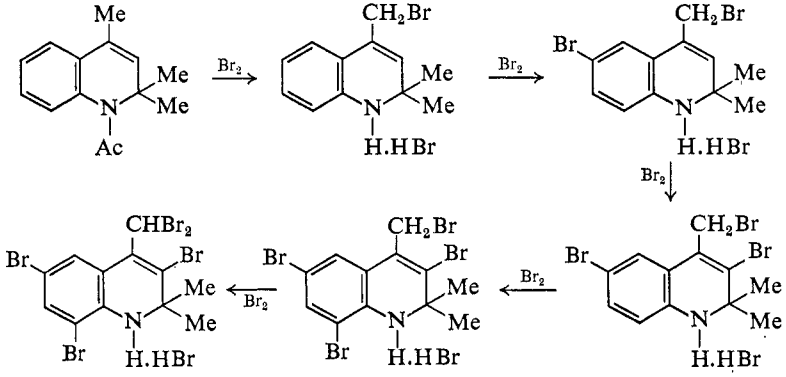
Subsequently bromination of 1,2-dihydroquinolines has become of importance from both a mechanistic viewpoint[21] and from the fact that the bromo-derivatives of this system show fungistatic activity at low concentrations.[203] Johnson and Ridd[21] have shown that 1-cyano-1,2-dihydro-2-hydroxyquinoline will react with bromine in a variety of buffered solutions, e.g. sodium acetate, to give the 3,4- addition product (e.g. **97**), which in strongly acidic media undergoes elimination of acetic acid and HOCN to yield 3-bromoquinoline. With an excess of bromine the pseudo-base is thought to undergo 3,4-bromine addition followed by rapid bromination at the

6-position, since on treatment of the reaction mixture with strong acid 3,6-dibromoquinoline is formed in high yield. 3,6,8-Tribromoquinoline results if a large excess of bromine is used. The mechanism of these reactions is discussed more fully in Section II.1.A.b.

Somewhat different products, however, have been obtained by Brown and Jackman[204] in their study of the bromination of "acetone-anil" and its 1-acetyl derivative. They showed, by chemical methods and by proton magnetic resonance measurements, that a series of bromo-compounds may be synthesized depending on the amount of bromine used in the reaction. None of the bromo-products obtained corresponds to the tetrabromo-compound reported by Cliffe,[202] and curiously no mention of this earlier work appears in the Brown and Jackman paper. The proposed bromination pathway of 1-acetyl-1,2-dihydro-2,2,4-trimethylquinoline, as put forward by Brown and Jackman, is outlined in Scheme 6. By means of a series of

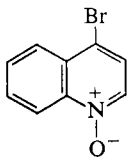


SCHEME 6

elegant and carefully controlled reactions involving varying quantities of bromine each of the bromo-compounds appearing in this scheme has been isolated and characterized.

A bromo-compound of unknown constitution is reported[205] from the bromination of 1,2-dihydro-1-methyl-2-phenylquinoline, and some doubt exists as to the structure of the dibromo-compounds obtained[89] from 1-benzoyl-1,2-dihydro-2,6-dimethyl- and 1-benzoyl-1,2-dihydro-2,6,8-trimethylquinoline.

(*v*) *Bromination of Quinoline* N-*Oxides*. The direct bromination of quinoline *N*-oxides has been studied by various Japanese workers. 4-Bromoquinoline *N*-oxide (**98**) was first prepared in 2–3% yield by Ochiai and Okamoto[206] who heated a



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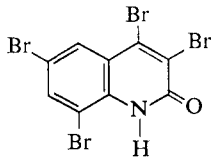

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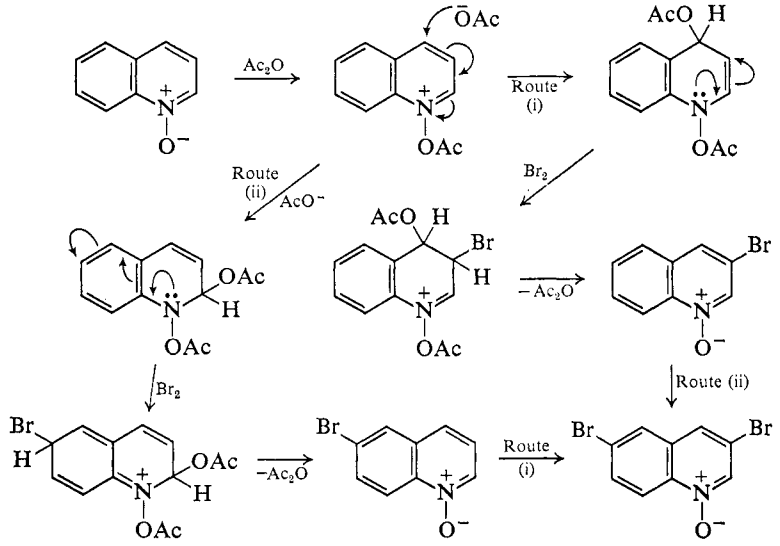
quinoline *N*-oxide–bromine addition compound with bromine water in a sealed tube at 100 °C. The yield of bromo *N*-oxide can be raised to 32% by carrying out the reaction at room temperature under aqueous conditions in a sealed tube, with a

5-molar excess of bromine. A by-product formed in the original experiment was shown to be 3,4,6,8-tetrabromo-2-quinolone (**99**).

In the course of proving the structure of this tetrabromo-compound Ochiai and Okamoto synthesized several polybromo-2-quinolones (see Table 2).

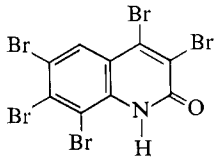
Later workers have shown[207] that the *N*-oxides of quinoline, 3-bromoquinoline, and 6-bromoquinoline may be brominated in a mixture of acetic anhydride and chloroform to yield 3,6-dibromoquinoline *N*-oxide in moderate yield. The brominations are considered to proceed via a similar mechanism (see Scheme 7) to that



SCHEME 7

proposed to explain the nitration of quinoline in acetic anhydride. From the reaction scheme it can be seen that the 3- and 6-bromo-compounds arise by complementary routes and once formed are brominated further as indicated. A similar mechanism has been invoked[208] to explain bromination, at the 6- and 3-positions, respectively, of 2-hydroxy- and 4-hydroxy-quinoline *N*-oxide.

7-Bromoquinoline *N*-oxide with aqueous bromine undergoes polybromination to give 3,4,6,7,8-pentabromo-2-quinolone (**100**).[206]



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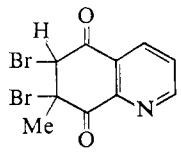

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(*vi*) *Bromination of Quinoline-quinones.* Quinoline-5,8-dione yields an impure dibromide on treatment with bromine in carbon tetrachloride.[209] 7-Methylquinoline-5,8-dione, however, yields the dibromo-adduct (**101**). In contrast, 6-methoxyquinoline-5,8-dione is brominated at the 7-position on treatment with bromine in acetic acid.[210]

These and other details are collected in Table 2.

TABLE 2. Bromoquinolines by Direct Bromination

Bromoquinoline*	Method of preparation (yield)	References
x-Bromo-8-ethoxy-1-ethyl-1,2,3,4-tetrahydro-	8-EtO-1-Et-1,2,3,4-tetraH-Q; $Br_2/CHCl_3$	188
x-Bromo-8-ethoxy-1,2,3,4-tetrahydro-	8-EtO-1,2,3,4-tetraH-Q; $Br_2/CHCl_3$	188
x-Bromo-*x*-sulphonic acid	Q-*x*-SO_2OH; Br_2/AcOH	216
x-Bromo-1,2,3,4-tetrahydro-	1-Ac-1,2,3,4-tetraH-Q; Br_2/AcOH warm; then boil with 20% HCl	187
2-Bromo-	Q/Br_2 at 500 °C; N_2 as diluent (53%)	2
3-BROMO-		
3-Bromo-	(i) Q/Br_2 at 300 °C in heated tube; (ii) 1-CN-Q'ium-BF_4.Br_2 in 60% $HClO_4$ for 3 h at 100 °C (47%) + 3,6-diBr-Q (26%); (iii) Q/S_2Cl_2/C_5H_5N; Br_2 at 95 °C for 1 h (65%)	2, 21, 101
2-Amino-3-bromo-7-methyl-4-quinolone	2-NH_2-7-Me-4-Q'one; Br_2/AcOH reflux (97%)	120
4-Amino-3-bromo-	4-NH_2-Q; $Br_2/CHCl_3$ or Br_2/AcOH	171, 172, 173
4-Amino-3-bromo-*N*-oxide	4-NH_2-Q *N*-oxide; Br_2/AcOH	174
3-Benzyl-3-bromo-1,2,3,4-tetrahydro-2,4-dioxo-	3-$PhCH_2$-4-HO-2-Q'one; Br_2/EtOH (93%)	128
3-Benzyl-3-bromo-1,2,3,4-tetrahydro-2,4-dioxo-1-methyl-	3-$PhCH_2$-4-HO-1-Me-2-Q'one; Br_2/dioxan H_2O at 30 °C for 15 min (85%)	128
3-Bromo-4-(bromomethyl)-2-quinolone	4-$BrCH_2$-2-Q'one; Br_2/AcOH	114
Et 3-bromo-5-chloro-4-quinolone-2-carboxylate	5-Cl-4-Q'one-2-CO_2Et; Br_2/AcOH (92%)	122
3-Bromo-6-chloro-	6-Cl-Q; $Br_2/CCl_4/C_5H_5N$ reflux 1 h (75%)	109
3-Bromo-6-chloro-4-quinolone	6-Cl-4-Q'one; Br_2/AcOH at 95 °C for 10 min	212
3-Bromo-6-chloro-4-methyl-2-quinolone	6-Cl-4-Me-2-Q'one; Br_2/AcOH	114
3-Bromo-7-chloro-1-ethyl-4-quinolone	7-Cl-1-Et-4-Q'one; Br_2/AcOH	211
3-Bromo-7-chloro-4-methyl-2-quinolone	7-Cl-4-Me-2-Q'one; Br_2/AcOH	114
Et 3-bromo-7-chloro-4-quinolone-2-carboxylate	7-Cl-4-Q'one-2-CO_2Et; Br_2/AcOH (94%)	122
3-Bromo-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxo-	1,3-diMe-4-HO-2-Q'one; Br_2 and u.v. light	129
3-Bromo-1,4-dimethyl-2-quinolone	1,4-diMe-2-Q'one; Br_2/H_2O	111

* See footnote to Table 1, p. 340.

TABLE 2 (*cont.*)

Bromoquinoline*	Method of preparation (yield)	References
3-Bromo-4,6-dimethyl-2-quinolone	4,6-diMe-2-Q'one; Br_2/AcOH	114
3-Bromo-1-ethyl-4-quinolone	1-Et-4-Q'one; Br_2/AcOH at 100 °C (68%)	124, 125
3-Bromo-2-(*n*-heptyl)-4-hydroxy- *N*-oxide	2-(*n*-C_7H_{15})-4-HO-Q *N*-oxide; $Br_2/CHCl_3$	123
3-Bromo-4-hydroxy-2-quinolone	4-HO-2-Q'one; Br_2/AcOH or HCO_2H 30 min reflux (90%)	119
3-Bromo-4-hydroxy-*N*-oxide	4-HO-Q *N*-oxide; $Br_2/CHCl_3/Ac_2O$/AcONa reflux 3 h	208
3-Bromo-6-methoxy-8-nitro-4-quinolone	6-MeO-8-NO_2-4-Q'one-3-CO_2Ag; Br_2/AcOH reflux 1 h (50%)	105
3-Bromo-4-methyl-2-quinolone	4-Me-2-Q'one; Br_2/H_2O or Br_2/AcOH	111, 112, 113, 114
3-Bromo-8-methyl-6-nitro-	8-Me-6-NO_2-Q; $Br_2/ClCH_2CO_2H$ reflux 15 min	107
3-Bromo-6-nitro-	(i) 6-NO_2-Q; Br_2/CCl_4 reflux 1 h then boil with C_5H_5N/CCl_4 for 18 h; (ii) 6-NO_2-Q; $Br_2/CCl_4/C_5H_5N$ reflux 2 h	108 109
3-Bromo-8-nitro-	8-NO_2-Q; Br_2/*o*-diClC_6H_4 reflux 1 h (55%)	106
3-Bromo-8-nitro-4-quinolone	8-NO_2-4-Q'one; Br_2/AcOH at room temp. for 12 h (71%)	116
3-Bromo-2-phenyl-4-quinolone	2-Ph-4-Q'one; Br_2/AcOH for 45 min at 70 °C (94%)	213
3-Bromo-1,2,3,4-tetrahydro-4-oxo-2-phenyl-*N*-(*p*-toluene-sulphonamido)-	2-Ph-*N*-(*p*-tosyl)-1,2,3,4-tetraH-4-oxo-Q; $Br_2/CHCl_3$	193, 194
3-Bromo-4-quinolone	4-Q'one; Br_2/AcOH at 100 °C for 12 h (94.7%); or at 70 °C for 10 min (79%)	118, 212
3-Bromo-4-quinolone-2-carboxylic acid	4-Q'one-2-CO_2H; Br_2/AcOH at room temp. for 5 h	121
Et 3-bromo-4-quinolone-2-carboxylate	4-Q'one-2-CO_2Et; Br_2/AcOH (95%)	122
3-Bromo-1,2,3,4-tetrahydro-4-oxo- *N*-(*p*-toluene-sulphonamido)-	*N*-(*p*-tosyl)-1,2,3,4-tetraH-4-oxo-Q; $Br_2/CHCl_3$	193
Et 3-bromo-1,2,3,4-tetrahydro-1,6,7-trimethyl-2-oxo-3-carboxylate	1,6,7-triMe-1,2,3,4-tetraH-2-oxo-Q-3-CO_2Et; $Br_2/CHCl_3$ (23%)	199
3-Bromo-2,6,8-trimethyl-4-quinolone	2,6,8-triMe-4-Q'one; Br_2/AcOH	117
3-Bromo-4,6,8-trimethyl-2-quinolone	4,6,8-triMe-2-Q'one; Br_2/AcOH	114
4-BROMO-		
4-Bromo- *N*-oxide	Q *N*-oxide; $5Br_2/H_2O$ at room temp. in sealed tube (32%)	206
4-Bromo-3-hydroxy-	3-HO-Q; Br_2/AcOH at 70–80 °C (78%)	56
4-Bromo-2-methoxy-	2-MeO-Q; Br_2 vapour	110

TABLE 2 (*cont.*)

Bromoquinoline*	Method of preparation (yield)	References
5-BROMO-		
5-Bromo-	Q/Ag_2SO_4/H_2SO_4/Br_2; isolated as oxalate (51%)	7
6-Acetamido-5-bromo-	6-AcNH-Q; Br_2/AcOH	177
8-Acetamido-5-bromo-	8-AcNH-Q; Br_2/80% AcOH at −15 °C (85–98%)	175, 178
8-Acetamido-5-bromo-6-methoxy-	8-AcNH-6-MeO-Q; Br_2/AcOH (96%)	180
8-Acetoxy-5-bromo-	8-AcO-Q; Br_2/$CHCl_3$/AcONa at room temp. for 5 h (71%)	141
6-Amino-5-bromo-	6-NH_2-Q; Br_2/AcOH	176, 177
5-Bromo-8-(*n*-butylthio)-	8-(*n*-BuS)-Q; Br_2/AcOH at 90 °C for 10 h (59%)	170
5-Bromo-4-chloro-8-hydroxy-2-methyl-3-vinyl-	4-Cl-8-HO-2-Me-3-(CH_2=CH)-Q; Br_2/AcOH	166
5-Bromo-6-chloro-	6-Cl-Q/$AlCl_3$; Br_2 at 100 °C for 1 h (84%)	33
5-Bromo-7-chloro-8-hydroxy-2-methyl-	5-Cl-8-HO-2-Me-Q; Br_2/85% HCO_2H at 0 °C for 3 h; or Br_2/AcOH (78%)	150, 163
5-Bromo-7-(diethylaminomethyl)-8-hydroxy-	7-Et_2NCH_2-8-HO-Q; Br_2/AcOH reflux for 3 h; other 5-Br-7-alkylamino-compounds are also reported	162
5-Bromo-8-(4-diethylamino-1-methylbutylamino)-	8-[$Et_2N(CH_2)_3CH(Me)NH$]-Q; Br_2/AcOH	50
5-Bromo-2,7-dimethyl-8-hydroxy-	2,7-diMe-8-HO-Q; Br_2/AcOH (94%)	163
5-Bromo-8-ethoxy-	8-EtO-Q; Br_2/AcOH	168
5-Bromo-8-(ethylthio)-	8-EtS-Q; Br_2/AcOH at 90 °C for 10 h (59%)	170
5-Bromo-7-formyl-8-hydroxy-	7-CHO-8-HO-Q; Br_2/AcOH at 15 °C for 1 h (74%)	160
5-Bromo-7-formyl-8-hydroxy-2-methyl-	7-CHO-8-HO-2-Me-Q; Br_2/AcOH at 18 °C (70%)	159
5-Bromo-6-hydroxy-	6-HO-Q; Br_2/AcOH; $CHCl_3$; or EtOH	132, 133
5-Bromo-6-hydroxy-7-isopropyl-	6-HO-7-Me_2CH-Q; Br_2/AcOH	134
5-Bromo-6-hydroxy-7-isopropyl-2-methyl-	6-HO-7-Me_2CH-2-Me-Q; Br_2/AcOH	134
5-Bromo-8-hydroxy-	8-HO-Q; Br_2/94% H_2SO_4 at −5 °C (57%)	139
5-Bromo-8-hydroxy-7-carboxylic acid	8-HO-Q-7-CO_2H; Br_2/AcOH	164
5-Bromo-8-hydroxy-2-methyl-4-phenoxy-3-vinyl-	8-HO-2-Me-4-PhO-3-(CH_2=CH)-Q; Br_2/AcOH	166
5-Bromo-8-hydroxy-7-methyl-	8-HO-7-Me-Q; Br_2/AcOH at room temp. for 1 h (72%)	157
5-Bromo-8-hydroxy-7-nitro-	7-NO_2-8-HO-Q; Br_2/AcOH at 50 °C for 1 h (86%)	214
5-Bromo-8-(isobutylthio)-	8-(isoBuS)-Q; Br_2/AcOH at 90 °C for 10 h (49%)	170
5-Bromo-8-(isopropylthio)-	8-(isoPrS)-Q; Br_2/AcOH at 90 °C for 10 h (59%)	170
5-Bromo-8-methoxy-2-methyl-	8-MeO-2-Me-Q; Br_2/AcOH at 15–20 °C for 2.5 h (44%)	169

* See footnote to Table 1, p. 340.

TABLE 2 (*cont.*)

Bromoquinoline*	Method of preparation (yield)	References
5-Bromo-6-methoxy-8-(2-methylpyrrolidinyl)-	8-(2-Me-pyrrolidinyl)-6-MeO-Q; Br_2/AcOH for 15 min at room temp.	179
5-Bromo-6-methoxy-8-nitro-	6-MeO-8-NO_2-Q; $Br_2/CHCl_3/H_2O/CaCO_3$ (85%)	135, 136
5-Bromo-6-methyl-8-nitro-	6-Me-8-NO_2-Q; Br_2/H_2O at 130 °C in a sealed tube	103
5-Bromo-8-(methylthio)-	8-MeS-Q; Br_2/AcOH at 90 °C for 10 h (63%)	170
5-Bromo-8-(*n*-propylthio)-	8-(*n*-PrS)-Q; Br_2/AcOH at 90 °C for 10 h (54%)	170
5-Bromo-8-(*p*-toluenesulphonamido)-	8-(*p*-TsNH)-Q; Br_2/AcOH at −4 °C then 12 h at room temp. (67.6%)	51
6-BROMO-		
3-Acetamido-6-bromo-1,2,3,4-tetrahydro-2-oxo-	3-AcNH-1,2,3,4-tetraH-2-oxo-Q; Br_2/AcOH	196
7-Acetamido-6-bromo-1,2,3,4-tetrahydro-2-oxo-	7-AcNH-1,2,3,4-tetraH-2-oxo-Q; Br_2/AcOH	197
1-Acetyl-4-(*N*-acetylanilino)-6-bromo-1,2,3,4-tetrahydro-2-methyl-	1-Ac-2-Me-4-[Ph(Ac)N]-1,2,3,4-tetraH-Q; $Br_2/CHCl_3$ with cooling	190
1-Benzoyl-4-(*N*-benzoylanilino)-6-bromo-1,2,3,4-tetrahydro-2-methyl-	1-Bz-2-Me-4-[Ph(Bz)N]-1,2,3,4-tetraH-Q; $Br_2/CHCl_3$ at room temp.	191
6-Bromo-4-(bromomethyl)-1,2-dihydro-2,2-dimethyl-	1-Ac- or 1,2-diH-2,2,4-triMe-Q; $2Br_2/CHCl_3$ at 0–10 °C for 4 h	203, 204, 205
6-Bromo-3-chloro-4-hydroxy-2-quinolone	4-HO-2-Q'one; Br_2/dioxan/HCl/H_2O heat 10 min (90%)	128
6-Bromo-1-ethyl-1,2,3,4-tetrahydro-	1-Et-1,2,3,4-tetraH-Q; $Br_2/CHCl_3$; (44%) 1-Me- and 1-isoPr-derivatives also prepared	186
6-Bromo-2-hydroxy-*N*-oxide	2-HO-Q *N*-oxide; $Br_2/CHCl_3/Ac_2O$/AcONa under reflux for 3 h	208
6-Bromo-1,2,3,4-tetrahydro-1-methyl-7-nitro-	1-Me-7-NO_2-1,2,3,4-tetraH-Q; $Br_2/CHCl_3$ (67.7%); other 1-alkyl-7-NO_2 compounds also prepared	186
6-Bromo-1,2,3,4-tetrahydro-2-methyl-	2-Me-1,2,3,4-tetraH-Q; $Br_2/CHCl_3$ for 30 min at 40 °C (67%)	184
6-Bromo-1,2,3,4-tetrahydro-4-oxo-2-phenyl-	2-Ph-1,2,3,4-tetraH-4-oxo-Q; $Br_2/CHCl_3$ (30%)	194
6-Bromo-1,2,3,4-tetrahydro-2-phenethyl-	2-($PhCH_2CH_2$)-1,2,3,4-tetraH-Q; $Br_2/CHCl_3$ for 1 h at 40 °C (71%)	185
6-Bromo-2-quinolone	2-Q'one; Br_2/AcOH (71%)	55
6-Bromo-1,2,3,4-tetrahydro-	1,2,3,4-tetraH-Q; $Br_2/CHCl_3$	182
6-Bromo-1,2,3,4-tetrahydro-8-sulphonic acid	1,2,3,4-tetraH-Q-8-SO_2OH; $Br_2/CHCl_3$	189
6-Bromo-1,2,3,4-tetrahydro-2-oxo-	1,2,3,4-tetraH-2-oxo-Q; Br_2/AcOH	195

TABLE 2 (*cont.*)

Bromoquinoline*	Method of preparation (yield)	References
6-Bromo-1,2,3,4-tetrahydro-2-oxo-4-carboxylic acid	1,2,3,4-tetraH-2-oxo-Q-4-CO_2H; Br_2/AcOH for 8 h at 100 °C	198
7-BROMO-		
7-Bromo-5-chloro-8-hydroxy-	5-Cl-8-HO-Q; Br_2/CCl_4	151
7-Bromo-5-chloro-8-hydroxy-2-methyl-	5-Cl-8-HO-2-Me-Q; Br_2/HCO_2H	83, 84, 150
7-Bromo-8-hydroxy-2,5-dimethyl-	2,5-diMe-8-HO-Q; Br_2/AcOH (78%)	157
7-Bromo-5-formyl-8-hydroxy-	5-CHO-8-HO-Q; Br_2/aq. EtOH cold for 20 min	155
7-Bromo-6-methoxy-5,8-dione	6-MeO-Q-5,8-dione; Br_2/AcOH	210
7-Bromo-8-hydroxy-	8-HO-Q; add to $Br_2/PhCH_3/t$-$BuNH_2$ at −70 °C (92%)	167
7-Bromo-8-hydroxy-5-sulphonic acid	8-HO-Q-5-SO_2OH; Br_2/AcOH	158
7-Bromo-8-hydroxy-5-iodo-	8-HO-5-I-Q; Br_2/EtOH (95%)	69
7-Bromo-8-hydroxy-5-(methoxymethyl)-	8-HO-5-($MeOCH_2$)-Q; Br_2/CCl_4 at room temp. for 1 h; several other 7-Br-5-$ROCH_2$-Q also reported	153, 154
7-Bromo-8-hydroxy-2-methyl-5-nitro-	8-HO-2-Me-5-NO_2-Q; Br_2/KOH at room temp. for 2 h	147
7-Bromo-8-hydroxy-5-methyl-	8-HO-5-Me-Q; Br_2/AcOH at room temp. for 2 h (71.5%)	156
7-Bromo-8-hydroxy-5-nitro-	8-HO-5-NO_2-Q; Br_2/KOH or Br_2/AcOH	147, 148, 149
8-BROMO-		
8-Bromo-	Q/$Ag_2SO_4/H_2SO_4/Br_2$; isolated as picrate (49%)	7
5-Acetamido-8-bromo-	5-AcNH-Q; Br_2/AcOH	175
8-Bromo-5-hydroxy-	5-HO-Q; Br_2/AcOH	130
8-Bromo-7-hydroxy-	7-HO-Q; Br_2/AcOH (86%)	137, 138
DIBROMO-		
x,*x*-Dibromo-6-methyl-	6-Me-Q; Br_2/50% oleum cold, then at 100 °C	98
x,*x*-Dibromo-2-ethyl-3,6-dimethyl-	3,6-diMe-2-Et-Q; Br_2/CS_2	93
x,*x*-Dibromo-4-hydroxy-2-quinolone	4-HO-2-Q'one; Br_2/AcOH or HCO_2H 30 min reflux; separated by fractional crystallization	119
x,*x*-Dibromo-1,2,3,4-tetrahydro-	1,2,3,4-tetraH-Q; ⅔ $Br_2/CHCl_3$ or AcOH	103, 104, 182
3,3-Dibromo-1,2,3,4-tetrahydro-4-oxo-1-(*p*-toluenesulphonamido)-	1-(*p*-tosyl)-1,2,3,4-tetraH-4-oxo-Q; excess of $Br_2/CHCl_3$	193
3,5-Dibromo-	3-Br-Q/Br_2/Ag_2SO_4 conc. H_2SO_4; ppt'd from reaction mixture at pH 3	7

* See footnote to Table 1, p. 340.

TABLE 2 (*cont.*)

Bromoquinoline*	Method of preparation (yield)	References
6-Amino-3,5-dibromo-	6-NH_2-3-Br-Q; Br_2/AcOH or $CHCl_3$ with cooling	177
3,6-Dibromo-	(i) Q/HCl; reflux with $Br_2/CHCl_3$ for 24 h; product ppt'd at pH 2.5; (ii) 6-Br-Q; $Br_2/CCl_4/C_5H_5N$; reflux 45 min (62%); (iii) by-product from reaction (ii) (10%); (iv) 3-Br-Q; Br_2/AcOH reflux; or with Br_2/H_2O at 130–150 °C in a sealed tube; (v) Q/HCl; Br_2 at 120–130 °C in a sealed tube	7 13 21 94 94
3,6-Dibromo *N*-oxide	Q-, or 3-Br-, or 6-Br-Q *N*-oxide; $Br_2/CHCl_3/Ac_2O$/AcONa reflux 3 h	207, 208
3,6-Dibromo-4-(bromomethyl)-1,2-dihydro-2,2-dimethyl-	2,2,4-TriMe-1,2-diH-Q; $3Br_2/CHCl_3$ at 0–10 °C for 4 h (60%)	203, 204
3,6-Dibromo-4-hydroxy-2-quinolone	4-HO-2-Q'one; Br_2/dioxan/HBr (64%)	128
3,6-Dibromo-4-methyl-2-quinolone	6-Br-4-Me-2-Q'one; Br_2/AcOH	114
3,6-Dibromo-4-quinolone	6-Br-4-Q'one; Br_2/AcOH at 95 °C for 10 min	212
3,8-Dibromo-	8-Br-Q; $Br_2/CCl_4/C_5H_5N$ reflux 45 min (70%)	13
5,6-Dibromo-	6-Br-Q/$AlCl_3$; Br_2 at 120 °C for 2 h (80%)	33
6-Acetamido-5,*x*-dibromo-	6-AcNH-5-Br-Q; Br_2/AcOH	177
6-Amino-5,*x*-dibromo-	6-NH_2-5-Br-Q; Br_2/AcOH	177
8-Amino-5,7-dibromo-	8-NH_2-Q; $2Br_2$/AcOH or $CHCl_3$ with cooling; or Br_2/80% AcOH at −15 °C	49, 175
8-Amino-5,7-dibromo-6-chloro-	8-NH_2-6-Cl-Q; Br_2/AcOH at room temp. (79%)	181
8-Amino-5,7-dibromo-6-methoxy-	5- or 7-Br-8-NH_2-6-MeO-Q; Br_2/AcOH reflux 5 min	180
5,7-Dibromo-4-chloro-8-hydroxy-2-methyl-	4-Cl-8-HO-2-Me-Q; $Br_2/CHCl_3$ (100%)	144
5,7-Dibromo-8-hydroxy-	(i) 8-HO-Q; Br_2/EtOH; Br_2/H_2O (90%); or Br_2/2N HCl/KBr (87%); (ii) 5-Br-8-HO-Q; Br_2/AcOH or $CHCl_3$; (iii) 7-Br-8-HO-Q; Br_2/AcOH or $CHCl_3$	69, 71, 132, 142, 152, 215, 131; 165
5,7-Dibromo-8-hydroxy *N*-oxide	8-HO-Q *N*-oxide; Br_2/AcOH (89%)	145
5,7-Dibromo-8-hydroxy-2-methyl-	8-HO-2-Me-Q; Br_2/HCO_2H	83, 84, 150
5,7-Dibromo-8-hydroxy-2-methyl-3-vinyl-	8-HO-2-Me-3-(CH_2=CH)-Q; Br_2/AcOH	166
5,7-Dibromo-8-nitro-	8-NO_2-Q; Br_2/H_2O at 130–135 °C in a sealed tube	103
5,8-Dibromo-	(i) Q/$AlCl_3$ complex at 80 °C; Br_2 for 6 h (86%); (ii) Q/$Ag_2SO_4/H_2SO_4/Br_2$; also with 5-Br- and 8-Br-Q (43%)	9 7
5,8-Dibromo-4-chloro-3-(2-chloroethyl)-8-hydroxy-2-methyl-	5-Br-3-($ClCH_2CH_2$)-4-Cl-8-HO-2-Me-Q; $Br_2/CHCl_3$	166
5,8-Dibromo-4-chloro-8-hydroxy-2-methyl-3-vinyl-	5-Br-4-Cl-8-HO-2-Me-3-(CH_2=CH)-Q; $Br_2/CHCl_3$	166

TABLE 2 (*cont.*)

Bromoquinoline*	Method of preparation (yield)	References
5,8-Dibromo-6-ethyl-	6-Et-Q/$AlCl_3$; Br_2 at 125 °C for 4 h (60%)	33
3-Acetamido-6,8-dibromo-1,2,3,4-tetrahydro-2-oxo-	3-AcNH-1,2,3,4-tetraH-2-oxo-Q; Br_2/AcOH	196
7-Acetamido-6,8-dibromo-1,2,3,4-tetrahydro-2-oxo-	7-AcNH-1,2,3,4-tetraH-2-oxo-Q; $2Br_2$/AcOH	197
4-(*N*-Acetylanilino)-6,8-dibromo-1,2,3,4-tetrahydro-2-methyl	2-Me-4-[Ph(Ac)N]-1,2,3,4-tetraH-Q; $Br_2/CHCl_3$ (65%)	189
5-Amino-6,8-dibromo-	5-NH_2-Q; Br_2/80% AcOH at −15 °C	175
6,8-Dibromo-5-hydroxy-	8-Br-5-HO-Q; Br_2/AcOH	130
6,8-Dibromo-1,2,3,4-tetrahydro-4-oxo-2-phenyl-	Minor product from reaction of 2-Ph-1,2,3,4-tetraH-4-oxo-Q; with $4Br_2/CHCl_3$	194
6,8-Dibromo-1,2,3,4-tetrahydro-2-oxo-	1,2,3,4-tetraH-2-oxo-Q; Br_2/AcOH	195
6,8-Dibromo-1,2,3,4-tetrahydro-2-oxo-4-carboxylic acid	1,2,3,4-tetraH-2-oxo-Q-4-CO_2H; excess of Br_2/AcOH at room temp.	87
POLYBROMO-		
3,4,6,7,8-Pentabromo-2-quinolone	7-Br-Q *N*-oxide; Br_2/H_2O	206
x,x,x,x-Tetrabromo-	1,2,3,4-tetraH-Q; Br_2 vapour	183
x,x,x,x-Tetrabromo-	Q; Br_2/CS_2	92
3,3,6,8-Tetrabromo-1,2,3,4-tetrahydro-2,4-dioxo-	6,8-diBr-4-HO-2-Q'one; Br_2/dioxan at 35 °C for 6 h (89%)	128
3,4,6,8-Tetrabromo-2-quinolone	3-, 4-, or 6-Br-Q *N*-oxide; or 4-Br-2-Q'one; Br_2/H_2O	206
3,4,6,8-Tetrabromo-1,2,3,4-tetrahydro-2,2,4-trimethyl-	2,2,4-triMe-1,2-diH-Q; excess of Br_2/MeOH	202
3,5,6,8-Tetrabromo-	3-Br-Q; (i) reflux with Br_2/AcOH; (ii) Br_2/H_2O at 130–150 °C in a sealed tube	95, 96
3,5,6,8-Tetrabromo-2-quinolone	5-Br-Q *N*-oxide or 5-, 3-, or 6- Br-2-Q'one; Br_2/H_2O	206
5,6,7,8-Tetrabromo-	5-Br-, 8-Br-, or 5,8-diBr-Q/$AlCl_3$ complex at 145 °C; Br_2 for 2 h; reaction residue extracted with 20% HCl	9
3,3,6-Tribromo-1,2,3,4-tetrahydro-2,4-dioxo-	(i) 4-HO-2-Q'one; Br_2/dioxan/H_2O reflux for 10 min (81%); (ii) 3,6-diBr-4-HO-2-Q'one; Br_2/dioxan (88%)	128
3,5,8-Tribromo-	3-Br-Q/Br_2/Ag_2SO_4/conc. H_2SO_4	7
3,6,8-Tribromo-	(i) Q/HCl; reflux with $Br_2/CHCl_3$ for 24 h. Product ppt'd at pH 1; (ii) 1-CN-1,2-diH-2-HO-Q; Br_2/EtOH/Na_2HPO_4 (50%); (iii) 6,8-diBr-Q; $Br_2/CHCl_3$ reflux; (iv) 3-Br-Q.HCl at 120–130 °C in a sealed tube with Br_2/H_2O; (v) 1,2,3,4-tetraH-Q; Br_2 (excess) in $CHCl_3$ or vapour phase	7 7 21 96 94 103, 104, 182, 184

* See footnote to Table 1, p. 340.

TABLE 2 (*cont.*)

Bromoquinoline*	Method of preparation (yield)	References
3,6,8-Tribromo-4-(bromomethyl)-1,2-dihydro-2,2-dimethyl-	1-Ac- or 1,2-diH-2,2,4-triMe-Q; with an excess of Br_2 (68%)	203, 204
3,6,8-Tribromo-1,2,3,4-tetrahydro-2-phenyl-4-oxo-	2-Ph-1,2,3,4-tetraH-4-oxo-Q; $4Br_2/CHCl_3$ (89%)	194
8-Amino-5,6,7-Tribromo-	8-NH_2-6-Br-Q; Br_2/AcOH at room temp. (81%)	181
5,6,8-Tribromo-	(i) 5-Br-, 8-Br-, or 5,8-diBr-Q/$AlCl_3$ complex at 145 °C; Br_2 for 2h (78%); (ii) 6-Br-, or 5,8-diBr-Q/Ag_2SO_4/H_2SO_4 with Br_2 (1 equiv.) for 6 h	9 7
6-Amino-5,8,*x*-tribromo-	6-NH_2-5,8-diBr-Q; Br_2/AcOH	217

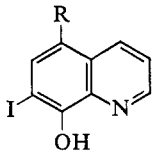
f. IODINATION† (*i*) *Of Quinoline and Alkyl- and Halo-substituted Quinolines.* Early investigations into the direct iodination of quinoline and alkylquinolines led only to the isolation of a series of unidentified mono- and di-iodo-derivatives. For example, Claus and Istel[92] found that quinoline and iodine in carbon disulphide solution give a dark green, unidentified di-iodo-compound, m.p. 90 °C, while La Coste[218] iodinated quinoline and 8-methylquinoline using a solution of iodine in potassium iodide at 160–170 °C in the presence of mercuric oxide. In each case an uncharacterized monoiodo-derivative was obtained. The melting point of the former product (63 °C) suggests (see Table 40, p. 704) that this derivative is in fact 3-iodoquinoline. By analogy, the iodinated 8-methylquinoline is probably the otherwise unreported 3-iodo-8-methylquinoline. Mechanistically these reactions may resemble the sulphonation of pyridine, which with oleum in the presence of mercuric ions yields the 3-sulphonic acid.

Iodination of various quinolines under acid conditions has also been investigated by early workers. 6-Methylquinoline reacts with powdered iodine in well-cooled 50% oleum to yield an uncharacterized di-iodo-6-methylquinoline.[98] Quinoline and 8-methylquinoline behave similarly,[219] although in the former case a tri-iodo-derivative (m.p. 189 °C) is formed. Iodination of quinoline in concentrated sulphuric acid, however, is reported to yield a mixture of 5-iodoquinoline and an unidentified di-iodo-derivative, m.p. 165 °C.[220] More recently Kiamuddin and Haque[221, 222] have shown that quinoline is readily iodinated in concentrated sulphuric acid containing silver sulphate. The reaction is essentially a modification of the Derbyshire and Waters method[5] and is identical with the chlorination and bromination procedures described in Sections II.1.A.d(i) and II.1.A.e(i). From the reaction there is obtained a mixture of 5-iodo-, 8-iodo- and 5,8-di-iodoquinoline, the last of these as the major product. Under the reaction conditions, further iodination of 5-iodo- and 8-iodoquinoline to give 5,8-di-iodoquinoline occurs readily, but attempts to prepare a tri-iodoquinoline from the 5,8-di-iodo-derivative failed. As is observed for chlorination and bromination under similar conditions, iodination fails completely when the sulphuric acid concentration falls below 80%, and when sulphuric acid is replaced by acetic, nitric, or hydrochloric acid. A comparison of melting points suggests that the unknown di-iodo-compound, m.p. 165 °C, obtained by Istrati[220] (see above) is in fact 5,8-di-iodoquinoline.

† See also Addenda, p. 675.

(ii) Iodination of Hydroxyquinolines and Quinolones. Other iodination studies on quinolines are confined mainly to 8-hydroxyquinoline and its 5- and 7-substituted derivatives.

8-Hydroxyquinoline reacts with iodine in boiling ethanol to yield the 5-iodo-derivative,[69, 223, 224] whereas when a solution of 8-hydroxyquinoline is allowed to stand with an aqueous ethanolic solution of iodine in potassium iodide at room temperature for 48 days, 8-hydroxy-5,7-di-iodoquinoline (**102**; R = I) is obtained.[224] A Russian paper claims that this di-iodo-compound is obtainable in 92.6% yield by treating 8-hydroxyquinoline with ethanolic iodine in the presence of sulphuric acid and potassium iodate.[225]



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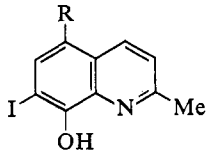

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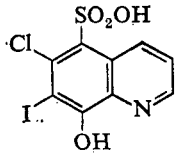
Attempts to monoiodinate 8-hydroxyquinoline with iodine in potassium iodide have been unsuccessful. Even at 0 °C, 8-hydroxy-5,7-di-iodoquinoline can be detected in the reaction products.[226] 8-Hydroxyquinoline *N*-oxide, however, yields what is thought to be the 5-iodo-derivative when treated with an alkaline solution of iodine in potassium iodide at room temperature.[147] Iodination of the 8-hydroxyquinoline–copper(II) chelate with iodine is complicated by the accompanying reduction of cupric to cuprous ion and the release of free 8-hydroxyquinoline.[81]

5-Chloro-8-hydroxy-7-iodoquinoline has been prepared by treating 5-chloro-8-hydroxyquinoline with iodine in aqueous potassium iodide[227, 228] or with iodine in aqueous sodium hydroxide[229] or in acetic acid.[76] 8-Hydroxy-2-methylquinoline is reported[70] to yield the 5-chloro-7-iodo-derivative (**103**; R = Cl) on treatment with iodine in boiling hydrochloric acid. 5-Fluoro-8-hydroxy-7-iodoquinoline (**102**; R = F) results from the treatment of 5-fluoro-8-hydroxyquinoline with iodine in aqueous sodium hydroxide at 100 °C,[230] and the 5-bromo-analogue (**102**; R = Br) is readily prepared from 5-bromo-8-hydroxyquinoline and iodine in aqueous-ethanolic potassium iodide.[155] 5-Formyl-,[155] 5-nitro-,[226] and 5-acetyl-8-hydroxyquinoline[231] under the latter conditions yield the 7-iodo-derivatives (**102**; R = CHO, NO_2, and Ac, respectively). Iodo-compound (**103**; R = NO_2) can be prepared by treating 8-hydroxy-5-nitroquinaldine with iodine in potassium hydroxide solution.[147]

Iodine in ethanol has proved to be successful for the monoiodination of both 7-formyl-[159] and 7-(*o*-carboxybenzoyl)-8-hydroxyquinoline[143] at the 5-position. A variety of 8-hydroxy-7-iodoquinolines bearing a carbonyl function (e.g. benzoyl, ethoxycarbonyl, etc.) at the 5-position have been prepared[231] by treating the corresponding 8-hydroxyquinolines with iodine in either methanol or aqueous sodium hydroxide. Iodination of 6-chloro-8-hydroxyquinoline-5-sulphonic acid in dilute ammonia solution yields the 7-iodo-derivative (**104**).[232] 8-Hydroxy-7-iodo-5-methylquinoline (**102**; R = Me), prepared by iodination of 8-hydroxy-5-methylquinoline in boiling acetic acid, is reported[152] to possess antiseptic properties.

Iodination of 7-chloro-8-hydroxyquinoline with iodine in 95% methanol yields the 5-iodo-derivative (**105**) (98%).[214] The observed melting point (205 °C) of the chloro-iodo-derivative is significantly different from that reported (148 °C) for this compound by Ghosh and his co-workers[74] who prepared it by chlorinating 8-hydroxy-5-iodoquinoline. However, gas-chromatographic analysis of the trimethylsilyl

derivative indicates[214] that the product melting at 148 °C is in fact a complex mixture containing the 7-chloro-, 5-iodo-, 5,7-dichloro-, and 5,7-di-iodo-derivatives of 8-hydroxyquinoline.



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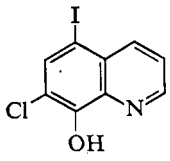

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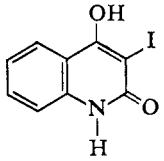

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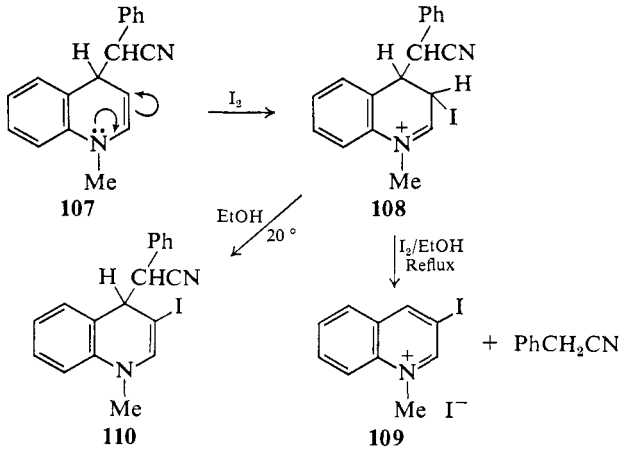
4-Hydroxy-2-quinolone reacts with iodine in dioxan solution in the presence of sodium carbonate to give 4-hydroxy-3-iodo-2-quinolone (**106**) in high yield (92%).[128]

Attempts[233] to aromatize the 1,4-dihydroquinoline (**107**) using iodine and potassium acetate in boiling ethanol led to the formation of a mixture of two methiodides, one of which was shown to be the expected 1-methylquinolinium iodide; the other, however, proved to be 3-iodoquinoline methiodide (**109**) which is thought to be formed via iodination of (**107**) at the 3-position giving the 3,4-dihydro-compound



SCHEME 8

(**108**), which undergoes elimination of benzyl cyanide to give the 3-iodo-compound (**109**) as indicated in Scheme 8. If the reaction is carried out under more mild conditions (iodine in ethanol at 20 °C), then intermediate (**110**) can be isolated.

3-Hydroxyquinoline reacts at 20 °C in 10% sodium hydroxide solution, with iodine and potassium iodide to give 3-hydroxy-4-iodoquinoline in 88% yield.[56]

These and further details are collected in Table 3.

*B. Indirect Halogenation**

a. INTRODUCTION. In this Section are considered methods of introducing halogen onto the quinoline nucleus which do not involve the use of elemental halogen. Several methods are available and some are of great value for the synthesis of haloquinolines.

* See also Addenda, p. 676.

TABLE 3. Iodoquinolines by Direct Iodination

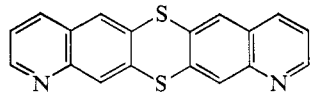
Iodoquinoline*	Method of preparation (yield)	References
x-Iodo-	Q; I_2/KI/HgO at 160–170 °C; or I_2/HIO_3/KI at 240 °C	218
3-IODO-		
4-(α-Cyanobenzyl)-1,4-dihydro-3-iodo-1-methyl-	4-[PhCH(CN)]-1-Me-1,4-diH-Q; I_2/AcOK/EtOH at 20 °C	233
3-Iodo-1-methylquinolinium iodide	From above reaction when carried out at 80 °C for 2 h (27%)	233
4-Hydroxy-3-iodo-2-quinolone	4-HO-2-Q'one; I_2/Na_2CO_3/dioxan at 5 °C (92%)	128
4-IODO-		
3-Hydroxy-4-iodo-	3-HO-Q; I_2/KI/10% aq. NaOH at 20 °C (88%)	56
5-IODO-		
5-Iodo-	Q; I_2/H_2SO_4; or I_2/H_2SO_4/Ag_2SO_4 at 150–200 °C for 1 h	220–222
7-(*o*-Carboxybenzoyl)-8-hydroxy-5-iodo-	7-(*o*-$HO_2CC_6H_4CO$)-8-HO-Q; I_2/HCl/EtOH	143
7-Chloro-8-hydroxy-5-iodo-	7-Cl-8-HO-Q; I_2/H_2O/MeOH reflux 15 min (98%)	214
7-Formyl-8-hydroxy-5-iodo-	7-OHC-8-HO-Q; I_2/EtOH (61%)	159
8-Hydroxy-5-iodo-	8-HO-Q; I_2/EtOH under reflux	69, 223, 224, 226
8-Hydroxy-5-iodo-*N*-oxide	8-HO-Q *N*-oxide; I_2/KI/0.2% aq. NaOH for 24 h at room temp.	147
7-IODO-		
5-Acetyl-8-hydroxy-7-iodo-	5-Ac-8-HO-Q; I_2/KI/AcONa/MeOH at 10 °C for 0.5 h (90%)	231
5-Benzoyl-8-hydroxy-7-iodo-	5-Bz-8-HO-Q; I_2/KI/AcONa/MeOH at 10 °C for 0.5 h (90%)	231
5-Bromo-8-hydroxy-7-iodo-	5-Br-8-HO-Q; I_2/EtOH/KI for 15 min at room temp.	155
5-Chloro-8-hydroxy-7-iodo-	5-Cl-8-HO-Q; (i) I_2/KI; (ii) I_2/NaOH (94%); (iii) I_2/AcOH (64%)	76, 227–229
5-Chloro-8-hydroxy-7-iodo-2-methyl-	5-Cl-8-HO-2-Me-Q; I_2/HCl under reflux	70
6-Chloro-8-hydroxy-7-iodo-5-sulphonic acid	6-Cl-8-HO-Q-5-SO_2OH; I_2/6% NH_4OH stir for 6 h	232
5-(Chloroacetyl)-8-hydroxy-7-iodo-	5-($ClCH_2CO$)-8-HO-Q; I_2/MeOH/AcOH/KI at 10 °C for 0.5 h (95%)	231
Et 8-Hydroxy-7-iodo-5-carboxylate	8-HO-Q-5-CO_2Et; as above (98%)	231
5-Fluoro-8-hydroxy-7-iodo-	5-F-8-HO-Q; I_2/NaOH for 5 h at 100 °C, then 12 h at room temp. (46%)	230
5-Formyl-8-hydroxy-7-iodo-	5-OHC-8-HO-Q; I_2/KI/H_2O/EtOH for 50 min cold	155

* See footnote to Table 1, p. 340.

TABLE 3 (*cont.*)

Iodoquinoline*	Method of preparation (yield)	References
8-Hydroxy-7-iodo-5-carboxylic acid	8-HO-Q-5-CO_2H; I_2/NaOH at 15 °C for 0.5 h (70%)	231
8-Hydroxy-7-iodo-5-methyl-	8-HO-5-Me-Q; I_2/AcOH under reflux	152
8-Hydroxy-7-iodo-2-methyl-5-nitro-	2-Me-5-NO_2-8-HO-Q; I_2/KOH at room temp. for 2 h	147
8-Hydroxy-7-iodo-5-nitro-	8-HO-5-NO_2-Q; I_2/KI for 1 h at room temp.	226
8-Hydroxy-7-iodo-5-(2,2,2-trichloro-1-hydroxyethyl)-	5-[$CCl_3CH(OH)$]-8-HO-Q; I_2/MeOH/AcONa at 10 °C for 1 h, then overnight (96%)	231
8-IODO-		
8-Iodo-	Q; I_2/H_2SO_4; or $I_2/H_2SO_4/Ag_2SO_4$ at 150–200 °C for 1 h	221, 222
DI- & TRI-IODO-		
x,*x*-Di-iodo-	Q; I_2/CS_2	92
x,*x*-Di-iodo-6-methyl-	6-Me-Q; I_2/50% oleum at 100 °C for 5–6 h	98
x,*x*-Di-iodo-8-methyl-	8-Me-Q; I_2/50% oleum as above	219
8-Hydroxy-5,7-di-iodo-	8-HO-Q; I_2/KI/aq. EtOH for 48 days at room temp.; or I_2/EtOH/H_2SO_4/KIO_3 (92.6%)	225
5,8-Di-iodo-	Q; 5-I-Q; or 8-I-Q with an excess of $I_2/H_2SO_4/Ag_2SO_4$ at 150–200 °C	222
x,*x*,*x*-Tri-iodo-	Q.H_2SO_4; I_2/50% oleum at 100 °C for 5–6 h	219

b. CHLORINATION. (*i*) *By Sulphur Chlorides.* The use of sulphur and chlorine or sulphur chlorides to effect the chlorination of quinolines was investigated by early researchers, particularly Edinger and his co-workers. They found[234, 235] that 6-hydroxyquinoline with disulphur dichloride (S_2Cl_2) or sulphur dichloride (SCl_2) gives an unidentified monochloro-6-hydroxyquinoline, whereas 8-hydroxyquinoline yields the 5,7-dichloro-derivative. Quinoline itself reacts with sulphur dichloride at 160 °C to give a mixture of 3-chloroquinoline (ca. 20%), an uncharacterized trichloroquinoline, m.p. 186 °C (ca. 10%), and a compound of molecular formula $C_{18}H_{10}N_2S_2$ (40%).[236, 237] On the basis of oxidative experiments the C_{18} product was assigned structure (**111**). A similar result is obtained by using disulphur dichloride. 8-Methylquinoline reacts with sulphur dichloride in a more complicated manner in that



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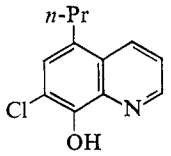
elimination of the methyl group is observed;[235, 238] the products isolated from the reaction are in fact 6,8-dichloroquinoline, an unidentified tetrachloroquinoline, m.p. 121 °C, and a compound of molecular formula $C_{18}H_{10}N_2S_2$ (m.p. > 360 °C), which is isomeric with the sulphur heterocycle (**111**) isolated previously.[235] In one

experiment a low-melting (30–40 °C) monochloroquinoline was also isolated but in low yield.

The reaction between 6-methylquinoline and sulphur dichloride is somewhat less confusing in that at 120 °C a mixture of unidentified di- and tri-chloro-6-methylquinolines is obtained.[98]

More recently sulphur chlorides have been used to bring about chlorination, at the 3-position, of particularly, quinolines bearing electron-withdrawing groups. For example, 6-nitro-[239] and 8-nitro-quinoline[240] give good yields of the corresponding 3-chloro-derivatives on treatment with sulphur dichloride.

Sulphuryl chloride (SO_2Cl_2) has also found use as a chlorinating agent and its action on quinoline *N*-oxide to give 4-chloroquinoline was one of the first reactions of quinoline *N*-oxide to be reported.[241] 8-Hydroxyquinoline reacts with sulphuryl chloride at 5 °C,[76] or in hydrochloric acid solution,[242] to give 5-chloro-8-hydroxyquinoline; in chloroform solution, however, a mixture of 5-chloro- and 5,7-dichloro-8-hydroxyquinoline results.[68] Similarly 8-hydroxyquinoline *N*-oxide reacts with sulphuryl chloride in chloroform solution at low temperature (< 5 °C) to give a mixture of 5-chloro- and 5,7-dichloro-8-hydroxyquinoline *N*-oxide, the latter as major product (80%).[145] 7-Chloro-8-hydroxy-5-(*n*-propyl)quinoline (**112**) results from the treatment of 8-hydroxy-5-(*n*-propyl)quinoline with sulphuryl chloride in acetic acid.[243]



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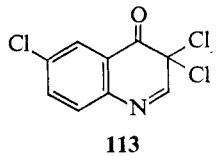

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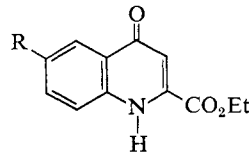

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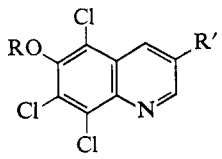
Treatment of 4-quinolone with sulphuryl chloride in an acetic acid/acetic anhydride mixture leads to formation of a trichloro-derivative thought to be the 3,3,6-trichloro-compound (**113**).[212] 6-Chloro- and 6-bromo-4-quinolone under the same conditions, however, react normally to give the corresponding 3-chloro-derivatives,[212] as does 6,8-dichloro-4-quinolone.[45] The 4-quinolone-2-carboxylic esters (**114**; R = H, F, or Cl) behave similarly.[45, 122, 244]

6-Methoxy-8-nitroquinoline undergoes a complicated reaction when heated under reflux with a large excess of sulphuryl chloride.[245] Five products are obtained, of which three have been definitely characterized, namely: 3,5,7,8-tetrachloro-6-methoxyquinoline (**115**; R = Me, R′ = Cl), 5,7,8-trichloro-6-hydroxyquinoline (**115**; R = R′ = H), and 5,7,8-trichloro-6-methoxyquinoline (**115**; R = Me, R′ = H). A fourth compound has been tentatively assigned the structure 3,5- or 3,7-dichloro-6-methoxy-8-nitroquinoline, while the remaining product—a trichloro-6-methoxy-8-nitroquinoline—remains uncharacterized.



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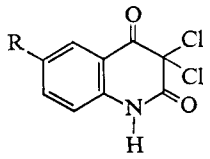

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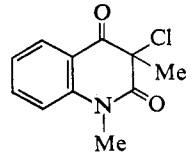

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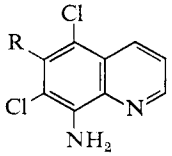
Sulphuryl chloride in hot dioxan solution converts 4-hydroxy-2-quinolone and its 6-fluoro- and 6-chloro-derivatives quantitatively into the 3,3-dichloro-compounds (**116**; R = H, F, and Cl, respectively).[57, 246] Other substituted 4-hydroxy-2-quinolones were shown later to behave similarly.[247, 248]

4-Hydroxy-1,3-dimethyl-2-quinolone is monochlorinated by sulphuryl chloride in boiling benzene at the 3-position to give the quinoline-2,4-dione (**117**).[129]

8-Amino-6-bromo- and 8-amino-6-chloro-quinoline react readily with sulphuryl chloride in acetic acid to give 8-amino-6-bromo-5,7-dichloro- and 8-amino-5,6,7-trichloro-quinoline (**118**; R = Br and R = Cl, respectively).[181]

1,2,3,4-Tetrahydro-2-oxoquinoline with sulphuryl chloride yields an unidentified monochloro-derivative;[249] 1-acetyl-1,2,3,4-tetrahydroquinoline, however, with sulphuryl chloride in carbon tetrachloride solution yields 1-acetyl-6-chloro-1,2,3,4-tetrahydroquinoline.[250]

1-Acetyl-1,2-dihydro-2,2,4-trimethylquinoline reacts with a two-molar excess of sulphuryl chloride to give what is thought, by analogy with the bromination studies discussed in Section II.1.A.e(iv), to be 6-chloro-4-(chloromethyl)-1,2-dihydro-2,2-dimethylquinoline (**119**) as the hydrochloride.[204]



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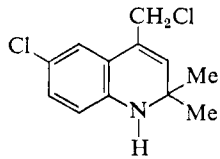

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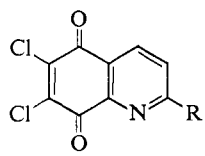

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The use of a large excess of sulphuryl chloride results in the formation of two crystalline products of molecular formula $C_{12}H_9Cl_8N$ and $C_{12}H_9Cl_{10}N$, which the authors consider to be a hexachloroquinoline dichloride and a hexachloroquinoline tetrachloride, respectively.

(*ii*) *Chlorination by Chlorates.* Alkali-metal chlorates in acid solution have enjoyed some success as chlorinating agents although they appear to have no special advantage over the chlorinating systems considered above.

4-Hydroxy-2-quinolone reacts[251] with potassium chlorate and hydrochloric acid to yield the previously reported[57] 3,3-dichloro-derivative (**116**; R = H). Friedländer and Weinberg[110] found that 2-quinolone with potassium chlorate in a mixture of hot acetic and hydrochloric acid yields an unidentified dichloro-derivative. Using a slightly modified procedure later workers[252] obtained an uncharacterized trichloro- rather than a dichloro-2-quinolone, and a similar result is obtained if the modified procedure is applied to 7-methoxy-2-quinolone.[253] Jaffé[254] found that 4-quinolone-2-carboxylic acid with sodium chlorate and hydrochloric acid gives an unidentified tetrachloro-compound.

Simultaneous oxidation and chlorination have been observed when using sodium chlorate in hot (60 °C) concentrated hydrochloric acid solution as a chlorinating agent. For example, under these conditions 5-amino-8-hydroxyquinoline yields 6,7-dichloroquinoline-5,8-dione (**120**; R = H).[255, 256] Similarly 5,8-diamino-2-methylquinoline yields the dichlorodione (**120**; R = Me).[257]

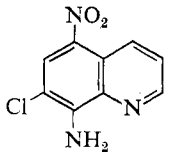
On the other hand, 8-amino-5-nitroquinoline under similar conditions reacts normally to give the 7-chloro-derivative (**121**),[258] whereas, its 1-acetyl derivative fails to chlorinate.

(*iii*) *Chlorination by Hypochlorites.* Späth[259] records that 6,8-dimethylquinoline with hot calcium hypochlorite solution gives an unidentified monochloro-6,8-

dimethylquinoline, m.p. 42 °C. The product is possibly 5-chloro-6,8-dimethylquinoline, which has m.p. 44 °C (see Table 42, p. 710). More recently 8-hydroxy-5-nitroquinoline has been reported[260, 261] to yield 7-chloro-8-hydroxy-5-nitroquinoline on treatment with alkaline sodium hypochlorite solution.

tert-Butyl hypochlorite in carbon tetrachloride has been employed by Fiedler[157] as a halogenating agent. The reagent smoothly converts 5-formyl-8-hydroxy-2-methylquinoline and 8-hydroxy-7-methylquinoline into the 7- and 5-chloro-derivative, respectively.

(*iv*) *Chlorination by Hydrochloric Acid and Hydrogen Peroxide.* Mixtures of hydrogen peroxide and hydrochloric acid have been used occasionally to effect chlorination of quinolines bearing electron-donating substituents. For example, 4-hydroxy-2-quinolone yields the previously mentioned 3,3-dichloro-compound (**116**; R = H).[57, 262] The optimum yield (91%) appears to be achieved in dioxan solution, while in ethanol only a 58% yield of the dichloro-compound is realized. 6-Substituted 4-hydroxy-2-quinolones behave similarly, while 3-substituted 4-hydroxy-2-quinolones are monochlorinated at the 3-position.[57] For example, 4-hydroxy-3-nitro-2-quinolone in dioxan-concentrated hydrochloric acid solution yields, on treatment with 30% hydrogen peroxide, the chloronitroquinolinedione



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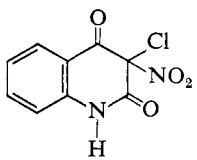

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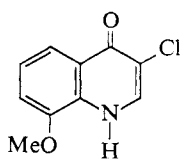

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(**122**).[263] 8-Hydroxyquinoline *N*-oxide yields 5,7-dichloro-8-hydroxyquinoline *N*-oxide when treated with concentrated hydrochloric acid–hydrogen peroxide mixture.[264]

An attempt[58] to prepare the *N*-oxide of 4-chloro-8-methoxyquinoline by using a mixture of hydrogen peroxide and acetic acid failed. The product obtained was in fact 3-chloro-8-methoxy-4-quinolone (**123**). Formation of this chloro-4-quinolone is explained on the basis of an acetic acid-induced hydrolysis of the initially formed 4-chloro-compound, giving the 4-quinolone, which is then chlorinated by chlorine formed *in situ* by the action of hydrogen peroxide on the hydrochloric acid liberated in the hydrolysis stage.

3-Hydroxyquinoline is chlorinated at the 4-position in 66% yield with a mixture of 15% hydrogen peroxide and concentrated hydrochloric acid at 70 °C.[56]

(*v*) *Chlorination during Metal–Hydrochloric Acid Reductions.* Chlorination as a side reaction during the metal–hydrochloric acid reduction of nitro-compounds is a well known feature of organic chemistry and several examples are recorded for the quinoline series. For example, Lippmann and Fleissner during their studies[265, 266] on 8-hydroxyquinolines showed that the 5-nitroso-compound, formed by nitrosating 8-hydroxyquinoline, can be reduced using tin and hydrochloric acid to give an unidentified 5-amino-*x*,*x*-dichloro-8-hydroxyquinoline.[265]

In some cases the presence of chlorine in the final product has caused confusion regarding the identity of the resulting haloquinoline. For example, Dikshoorn[267] reports that reduction of 8-nitroquinoline with stannous chloride and hydrochloric acid yields a mixture of 8-aminoquinoline, 8-amino-3-chloroquinoline (not confirmed), and a second chloro-amine that, on the basis of an earlier report,[268] is assigned the structure 8-amino-5-chloroquinoline. However, it has since been

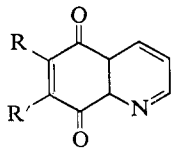
shown[116, 269] that the products are in fact 8-amino-5- and -7-chloroquinoline, respectively. Reduction of 5-chloro-8-nitroquinoline with stannous chloride and hydrochloric acid is accompanied by nuclear halogenation and 8-amino-5,7-dichloroquinoline is formed together with the monochloroamine.[269] Reduction of the nitro-compound with iron and acetic acid, however, gives the expected 8-amino-5-chloroquinoline in 79.4% yield. Noelting and Trautmann[270] report that 6-methyl-8-nitroquinoline is reduced by tin and dilute hydrochloric acid to 8-amino-5-chloro-6-methylquinoline.

(*vi*) *Chlorination by Phosphorus Pentachloride.* A report has appeared[90] that indicates 6-methoxyquinoline to react on heating with phosphorus pentachloride to give 5-chloro-6-methoxyquinoline in 62% yield. Also 2,3,4,5,6,7,8-heptachloroquinoline can be obtained in good yield (78%) by heating a mixture of penta- and tetrachloroquinolines with phosphorus pentachloride in an autoclave at around 300 °C for 5 hours.[35, 36] Other instances of chlorination with phosphorus pentachloride have also appeared[165, 271] but in each of these cases chlorination appears to be accidental rather than planned. Nuclear chlorination has been observed on several occasions during the conversion of quinolones into chloroquinolines by phosphorus chlorides. These reactions are discussed in Section II.1.D.b(i) and (ii).

(*vii*) *Miscellaneous.* An uncharacterized monochloro-2-methylquinoline, m.p. 94.5 °C, has been obtained by heating the zinc chloride double salt of 2-methylquinoline;[272] the product could well be 6-chloro-2-methylquinoline, m.p. 96 °C (see Table 41, p. 707).

Various chloroquinoline-quinones have been prepared by treating the appropriate quinone with either hydrogen chloride or hydrochloric acid. For instance, quinoline-5,8-dione (**124**; R = R′ = H) reacts with boiling concentrated hydrochloric acid to give 6- or 7-chloroquinoline-5,8-dione, m.p. 164 °C, whereas with hydrogen chloride in carbon tetrachloride solution the 6,7-dichloro-compound (**124**; R = R′ = Cl) is readily obtained.[209]

7-Methylquinoline-5,8-dione under the former conditions yields the 6-chloro-derivative (**124**; R = Cl, R′ = Me). Pratt and Drake[260] have shown subsequently that the chloroquinoline-5,8-dione (m.p. 164 °C), mentioned above, is in fact the 6-chloro-compound (**124**; R = Cl, R′ = H).



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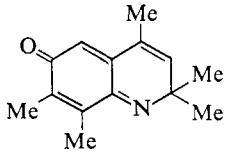

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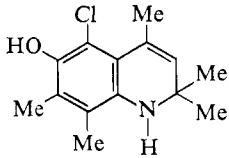

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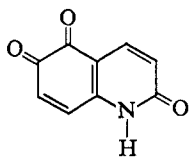
The pentamethylquinolin-6-one (**125**) reacts with ethereal hydrogen chloride over 24 h at 5 °C to give the 5-chloro-6-hydroxyquinoline (**126**) in 87% yield.[273]

Quinoline-2,5,6-trione (**127**) in chloroform solution adds hydrogen chloride, and when the product is boiled with aqueous acetic acid the chlorodihydroxy-2-quinolone (**128**) is obtained.[274] Under similar conditions the trione (**129**) yields 3-(*n*-butyl)-4,8-dichloro-5,6-dihydroxy-2-quinolone.

Urbanski[275] has shown that the *N*-sulphonylhydroxylamine (**130**) is converted into 6,7-dichloro-5,8-dihydroxyquinoline (**131**) when boiled with concentrated hydrochloric acid. Reaction is thought to proceed via hydrolysis of the hydroxylamine to give 5,8-dihydroxyquinoline and hydroxylamine-*N*-sulphonic acid ($HOSO_2NHOH$),



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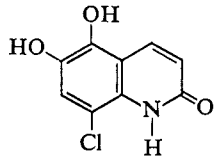

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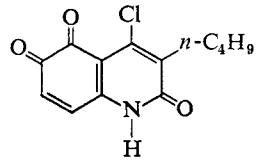

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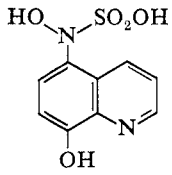
which reacts further with concentrated hydrochloric acid to give ammonia, sulphuric acid, and chlorine. The chlorine produced is thought then to chlorinate the dihydroxyquinoline to give dichloro-compound (**131**).



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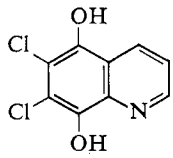

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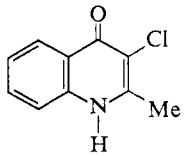

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A patent[276] describes the preparation of 3-chloro-2-methyl-4-quinolone (**132**) by heating 2-methyl-4-quinolone with *N*-chlorosuccinimide in acetic acid at 55–60 °C for 1 hour. *N*-Chlorosuccinimide has also been used to effect the chlorination of both 8-hydroxyquinoline[277] and its copper(II) chelate.[278] In the former case little reaction is observed at ambient temperature, whereas at 40–60 °C a slow reaction to give 5-chloro- (6%), 7-chloro- (17%), and 5,7-dichloro-8-hydroxy-quinoline (trace) takes place. In contrast, the copper(II) chelate reacts[81, 279] rapidly at room temperature to give these products in yields of 33, 52, and 11%, respectively.

These and further details are collected in Table 4.

TABLE 4. Chloroquinolines by Indirect Chlorination

Chloroquinoline*	Method of preparation (yield)	References
x-Chloro-2-methyl-	Heat 2-Me-Q.$ZnCl_2$	272
x-Chloro-6-hydroxy-	6-HO-Q; heat with either SCl_2 or S_2Cl_2	234, 235
x-Chloro-6,8-dimethyl-	6,8-diMe-Q; $Ca(OCl)_2$ at 100 °C	259
x-Chloro-1,2,3,4-tetrahydro-2-oxo-quinoline	1,2,3,4-tetraH-2-oxo-Q; SO_2Cl_2	249
3-CHLORO-		
3-Chloro-	Q; SCl_2 at 160 °C or with S_2Cl_2 (20%)	236, 237
Et 3-chloro-4-quinolone-2-carboxylate	4-Q'one-2-CO_2Et; SO_2Cl_2/AcOH	122
3-Benzyl-3-chloro-1,2,3,4-tetrahydro-2,4-dioxo-	3-$PhCH_2$-4-HO-2-Q'one; SO_2Cl_2/dioxan (96%); 1-Me derivative behaves similarly	57
6-Bromo-3-chloro-4-quinolone	6-Br-4-Q'one; SO_2Cl_2/AcOH/Ac_2O at 100 °C for 30 min	212

* See footnote to Table 1, p. 340.

TABLE 4 (*cont.*)

Chloroquinoline*	Method of preparation (yield)	References
3-Chloro-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxo-	1,3-diMe-4-HO-2-Q'one; SO_2Cl_2/C_6H_6 under reflux for 1.5 h	129
Et 3-chloro-6-fluoro-4-quinolone-2-carboxylate	6-F-4-Q'one-2-CO_2Et; SO_2Cl_2/AcOH/Ac_2O	244
3-Chloro-2-methyl-4-quinolone	2-Me-4-Q'one; N-Cl-succinimide/AcOH at 55–60 °C for 1 h (90%)	276
3-Chloro-1,2,3,4-tetrahydro-3-nitro-2,4-dioxo-	4-HO-3-NO_2-2-Q'one; HCl/dioxan/30% H_2O_2 (34%)	263
3-Chloro-6-nitro-	6-NO_2-Q; SCl_2 heat 4 h at 100 °C in sealed tube	239
3-Chloro-8-nitro-	8-NO_2-Q; S_2Cl_2/Cl_2 for 1 h then reflux for 3 h	240
4-CHLORO-		
4-Chloro-	Q *N*-oxide; heat with SO_2Cl_2	241
4-Chloro-3-hydroxy-	3-HO-Q; HCl/15% H_2O_2 at 60–70 °C for 1 h (66%)	56
5-CHLORO-		
5-Chloro-8-hydroxy-	8-HO-Q; SO_2Cl_2/HCl or $SO_2Cl_2/CHCl_3$	68, 76, 242
5-Chloro-8-hydroxy-7-methyl-	8-HO-7-Me-Q; *t*-BuOCl/CCl_4 at 80 °C for 1 h (66%)	157
5-Chloro-8-hydroxy-7-nitro-	7-NO_2-8-HO-Q; KOH/MeOH/NaOCl at 70 °C for 1 h (84%)	214
5-Chloro-6-methoxy-	6-MeO-Q; heat 10 min with PCl_5 (62%)	90
6-CHLORO-		
1-Acetyl-6-chloro-1,2,3,4-tetrahydro-	1-Ac-1,2,3,4-tetraH-Q; SO_2Cl_2/CCl_4	250
6-Chloro-4-(chloromethyl)-1,2-dihydro-2,2-dimethyl-	1-Ac-1,2-diH-2,2,4-triMe-Q; CCl_4/SO_2Cl_2 at 25 °C for 2 h	204
7-CHLORO-		
8-Amino-7-chloro-5-nitro-	8-NH_2-5-NO_2-Q; HCl/$KClO_3$	258
7-Chloro-5-formyl-8-hydroxy-2-methyl-	5-CHO-8-HO-2-Me-Q; *t*-BuOCl/CCl_4 heat 15 min (68%)	157
7-Chloro-8-hydroxy-5-sulphonic acid	8-HO-Q-5-SO_2OH; gently heat with PCl_5	165
7-Chloro-8-hydroxy-5-nitro-	8-HO-5-NO_2-Q; NaOCl/NaOH at 30 °C for 1 h	260, 261
7-Chloro-8-hydroxy-5-(*n*-propyl)-	8-HO-5-(*n*-C_3H_7)-Q; AcOH/SO_2Cl_2 reflux 1 h	243
DICHLORO-		
x,*x*-Dichloro-6-methyl-	6-Me-Q; SCl_2 at 120 °C	98
x,*x*-Dichloro-2-quinolone	2-Q'one; HCl/AcOH/$KClO_3$	110
3,3-Dichloro-1,2,3,4-tetrahydro-2,4-dioxo-	4-HO-2-Q'one; (i) SO_2Cl_2/dioxan boil for few min (90%); (ii) HCl/$KClO_3$; (iii) H_2O_2/HCl/AcOH (70%)	57, 246, 251, 262

TABLE 4 (*cont.*)

Chloroquinoline*	Method of preparation (yield)	References
3,3-Dichloro-1,2,3,4-tetrahydro-1-methyl-2,4-dioxo-	1-Me-4-HO-2-Q'one; SO_2Cl_2/dioxan or HCl/$KClO_3$ (96%)	246, 248, 251
3,3-Dichloro-1,2,3,4-tetrahydro-2,4-dioxo-1-phenyl-	1-Ph-4-HO-2-Q'one; SO_2Cl_2/dioxan or HCl/$KClO_3$	246, 251
Et 3,5-dichloro-4-quinolone-2-carboxylate	5-Cl-4-Q'one-2-CO_2Et; as above; also with 6-Cl and 7-Cl derivatives	45, 122
3,5- or 3,7-Dichloro-6-methoxy-8-nitro-	6-MeO-8-NO_2-Q; SO_2Cl_2 reflux for 15 min	245
3,6-Dichloro-	6-Cl-Q; S_2Cl_2 for 2 h at 160 °C (33%)	55
3,6-Dichloro-4-quinolone	6-Cl-4-Q'one; SO_2Cl_2/AcOH/Ac_2O at 65 °C for 30 min	212
3-(*n*-Butyl)-4,8-dichloro-5,6-dihydroxy-2-quinolone	4-Cl-3-(*n*-Bu)-2-Q'one-5,6-dione; HCl/$CHCl_3$ (88%)	274
8-Amino-5,7-dichloro-	8-NH_2-Q; SO_2Cl_2/AcOH at 75 °C for 20 min (60%)	181
8-Amino-6-bromo-5,7-dichloro-	8-NH_2-6-Br-Q; SO_2Cl_2/AcOH at 75 °C for 20 min (77%)	181
5,7-Dichloro-8-hydroxy-	8-HO-Q; *t*-BuOCl/CCl_4 at 70 °C for 30 min (84%); heat with S_2Cl_2; or SCl_2; or SO_2Cl_2/$CHCl_3$	68, 152, 235
5,7-Dichloro-8-hydroxy-*N*-oxide	8-HO-Q *N*-oxide; HCl/H_2O_2; or SO_2Cl_2/$CHCl_3$ at < 5 °C	145, 264
5,7-Dichloro-8-hydroxy-2-methyl-	8-HO-2-Me-Q; or its 7-Cl derivative; *t*-BuOCl/CCl_4 at 80 °C for 1 h (52%)	163
6,7-Dichloro-5,8-dioxo-	5-NH_2-8-HO-Q; HCl/$NaClO_3$ at 60 °C; Q-5,8-dione; CCl_4/HCl	209, 255, 256
6,7-Dichloro-2-methyl-5,8-dioxo-	5,8-diNH_2-2-Me-Q; conc. HCl/$NaClO_3$ at 55 °C for 1 h (87%)	257
6,7-Dichloro-5,8-dihydroxy-	8-HO-5-[N(OH)SO_2OH]-Q; boil with conc. HCl	260
6,8-Dichloro-	8-Me-Q; SCl_2 at 140–150 °C	235, 238
POLYCHLORO-		
2,3,4,5,6,7,8-Heptachloro-	tetra- and penta-Cl-Q; PCl_5 in autoclave at 300 °C for 5 h (78%)	35, 36
x,x,x,x-Tetrachloro-	8-Me-Q; SCl_2 at 140–150 °C	235, 238
x,x,x,x-Tetrachloro-4-quinolone-2-carboxylic acid	4-Q'one-2-CO_2H; $NaClO_3$/HCl	254
3,5,7,8-Tetrachloro-6-methoxy-	6-MeO-8-NO_2-Q; SO_2Cl_2 reflux for 15 min	245
x,x,x-Trichloro-	Q; SCl_2 at 160 °C or with S_2Cl_2 (10%)	236, 237
x,x,x-Trichloro-2-quinolone	2-Q'one; HCl/AcOH/$KClO_3$ at 60 °C	252
x,x,x-Trichloro-6-methoxy-8-nitro-	6-MeO-8-NO_2-Q; SO_2Cl_2 reflux for 15 min	245

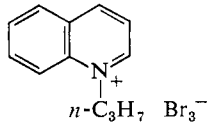
* See footnote to Table 1, p. 340.

TABLE 4 (*cont.*)

Chloroquinoline*	Method of preparation (yield)	References
x,x,x-Trichloro-7-methoxy-2-quinolone	7-MeO-2-Q'one; HCl/AcOH/$KClO_3$ at 60 °C (90%)	253
x,x,x-Trichloro-6-methyl-	6-Me-Q; SCl_2 at 120 °C	98
3,3,*x*-Trichloro-6-ethoxy-1,2,3,4-tetrahydro-2,4-dioxo-	6-EtO-4-HO-2-Q'one; SO_2Cl_2/dioxan at 50 °C (100%); 6-MeO- and 6-Ph derivatives behave similarly	247
3,3,6-Trichloro-1,2,3,4-tetrahydro-2,4-dioxo-	6-Cl-4-HO-2-Q'one; SO_2Cl_2/dioxan at 50 °C; several other 3,3-diCl-6-substituted 2,4-dioxo-Q's also reported	57, 247
8-Amino-5,6,7-trichloro-	8-NH_2-6-Cl-Q; SO_2Cl_2/AcOH at 75 °C for 20 min (67%)	181
5,7,8-Trichloro-6-hydroxy-	6-MeO-8-NO_2-Q; SO_2Cl_2 reflux for 15 min	245
5,7,8-Trichloro-6-methoxy-	6-MeO-8-NO_2-Q; SO_2Cl_2 reflux for 15 min	245

c. BROMINATION. (*i*) *By Thermolysis of Quinoline–Bromine Complexes.* The bromination of quinoline under neutral and low acidity conditions has been discussed in Section (II.1.A.b). Eisch[13] has emphasized that the mechanism of bromination under these conditions is somewhat obscure. He found that at low temperatures quinoline and bromine react to form a complex which on thermolysis yields 3-bromoquinoline and polybromoquinolines. Similar bromine–quinoline addition complexes have been known for some time, and Claus and his co-workers[10] found that the thermolysis of quinolinium perbromides (Q.HBr.Br_2)† constitutes a convenient preparative route to 3-bromoquinolines. As pointed out by Eisch, monobromination is often accompanied by polybromination and difficultly separable mixtures of bromoquinolines result. The tendency of early workers to use vigorous conditions to effect decomposition of the quinoline–bromine complex presumably enhances the probability of mixture formation, a factor that could well explain the discrepancies found in the melting points of many bromoquinolines prepared by this method. It is possible that in most cases bromination of quinoline under neutral conditions proceeds by initial formation of a quinoline–bromine complex. However, in this Section only those reactions in which the addition complex is preformed, or is isolated as a definite intermediate, are discussed.

An early report by La Coste[97] indicates that quinoline hydrochloride and bromine react in aqueous solution to form an unstable quinoline–bromine complex. However, it appears that Claus and Collischonn[10, 280] were the first to isolate such a complex, namely the *N*-propylquinolinium perbromide (**133**), and showed that on thermolysis at 170–190 °C the complex decomposes to yield 3-bromoquinoline. Subsequently they found[10] that quinoline with bromine in dry ether gives the quinolinium perbromide (**134**; R = H) which also undergoes thermolysis to yield 3-bromoquinoline



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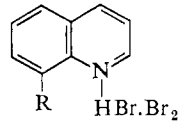

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† See footnote to Table 5, p. 375.

(68%). Thereafter, a series of publications appeared in which many 3-bromoquinolines were prepared from the appropriate quinolinium perbromides. For a complete list of 3-bromoquinolines prepared by this method see Table 5 (p. 375).

It is to be noted that much confusion exists in the early literature regarding the structure of the bromoquinolines prepared in this manner. Claus and his co-workers[94, 281–283] originally thought that bromination was taking place at the 4-position of the quinoline nucleus. Decker[284] challenged this view and argued that bromination was in fact occurring at the 3-position. It was only after some debate[285] that Claus accepted this view, and showed,[171] by unambiguous synthesis, that the product from the decomposition of quinoline perbromide is 3-bromoquinoline rather than, as he had previously thought, the 4-bromo-isomer.

Quinolinium perbromides are normally prepared by treating the quinoline hydrobromide salt with bromine in chloroform solution and detailed experimental instructions are available.[286] Many of the perbromides have been isolated as stable deep-red crystalline compounds and their physical properties are given in Table 36 (p. 620).

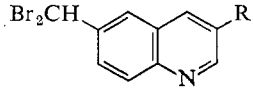
Quinoline reacts at room temperature with bromine in dry carbon tetrachloride to give a light-sensitive complex $C_9H_7NBr_2$.[3] The complex is found[3, 13] to undergo thermolysis in a variety of solvents to yield a number of bromoquinolines. For example, when the complex is heated in carbon tetrachloride containing a molar equivalent of pyridine, 3-bromoquinoline (82%) is obtained together with a trace (1.5%) of 3,6-dibromoquinoline. However, thermolysis in acetic acid at 120 °C for 14 hours yields a mixture of 3-bromo- (3%), 3,6-dibromo- (15%), and 3,6,8-tribromoquinoline (8%). In contrast, decomposition of the molten complex at 190 °C over 3 hours yields only 3-bromoquinoline (46%) plus traces of 3,8-dibromo- and possibly 3,6,8-tribromo-quinoline. Surprisingly, treatment of 3-bromoquinoline with bromine in carbon tetrachloride, with or without the presence of pyridine, over 96 hours yields only starting material. However, when either 6-bromo- or 8-bromoquinoline is treated under similar conditions, 3,6- (62%) and 3,8-dibromoquinoline (70%) are obtained.[13] Recently 3-bromo-6-chloroquinoline has been prepared by this method.[109]

Decomposition of quinolinium perbromides has proved to be a useful preparative method, and many examples of the synthesis of 3-bromoquinolines possessing chloro-,[171, 281] bromo-,[94, 283, 287] and hydroxy groups[131] have appeared. The method is particularly useful for the preparation of 3-bromonitroquinolines[175, 177, 288, 289] which are somewhat difficult to obtain by other methods. Attempts to prepare 3-bromo-8-nitroquinoline, however, by thermolysis of the perbromide complex of 8-nitroquinoline (**134**; R = NO_2) resulted in displacement of the nitro-group and formation of 3,8-dibromoquinoline.[95] The melting point (120 °C) reported by Claus and Hartmann[288] for 3-bromo-6,8-dinitroquinoline prepared by this method is in error and has since been found[289] to be 159 °C.

Decomposition of the $HBr.Br_2$ complex of 5-bromo-6-hydroxyquinoline results in further dibromination to yield either 3,5,7- or 3,5,8-tribromo-6-hydroxyquinoline.[131]

3-Bromoquinoline formation is not observed if the quinoline nucleus bears an alkoxy- or alkyl group. Thus 8-ethoxyquinolinium perbromide (**134**; R = EtO), heated at 200 °C, yields not the expected 3-bromo-derivative but a mixture of 5-bromo- and 5,7-dibromo-8-ethoxyquinoline.[168] Obviously in the latter reactions the site of bromination is determined by the strongly electron-donating hydroxy- and alkoxy-substituents. If the positions *ortho* and *para* to the hydroxy-function are blocked, however, then the reaction proceeds normally. For example, 5,7-dibromo-8-hydroxyquinolinium perbromide decomposes at 250 °C to yield 3,5,7-tribromo-8-hydroxyquinoline.[131]

The presence of a methyl group in the quinoline ring causes the reaction to become far more complex since mono- and di-bromination of the alkyl side chain may occur along with nuclear bromination. Howitz and Philipp[290] showed that the perbromide of 6-methylquinoline, when heated at 180 °C with an excess of bromine, yields a mixture of 6-(dibromomethyl)- and 3-bromo-6-(dibromomethyl)quinoline (**135**; R = H and Br, respectively).



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Similarly, warming 8-methylquinolinium perbromide with hydrochloric acid yields a product which the authors[291] originally formulated as 3-bromo-8-(bromomethyl)quinoline. However, later studies[292] indicated that halogen exchange had taken place during the decomposition and the haloquinoline formed was in fact 8-(chloromethyl)-3-bromoquinoline. 8-(Bromomethyl)quinoline is obtained[107] when the perbromide is heated at its melting point. A somewhat different reaction is observed on thermolysing 6-methoxy-8-methylquinolinium perbromide;[107] in this instance bromination occurs neither at the 3-position nor at the alkyl side chain, but rather at the electron-rich 5-position.

It has been suggested[293] that the bromination of styrylquinolines in dry chloroform involves initial formation of a $HBr.Br_2$ complex, which on heating decomposes to give the observed α- or β-bromostyrylquinoline.

4,7-Dichloroquinolinium perbromide has been used as a brominating agent for various phenols.[294] For example, salicylic acid in acetic acid–chloroform mixture in the presence of a sodium acetate buffer, yields 3,5-dibromosalicylic acid, whereas in aqueous solution 2,4,6-tribromophenol is formed.

Bromoquinolines prepared by thermolysis are listed in Table 5.

TABLE 5. Bromoquinolines by Thermolysis of Quinolinium Perbromides* ($Q.HBr.Br_2$)

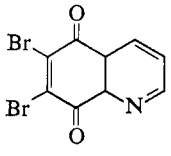
Bromoquinoline	References	Bromoquinoline	References
3-Bromo-[a]	10, 280, 286, 295	3,*x*-Dibromo-	287
		3,5-Dibromo-	282
3-Bromo-6-chloro-	96, 171, 281	3,6-Dibromo-	94, 287
		3,7-Dibromo-	94, 96, 287
3-Bromo-8-(bromomethyl)-	292		
3-Bromo-6-(chloromethyl)-[b]	291	3,8-Dibromo-	95, 287
3-Bromo-6-(dibromomethyl)-	290	5,*x*-Dibromo- (5,7- ?)	287
		5,7-Dibromo-8-ethoxy-	168
3-Bromo-5,7-dinitro-	288	3,5,6,8-Tetrabromo-	96
3-Bromo-5,8-dinitro-	288	3,5,6-Tribromo-[d]	298
3-Bromo-6,8-dinitro-[c]	288, 289	3,5,7-Tribromo-	283
3-Bromo-5-nitro-	175	3,5,7- or 3,5,8-Tribromo-6-hydroxy-	131
3-Bromo-6-nitro-	180, 289		
5-Bromo-8-ethoxy-	168	3,5,8-Tribromo-	296, 297
5-Bromo-6-methoxy-8-methyl-	107	3,6,7-Tribromo-	298
		3,6,8-Tribromo-	297

* This name is used throughout this Chapter to describe molecular halogen complexes of type $Q.HBr.Br_2$. Other names, however, are in common usage (see refs. 286 and 1701).

[a] Yield 36.5%. [b] Yield 35%. [c] Yield 69%. [d] Yield 60%.

(*ii*) *Bromination by Sulphur Bromides.* Edinger has investigated the bromination of quinolines using disulphur dibromide (S_2Br_2). In the original work[234] a mixture of bromine and sulphur at 180–190 °C was used, and more recently reports of the preparation of 3-bromoquinoline utilizing these conditions have appeared.[299, 300] Treatment of quinoline with disulphur dibromide at low temperature yields a mixture of 3-bromoquinoline and an unidentified tribromoquinoline,[234, 236, 237] while 6-methylquinoline yields an uncharacterized monobromoquinoline (m.p. 85 °C) when treated with disulphur dibromide at 120 °C.[98]

(*iii*) *Bromination by Bromates.* Bromate salts have proved to be of particular use in the preparation of bromoquinoline-5,8-diones, which have been shown[256] to possess both fungistatic and bacteriostatic activity. A useful starting material for these syntheses is 5-amino-8-hydroxyquinoline which, on treatment with sodium[257] or potassium bromate[256] in hydrobromic acid, suffers both oxidation and dibromination to yield 6,7-dibromoquinoline-5,8-dione (**136**).



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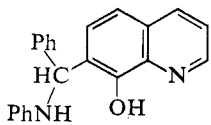

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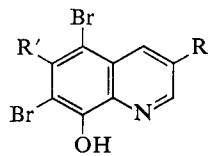

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The (anilinobenzyl)-8-hydroxyquinoline (**137**), on treatment with a bromide–bromate mixture in 4*N*-hydrochloric acid yields 5,7-dibromo-8-hydroxyquinoline, along with 2,4,6-tribromoaniline.[301, 302] The reaction is thought to proceed by initial hydrolysis of the anilinobenzyl group to give benzaldehyde, aniline, and 8-hydroxyquinoline. The last two products subsequently undergo tri- and di-bromination, respectively.

The reaction between 8-hydroxyquinoline and bromate ion in acid solution is very fast and serves as a quantitative volumetric method for the determination of 8-hydroxyquinoline.[303] Under these conditions 5-bromo-8-hydroxyquinaldine yields the 5,7-dibromo-derivative,[169] whereas 3-bromo- and 6-bromo-8-hydroxyquinoline yield the corresponding tribromo-derivatives (**138**; R = Br, R′ = H) and (**138**; R = H, R′ = Br) respectively.[304]

Corsini and Graham,[305] however, have found that whereas the 2-methyl-, 6-methyl-, and 2-phenyl-derivatives of 8-hydroxyquinoline are dibrominated rapidly and quantitatively by acidic potassium bromide–bromate mixture, 4-methyl-8-hydroxyquinoline reacts comparatively slowly. These authors consider that in the case of the 4-methyl compound steric effects at the 5-position, which has been shown[306] to be the site for initial bromination, are unfavourable. On the basis of molecular models the authors indicate that there is more steric hindrance in the 4-methyl than in the 6-methyl compound, and in fact the latter is brominated rapidly at the 5- and 7-positions.

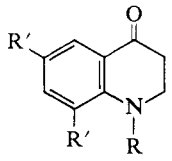
Other 8-hydroxyquinolines that have been brominated by using bromate ion in the presence of acid include 5-formyl-8-hydroxy-2-methylquinoline[157] and 5-acetyl-8-hydroxyquinoline.[307] In each case the respective 7-bromo-derivative is formed in high yield. However, other studies indicate[308] that 5-acetyl-8-hydroxyquinoline in the presence of an excess of brominating mixture undergoes further bromination with loss of the acetyl group, to give 5,7-dibromo-8-hydroxyquinoline. Bromination of the acetyl group is not observed.

4-Hydroxyquinoline *N*-oxide reacts with potassium bromate–bromide–hydrochloric acid mixture at room temperature to give 3-bromo-4-hydroxyquinoline *N*-oxide.[309] In a similar manner 4-amino-3-bromoquinoline *N*-oxide can be prepared from 4-aminoquinoline *N*-oxide.[174] However, attempts to prepare 3-bromo-4-methoxyquinoline *N*-oxide by this method failed.[174]

(*iv*) *Bromination by Phosphorus Bromides.* Occasionally reports have appeared in the literature indicating that nuclear bromination can be brought about by heating quinolines with phosphorus bromides. Normally these reactions are observed as side reactions during the standard conversion of quinolones and hydroxyquinolines into the bromo-derivative by use of phosphorus tri- and penta-bromide (see Section II.1.D.c). Decker[284] found that 3-bromo-2-quinolone with phosphorus pentabromide at 120 °C yields not only the expected 2,3-dibromoquinoline but also an unidentified tribromoquinoline, m.p. 174 °C. Later work by Claus and Howitz[171] indicates that 4-quinolone with phosphorus pentabromide at 130 °C gives a mixture of 4-bromo- and 3,4-dibromo-quinoline. Similarly 5,7-dibromo-8-hydroxyquinoline, when heated with phosphorus pentabromide, yields 3,5,7-tribromo-8-hydroxyquinoline.[131, 165, 304]

(*v*) *Bromination by* N-*Bromosuccinimide.* *N*-Bromosuccinimide has been used to bring about nuclear bromination of several quinoline derivatives. Mann and Ittyerah[126] found that 1,2,3,4-tetrahydro-1-methyl- and 1,2,3,4-tetrahydro-1-phenyl-4-oxoquinoline (**139**; R′ = H, R = Me and Ph, respectively) react at room temperature with *N*-bromosuccinimide in carbon tetrachloride to give the corresponding 6-bromo-derivatives in high yield. If the reaction is carried out on the 1-methyl derivative over a longer period of time, and in the presence of benzoyl peroxide, then 6,8-dibromo-1,2,3,4-tetrahydro-1-methyl-4-oxoquinoline (**139**; R = Me, R′ = Br) results. In no case is bromination at the 2- or 3-position observed.

Investigations[277] reveal that 8-hydroxyquinoline with *N*-bromosuccinimide (1 molar equivalent) at ambient temperatures gives a mixture of 5-bromo- (14%), 7-bromo- (50%), and 5,7-dibromo-8-hydroxyquinoline (20%). Similar yields are obtained on carrying out the reaction at 40–60 °C. However, with a 3-molar excess of halogenating agent a quantitative yield of the 5,7-dibromo-derivative is obtained, regardless of the reaction temperature.



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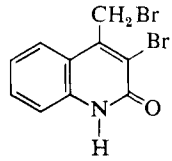

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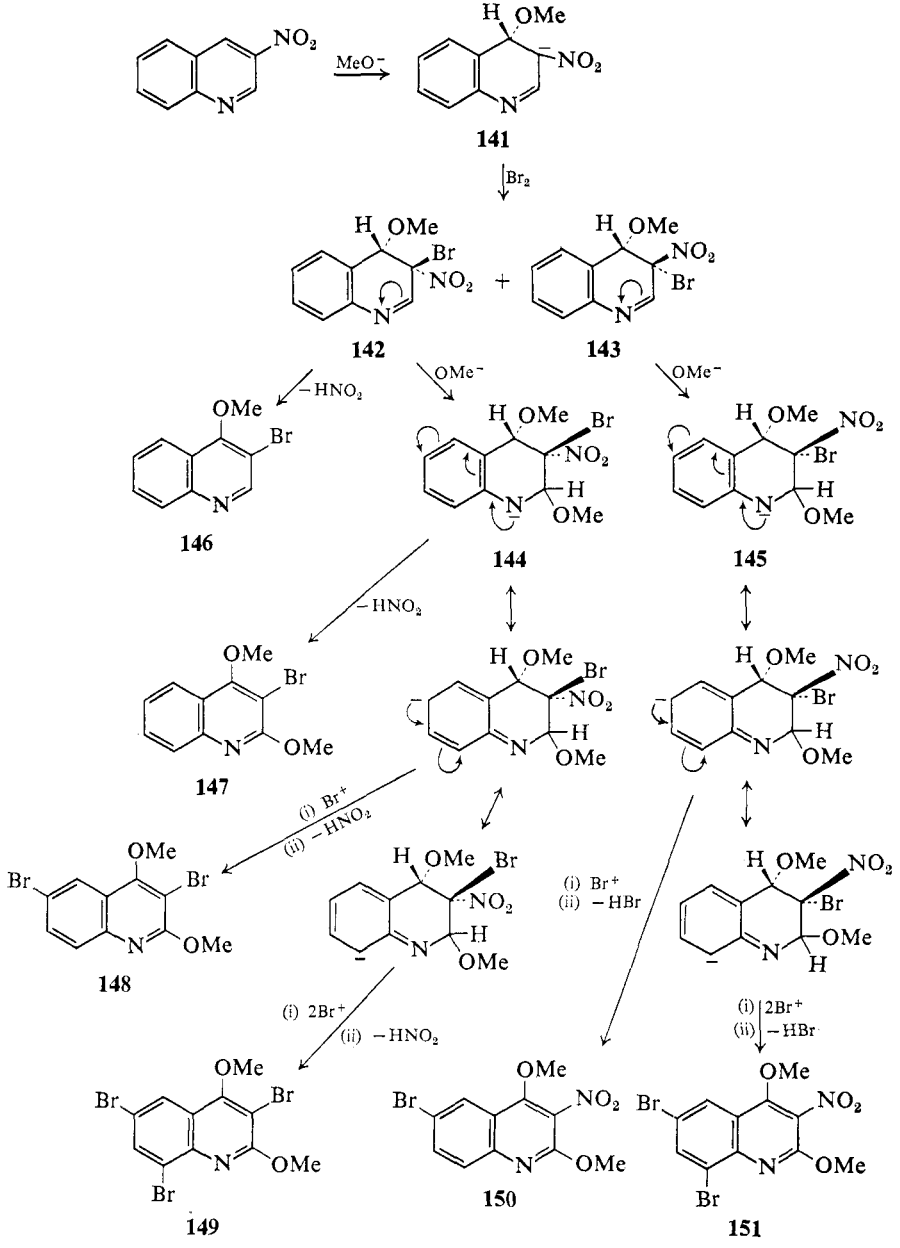
8-Hydroxyquinoline as the copper(II) complex is reported to be brominated at the 5-position by *N*-bromosuccinimide in chloroform solution.[278] However, a detailed examination[81, 279] of the products reveals that, whereas at ambient temperatures, a high yield (80%) of the 5-bromo-derivative is achieved, at higher temperatures (40–60°), or with an excess of brominating agent, quantitative yields of the 5,7-dibrominated copper(II) chelate are obtained. The influence of solvent on the reaction of *N*-halosuccinimides with 8-hydroxyquinoline has been discussed in some detail.[81]

Simultaneous side-chain and nuclear bromination is observed with 4-methyl-2-quinolone which, when heated with *N*-bromosuccinimide in chloroform for 8 hours, yields the dibromo-compound (**140**).[114]

(*vi*) *Bromination by Hypobromites.* 3-Nitroquinoline undergoes a complex series of reactions with sodium hypobromite in methanolic potassium hydroxide at 0–5 °C as

indicated in Scheme 9.[310, 311] Initial formation of the σ-complex (**141**) is followed by bromination at the 3-position and then by further attack by methoxide ion at the 2-position to give the anionic species (**144** and **145**). Further bromination of the mesomeric anion as indicated (Scheme 9) leads to the formation of the 3,6-dibromo-,



SCHEME 9

and 3,6,8-tribromo-derivatives (**148** and **149**), respectively. Since in the initial bromination step two conformations of the adduct (i.e. **142** and **143**) are possible, the resulting brominated species may, by a *trans*-elimination, lose either hydrogen bromide or nitrous acid to give the respective products (**146–151**) as indicated.

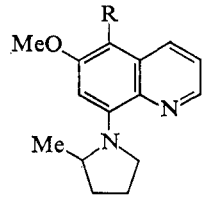
The product ratio varies with temperature and at 40 °C reaction is even more complex in that 2,4,6-tribromoaniline and 2,4,6-tribromo-3-methoxyaniline are also formed.

Further studies[312] indicate that analogous reactions occur with 4-, 5-, 6-, and 8-nitroquinoline. 2-Nitroquinoline, however, undergoes normal nucleophilic displacement of the nitro-group to yield 2-methoxyquinoline.

7-(*o*-Carboxybenzoyl)-8-hydroxyquinoline is brominated at the 5-position by sodium hypobromite.[143]

(*vii*) *Miscellaneous.* An instance of nuclear bromination has been reported[179] to occur during the attempted von Braun cyanogen bromide reaction on the tertiary amino-substituted quinoline (**152**; R = H). A bromo-compound, thought to be the 5-bromo-derivative (**152**; R = Br), was isolated in 27% yield. Bromination of the tertiary base in acetic acid yields an identical product.

3-Hydroxyquinoline with bromine in 10% aqueous sodium hydroxide at 20 °C gives 4-bromo-3-hydroxyquinoline in 76–78% yield.[56]



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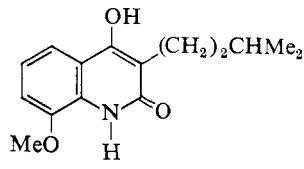

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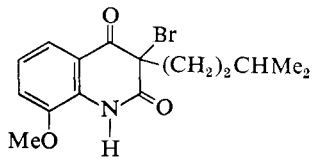

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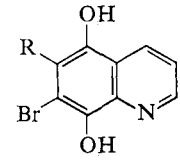

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Treatment of the 4-hydroxy-2-quinolone (**153**) with pyridinium perbromide* in acetic acid leads to the formation of the 3-bromo-2,4-dioxoquinoline (**154**) in high yield (87%).[313] The reaction proceeds similarly with *N*-bromosuccinimide, but in a much lower yield (31%).

8-Hydroxyquinoline-5-sulphonic acid is readily brominated at the 7-position with a mixture of potassium bromide and sodium hypochlorite.[69]

An unusual reaction is observed[148] when the substituted 8-hydroxy-5-(hydroxyamino)quinoline (**130**) is heated under reflux with constant-boiling hydrobromic acid; the hydroxylamine side chain is replaced by a hydroxyl group and nuclear bromination occurs to give 7-bromo-5,8-dihydroxyquinoline (**155**; R = H) as major product (85%), along with 6,7-dibromo-5,8-dihydroxyquinoline (**155**; R = Br) (10%). This reaction is somewhat different from that observed with concentrated hydrochloric acid [see Section II.1.B.b(vii)].

* See footnote to Table 5, p. 375.

Diazotization of 4-aminoquinoline in hydrobromic acid is reported to give a mixture of 3-bromoquinoline and 4-amino-3-bromoquinoline.[314] Carbonyl bromide ($COBr_2$) reacts with 8-hydroxyquinoline to give a mixture of 5-bromo- and 5,7-dibromo-8-hydroxyquinoline.[315]

Further detail is assembled in Table 6.

TABLE 6. Bromoquinolines by Indirect Bromination

Bromoquinoline*	Method of preparation (yield)	References
x-Bromo-6-methyl-	6-Me-Q; S_2Br_2 at 120 °C	98
3-BROMO-		
3-Bromo-	Q; S/Br_2 heat at 180–190 °C for 5 h (50%)	234, 236, 299, 300
4-Amino-3-bromo-	4-NH_2-Q *N*-oxide; $NaNO_2$/conc. HBr	314
4-Amino-3-bromo- *N*-oxide	4-NH_2-Q *N*-oxide; $KBrO_3$/HBr	174
3-Benzyl-3-bromo-1,2,3,4-tetrahydro-1-methyl-2,4-dioxo-	1-Me-3-$PhCH_2$-2,4-dioxo-1,2,3,4-tetraH-Q; AcOH/$C_5H_5N.HBr.Br_2$ stand for 12 h (80%)	313
3-Bromo-4-(bromomethyl)-2-quinolone	4-Me-2-Q'one; NBS/$CHCl_3$ under reflux for 8 h	114
3-Bromo-4-hydroxy *N*-oxide	4-HO-Q *N*-oxide; KBr/$KBrO_3$/5% HCl at room temp.	309
3-Bromo-1,2,3,4-tetrahydro-8-methoxy-3-(3-methylbutyl)-2,4-dioxo-	3-($Me_2CHCH_2CH_2$)-4-HO-8-MeO-2-Q'one; AcOH/$C_5H_5N.HBr.Br_2$ stand for 12 h (87%). Also with NBS	313
4-Bromo-3-hydroxy-	3-HO-Q; Br_2/10% NaOH at 20 °C (76–78%)	56
5-BROMO-		
5-Bromo-7-(*o*-carboxybenzoyl)-8-hydroxy-	7-(*o*-$HO_2C.C_6H_4CO$)-8-HO-Q; NaOBr/HBr	143
5-Bromo-8-hydroxy-	8-HO-Q as Cu(II) chelate; NBS in $CHCl_3$	278, 279
5-Bromo-6-methoxy-8-(2-methylpyrrolidinyl)-	6-MeO-8-(2-Me-C_4H_7N)-Q; BrCN/Et_2O reflux 3 h	179
6-BROMO-		
6-Bromo-1,2,3,4-tetrahydro-1-methyl-4-oxo-	1-Me-1,2,3,4-tetraH-4-oxo-Q; NBS/CCl_4 shake at room temp. for 2 h (78%)	126
6-Bromo-1,2,3,4-tetrahydro-4-oxo-1-phenyl-	1-Ph-1,2,3,4-tetraH-4-oxo-Q; reacted as above	126
7-BROMO-		
5-Acetyl-7-bromo-8-hydroxy-	5-Ac-8-HO-Q; (i) KBr/$KBrO_3$/48% HBr; (ii) 0.1 N-$KBrO_3$/KBr/HCl at 5 °C for 1 h (89%)	307, 308
5-Acetyl-7-bromo-8-hydroxy-2-methyl-	5-Ac-8-HO-2-Me-Q; KBr/$KBrO_3$/48% HBr (78%)	307
7-Bromo-5,8-dihydroxy-	5-[$HOSO_2N(OH)$]-8-HO-Q; 48% HBr under reflux for 30 min, then 6 h at room temp. (85%)	148

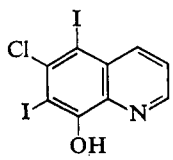
* See footnote to Table 1, p. 340.

TABLE 6 (*cont.*)

Bromoquinoline*	Method of preparation (yield)	References
7-Bromo-5-formyl-8-hydroxy-2-methyl-	5-CHO-8-HO-2-Me-Q; NaBr/$NaBrO_3$/HBr (67%)	157
7-Bromo-8-hydroxy-5-sulphonic acid	8-HO-Q-5-SO_2OH; KBr/NaOCl at 15–20 °C (90%)	69
DI- and TRI-BROMO-		
5,7-Dibromo-8-hydroxy-	(i) 7-[PhNHCH(Ph)]-8-HO-Q; 0.5 N-KBr/$KBrO_3$/4N- HCl for 2 h at room temp.; (ii) 8-HO-Q with $COBr_2$; (iii) 8-HO-Q with NBS	301 277, 315
5,7-Dibromo-8-hydroxy-2-methyl-	5-Br-8-HO-2-Me-Q; 6 N HCl/KBr/$KBrO_3$ (81%)	169
6,7-Dibromo-5,8-dioxo-	5-NH_2-8-HO-Q; $KBrO_3$/HBr or $NaBrO_3$/HBr at 60 °C for 30 min (70%)	256, 257
6,8-Dibromo-1,2,3,4-tetrahydro-1-methyl-4-oxo-	1-Me-1,2,3,4-tetraH-4-oxo-Q; NBS/CCl_4/Bz_2O_2 shake for 4 h, then stand at room temp. for 12 h (88%)	126
x,*x*,*x*-Tribromo-	Q; S_2Br_2 heat at 180–190 °C for 5 h	234, 236, 237
2,3,*x*-Tribromo-	3-Br-2-Q'one; PBr_5 at 120 °C	284
3,5,7-Tribromo-8-hydroxy-	3-Br-8-HO-Q; (i) HBr/KBr/$KBrO_3$/H_2O; or (ii) 5,7-diBr-8-HO-Q; PBr_5 heat	304, 131, 165
5,6,7-Tribromo-8-hydroxy-	6-Br-8-HO-Q; HBr/KBr/$KBrO_3$/H_2O	304

d. IODINATION. (i) *By Iodine Chlorides.* Iodine monochloride has proved to be a valuable iodinating agent particularly for 8-hydroxyquinolines. 8-Hydroxyquinoline itself reacts with two equivalents of iodine monochloride in hydrochloric acid at room temperature to yield 8-hydroxy-5,7-di-iodo-quinoline.[316, 317] If one equivalent of the reagent is used then 8-hydroxy-5-iodoquinoline is obtained.[316] These results are at variance with those of Sen-Gupta[68] who reports that 8-hydroxyquinoline fails to react with iodine monochloride in acetic acid solution. A mixture of 8-hydroxy-5-iodo- and 8-hydroxy-5,7-di-iodoquinoline results when an alkaline solution of 8-hydroxyquinoline is allowed to react with ethanolic iodine monochloride.[74]

6-Chloro-8-hydroxyquinoline and iodine monochloride in acetic acid give 6-chloro-8-hydroxy-5,7-di-iodoquinoline (**156**) in high yield.[232] Several 3-alkyl-substituted 8-hydroxyquinaldines have been di-iodinated (5- and 7-positions) with



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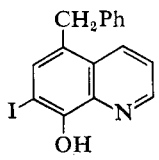

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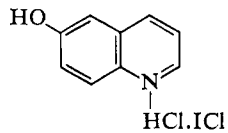

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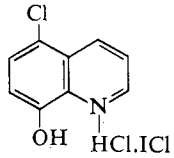
a solution of iodine monochloride in dilute hydrochloric acid,[318] while treatment of 5-benzyl-8-hydroxyquinoline under similar conditions yields the 7-iodo-compound (**157**) in high yield.[319]

Quinolones are reported to undergo iodination at the 3-position with iodine monochloride in hot acetic acid.[122, 320, 321] 5-Hydroxyquinoline is iodinated, as expected, to give either 5-hydroxy-8-iodo- or 5-hydroxy-6,8-di-iodoquinoline depending on the amount of iodine monochloride used.[316] However, 6-hydroxyquinoline, like quinoline itself,[322] with iodine monochloride in hydrochloric acid forms an iodine monochloride–hydrochloride adduct (**158**).[316]

The formation of iodine monochloride–quinoline complexes, first reported by Dittmar,[323] have been discussed by Das and Mukherji.[324] The latter workers find that iodine monochloride with 5-chloro-8-hydroxyquinoline in concentrated hydrochloric acid gives initially the iodine monochloride–hydrochloride addition compound (**159**). Decomposition of the complex with water results in iodination and formation of 5-chloro-8-hydroxy-7-iodoquinoline. Similar reactions are observed with 8-hydroxy-5-iodoquinoline and the corresponding quinaldines. It is of interest that the addition compounds are not formed when the reactions are carried out in acetic acid, ethanol, or chloroform solution. Addition complexes are also observed with 5- and 6-aminoquinoline, whereas 8-aminoquinoline yields the expected 5,7-di-iodo- or 5-iodo-derivative depending on the quantity of iodine monochloride used.[316]



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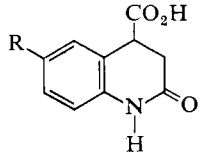

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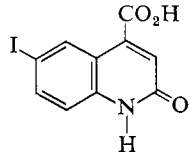

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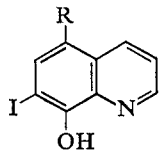
As expected, 1,2,3,4-tetrahydro-2-oxoquinolines and iodine monochloride in acetic acid react to give the 6-iodo-derivatives.[198, 325] In the case of the tetrahydro-2-oxoquinoline-4-carboxylic acid (**160**; R = H) treatment with iodine monochloride in boiling acetic acid for 4 hours yields the iodo-2-quinolone (**161**).[198] However, with iodine monochloride in acetic acid at room temperature for 48 hours, the 6-iodo-derivative (**160**; R = I) is formed, unaccompanied by dehydrogenation.

Iodine trichloride is usually thought of as a chlorinating agent. Instances have been reported, however, of its use as a nuclear iodinating agent for several quinoline derivatives. The literature is a little confusing on the exact nature of these reactions. 8-Hydroxyquinoline and iodine trichloride react, to form initially what is thought to be 5-chloro-8-hydroxyquinoline that is isolated as the hydrochloride–iodine monochloride adduct (**159**).[324] Subsequent decomposition of the complex with water yields the final product 5-chloro-8-hydroxy-7-iodoquinoline. In contrast Lasker and Ghosh[326] report that 8-hydroxyquinoline and iodine trichloride react to give mainly 8-hydroxy-5,7-di-iodoquinoline, together with a small amount of the 5-chloro-7-iodo-derivative. A German patent[327] describes a direct synthesis of 5-chloro-8-hydroxy-7-iodoquinoline by treating 8-hydroxyquinoline with iodine trichloride in carbon tetrachloride, water, or acetic acid solution.

(*ii*) *Iodination by Iodide–Hypochlorite Mixture.* Early workers on the synthesis of the antiamoebicides "Vioform" (**162**; R = Cl) and "Loretin" (**162**; R = SO_2OH) employed potassium iodide–sodium or calcium hypochlorite mixtures as reliable iodinating agents. Under these conditions 5-chloro-8-hydroxyquinoline yields the 7-iodo-derivative (**162**; R = Cl),[68, 69, 227] while 8-hydroxyquinoline-5-sulphonic acid[69, 328, 329] and 5-hydroxyquinoline-8-sulphonic acid[330] yield the 7-iodo- and 6-iodo-derivative, respectively. A mixture of potassium iodide and sodium hypochlorite has

been used[69] to effect the 5,7-di-iodination of 8-hydroxyquinoline, whereas with potassium iodide and calcium hypochlorite, 6-hydroxyquinoline is monoiodinated at the 5-position.[331]



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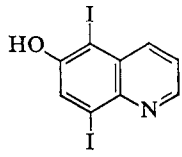

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(*iii*) *Miscellaneous.* 8-Hydroxy-5,7-di-iodoquinoline can be prepared by treating 8-hydroxyquinoline with a mixture of potassium iodide and potassium iodate in hydrochloric acid at 100 °C.[332] Under similar conditions 6-hydroxyquinoline yields the 5,8-di-iodo-derivative **163**.

8-Hydroxyquinoline-5-arsonic acid is reported[333] to yield the 7-iodo-derivative [**162**; R = $AsO(OH)_2$] when treated with potassium iodide and potassium bromate in dilute sulphuric acid for 12 hours. "Vioform" (**162**; R = Cl) and 8-hydroxy-5,7-di-iodoquinoline (**162**; R = I) have been prepared by treating the appropriate 5-halo-8-hydroxyquinolines with potassium dichloroiodate ($KICl_2$).[334]

N-Iodosuccinimide has been utilized to bring about iodination of 8-hydroxyquinoline.[277] At ambient temperatures and with 1-molar equivalent of the halogenating agent a 94% yield of 8-hydroxy-5-iodoquinoline, together with minor amounts of 8-hydroxy-7-iodo- (< 1%) and -5,7-di-iodo-quinoline (5%) are obtained. At higher temperatures or with an excess of *N*-iodosuccinimide, 8-hydroxy-5,7-di-iodoquinoline is the sole product (100%). In contrast the copper(II) chelate of 8-hydroxyquinoline reacts at room temperature with *N*-iodosuccinimide (2 mol) to give a quantitative yield of 8-hydroxy-7-iodoquinoline;[279] an increase in reaction temperature, or the use of an excess of iodinating agent, leads to formation of the 5,7-di-iodo-derivative in high yield; under no conditions could the authors (Gershon *et al.*) detect the formation of 8-hydroxy-5-iodoquinoline; this result is of interest since under certain conditions [see Section II.1.B.c(v)] *N*-bromosuccinimide yields 5-bromo-7-hydroxyquinoline as the major product (80%), whereas with *N*-chlorosuccinimide mixtures of mono- and di-chloro-compound are obtained. The authors do not advance any mechanistic explanation of their results, but point out that the earlier findings of Prasad and his co-workers,[278] on the reaction of 8-hydroxyquinoline with *N*-halosuccinimides, are in error.

Claus and Frobenius[314] report the isolation of 4-amino-3-iodoquinoline after diazotization of 4-aminoquinoline in hydriodic acid.

An electrochemical procedure for the preparation of both 8-hydroxy-5-iodo- and 8-hydroxy-5,7-di-iodo-quinoline has been described.[335] Under optimum conditions the yield of 5-iodo-compound is 68% (current efficiency 34%), and for the 5,7-di-iodo-compound a yield of 82.4% (current efficiency 32.4%) is cited. The authors claim the method to be superior to all the published chemical methods for the preparation of 8-hydroxy-mono- and -di-iodoquinolines.

An uncharacterized decahydrodi-iodoquinoline has been isolated by Bamberger and Williamson[336] from the phosphorus–hydrogen iodide reduction of 1,2,3,4-tetrahydroquinoline.

e. Polyvalent Iodine Compounds. There appears to be only one report in the literature concerning the formation of polyvalent iodine derivatives of quinoline:

Willgerodt[337] found that 8-iodo-6-methylquinoline with chlorine in acetic acid solution yields 8-(dichloroiodo)-6-methylquinoline (**164**).

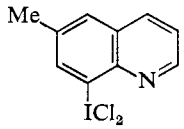

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Table 7 lists details of the indirect iodinations.

TABLE 7. Iodoquinolines by Indirect Iodination

Iodoquinoline*	Method of preparation (yield)	References
3-IODO-		
3-Iodo-2-quinolone	2-Q'one; ICl/AcOH for 1 h at 130 °C	320
Et 3-iodo-4-quinolone-2-carboxylate	4-Q'one-2-CO_2Et; ICl/AcOH at 80 °C (94%)	122
Et 5-chloro-3-iodo-4-quinolone-2-carboxylate	5-Cl-4-Q'one-2-CO_2Et; ICl/AcOH at 80 °C (94%)	122
Me 7-chloro-3-iodo-4-quinolone-2-carboxylate	7-Cl-4-Q'one-2-CO_2Me; ICl/AcOH stir for 4 h (56%)	321
Et 7-chloro-3-iodo-4-quinolone-2-carboxylate	7-Cl-4-Q'one-2-CO_2Et; ICl/AcOH at 80 °C (90%)	122
5-IODO-		
8-Amino-5-iodo-	8-NH_2-Q; ICl/HCl	316
6-Hydroxy-5-iodo-	6-HO-Q; KOH/KI/$Ca(OCl)_2$	331
8-Hydroxy-5-iodo-	8-HO-Q; ICl/HCl; or ICl/EtOH at 0 °C	74, 316
8-hydroxy-5-iodo-7-nitro-	7-NO_2-8-HO-Q; ICl/DMF at 100 °C for 2 h (76%)	214
6-IODO-		
3-Acetamido-1,2,3,4-tetrahydro-6-iodo-2-oxo-	3-AcNH-1,2,3,4-tetraH-2-oxo-Q; ICl/AcOH	325
5-Hydroxy-6-iodo-8-sulphonic acid	5-HO-Q-8-SO_2OH; KI/$Ca(OCl)_2$/HCl	330
6-Iodo-2-quinolone-4-carboxylic acid	1,2,3,4-tetraH-2-oxo-Q or -4-Q'one-2-CO_2H; ICl/AcOH under reflux for 4 h (20%)	198
1,2,3,4-Tetrahydro-6-iodo-2-oxo-4-carboxylic acid	1,2,3,4-tetraH-2-oxo-Q-4-CO_2H; ICl/AcOH under reflux for 4 h	198, 337, 338
7- and 8-IODO-		
5-Benzyl-8-hydroxy-7-iodo-	5-$PhCH_2$-8-HO-Q; ICl/HCl shake for a few min	319

* See footnote to Table 1, p. 340.

TABLE 7 (*cont.*)

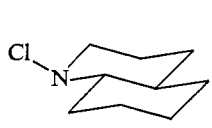
Iodoquinoline*	Method of preparation (yield)	References
5-Chloro-8-hydroxy-7-iodo-	5-Cl-8-HO-Q; (i) KOH/KI/5% $Ca(OCl)_2$ or NaOCl; (ii) $KICl_2$/N- HCl; (iii) ICl or ICl_3 in HCl or H_2O or CCl_4	68, 69, 227, 324, 327, 337
5-Chloro-8-hydroxy-7-iodo-2-methyl-	5-Cl-8-HO-2-Me-Q; ICl then decompose with H_2O (70%)	324
8-Hydroxy-7-iodo-5-arsonic acid	8-HO-Q-5-$AsO(OH)_2$; KI/$KBrO_3$ for 12 h	333
8-Hydroxy-7-iodo-5-sulphonic acid	8-HO-Q-5-SO_2OH; (i) KI/K_2CO_3/$Ca(OCl)_2$ boil in aq. solution (63%); (ii) KI/NaOCl	69, 328, 329
8-Hydroxy-7-iodo-6-methyl-5-sulphonic acid	8-HO-6-Me-Q-5-SO_2OH; KI/$Ca(OCl)_2$/HCl	330
5-Hydroxy-8-iodo-	5-HO-Q; ICl/HCl	316
DI-IODO-		
8-Amino-5,7-di-iodo-	8-NH_2-Q; 2ICl/HCl	316
3-(*n*-Butyl)-8-hydroxy-5,7-di-iodo-2-methyl-	8-HO-3-(*n*-Bu)-2-Me-Q; ICl/dil. HCl	318
6-Chloro-8-hydroxy-5,7-di-iodo-	6-Cl-8-HO-Q; ICl/AcOH (90%)	232
3-(*n*-Hexyl)-8-hydroxy-5,7-di-iodo-2-methyl-	3-(*n*-C_6H_{13})-8-HO-2-Me-Q; ICl/dil. HCl	318
8-Hydroxy-5,7-di-iodo-	8-HO-Q; (i) 2ICl at room temp.; (ii) ICl/15% HCl (92.5%); (iii) ICl/EtOH at 0 °C; (iv) ICl_3/AcOH; (v) KI/KIO_3; (vi) $KICl_2$ in N- HCl; (vii) electrolytically; (viii) *N*-I-succinimide/$CHCl_3$ at 40–60 °C (99%)	68, 69, 74, 277, 317, 326, 332–335
8-Hydroxy-5,7-di-iodo-2-methyl-	5-I-8-HO-2-Me-Q; ICl then decompose with H_2O (64%)	324
8-Hydroxy-5,7-di-iodo-2-methyl-3-(*n*-pentyl)-	3-(*n*-C_5H_{11})-8-HO-2-Me-Q; ICl/dil. HCl	318
6-Hydroxy-5,8-di-iodo-	6-HO-Q; KI/KIO_3/HCl at 90–100 °C	332
5-Hydroxy-6,8-di-iodo-	5-HO-Q; 2ICl/HCl	316

C. N-*Halogenation*

Bamberger and Williamson[336] report that decahydroquinoline on treatment with calcium hypochlorite in acetic acid yields an *N*-chloro-derivative, m.p. 125.5 °C. Ripperger and Schreiber,[339] during their studies on the absolute configuration of laevorotatory *trans*-decahydroquinoline, prepared *trans*-*N*-chlorodecahydroquinoline (**165**) by treating decahydroquinoline with *N*-chlorosuccinimide in methylene chloride solution. They were able to isolate the *N*-chloro-compound as a yellow oil, in contrast to the solid derivative obtained by Bamberger. Curiously, no reference is made to the earlier work.

Einhorn and Lauch[340] showed that quinoline borate will react exothermally with calcium hypochlorite to yield a chloro-compound of molecular formula C_9H_6ClNO. In a later paper[341] this product was formulated as *N*-chloro-2-quinolone (**166**; R = H), and using this method the authors were able to synthesize a series of substituted *N*-chloro-2-quinolones. 1,6-Dichloro-2-quinolone (**166**; R = Cl) was also obtained by reaction of 6-chloro-2-quinolone with alkaline sodium hypochlorite.

More recently Williams and his co-workers[342] have prepared a series of *N*-chloro-2-quinolones by treating the appropriate 2-quinolone with *tert*-butyl hypochlorite. There is a significant difference in the melting point of *N*-chloro-2-quinolone as prepared by Williams (m.p. 98 °C) and the earlier workers (m.p. 112 °C), and again, the later authors do not mention the earlier results.



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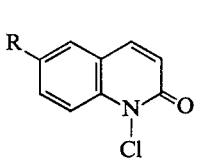

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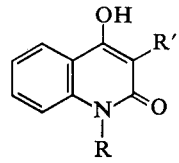

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Ziegler and his co-workers[57] have shown that 3-substituted 4-hydroxy-2-quinolones are monochlorinated at the 3-position when treated with sulphuryl chloride in dioxan (see p. 337). In contrast, de Diesbach and his co-workers[343] have found that the 3-aryl-substituted 4-hydroxy-2-quinolone (**167**; R = H, R′ = *o*-$NO_2C_6H_4$) undergoes *N*-chlorination to give the *N*-chloro-compound (**167**; R = Cl, R′ = *o*-$NO_2C_6H_4$) on treatment with boiling thionyl chloride.

These results and others are summarized in Table 8.

TABLE 8. Preparation of *N*-Chloroquinolines

N-Chloroquinoline*	Method of preparation (yield)	References
N-Chloro-2-quinolone	(i) Q.H_3BO_3; $Ca(OCl)_2$; (ii) K^+ salt of 2-Q'one and NaOCl; (iii) 2-Q'one; *t*-BuOCl (61%)	340, 341, 342
N-Chlorodecahydro-	decaH-Q; $Ca(OCl)_2$/AcOH	336
N-Chloro-(−)-*trans*-decahydro-	(−)-*trans*-decaH-Q; *N*-Cl-succinimide/CH_2Cl_2 at 20 °C for 1 h	339
N-Chloro-4-hydroxy-3-(*o*-nitrophenyl)-2-quinolone	4-HO-3-(*o*-$NO_2C_6H_4$)-2-Q'one; $SOCl_2$ under reflux for 24 h	343
N-Chloro-6-methyl-2-quinolone	6-Me-Q; $Ca(OCl)_2/H_3BO_3$	341
N-Chloro-1,2,3,4-tetrahydro-6-methyl-2-oxo-4-phenyl-	6-Me-2-oxo-4-Ph-1,2,3,4-tetraH-Q; *t*-BuOCl (75%)	342
N-Chloro-1,2,3,4-tetrahydro-2-oxo-4-phenyl-	2-Oxo-4-Ph-1,2,3,4-tetraH-Q; *t*-BuOCl (90%)	342
1,5-Dichloro-2-quinolone	5-Cl-Q; $Ca(OCl)_2/H_3BO_3$	341
1,6-Dichloro-2-quinolone	(i) 6-Cl-Q; $Ca(OCl)_2/H_3BO_3$; (ii) 6-Cl-2-Q'one; OH^-/NaOCl	341 341

D. Preparation from Quinolones and Hydroxyquinolines†

a. INTRODUCTION. The reaction of 2- and 4-quinolones with phosphorus halides is by far the most convenient method of preparing 2- and 4-haloquinolines. Chloro-compounds are the most accessible by this route and in general high yields of 2- and

* See footnote to Table 1, p. 340.

† See also Addenda, p. 677.

4-chloroquinolines may be obtained by treating the quinolone with a mixture of phosphorus oxychloride and phosphorus pentachloride at a temperature of 120–180 °C. Only rarely is a solvent used. Occasionally side reactions occur; for example, nuclear halogenation; or, as can happen with carboxylic acids and carboxamides, acyl halide and cyanide formation, respectively. Hydroxyquinoline *N*-oxides undergo chlorination accompanied by deoxygenation.

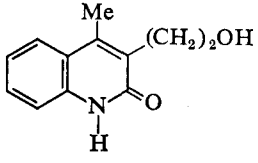
Phosphorus bromides have been used for the preparation of bromoquinolines but the reaction has not been exploited as much as the chlorination procedure. Iodination by means of phosphorus iodides does not appear to have been used as a preparative technique.

Hydroxyquinolines, like ordinary phenols, do not suffer replacement of the hydroxyl group by halogen unless there is a strongly electron-withdrawing substituent at the *ortho*- or *para*-position to the hydroxyl function.

A short review on the preparation of 2- and 4-chloroquinolines from the corresponding quinolones has appeared.[344]

b. CHLORO-COMPOUNDS. (*i*) *From 2-Quinolones*. The first recorded[345] preparation of 2-chloroquinoline involved heating 2-quinolone with a mixture of phosphorus pentachloride and phosphorus oxychloride at 140 °C. 2-Chloro-4-methylquinoline can be prepared from 4-methyl-2-quinolone in a similar manner[111] or by simply heating the 2-quinolone with phosphorus oxychloride.[346–349] A detailed method for the preparation of 2-chloro-4-methylquinoline is available.[350] 2-Chloro-3,4-dimethylquinoline is obtained[351] by heating 3,4-dimethyl-2-quinolone with phosphorus pentachloride, while 2-chloro-4,8-dimethylquinoline has been prepared[352, 353] by using phosphorus oxychloride. Many other 2-chloro-substituted alkylquinolines are accessible by these methods since the precursory 2-quinolones are readily available by the Knorr cyclization of acetoacetanilides.

Treatment of the 3-(2-hydroxyethyl)-2-quinolone (**168**) with phosphorus oxychloride yields, as expected, the dichloro-compound (**169**).[354] The acetyl derivative



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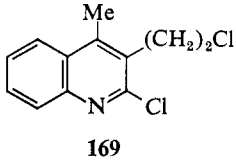

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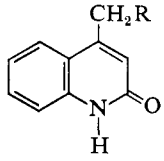

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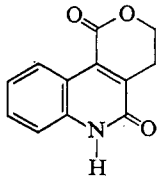
(**170**; R = AcO) under similar conditions yields the 2-chloro-derivative,[355] as does the ester (**170**; R = CO_2Et).[356]

Aryl substituted-2-quinolones react normally with phosphorus halides and several aryl-2-chloroquinolines have been reported.[357–360] 5,6,7,8-Tetrahydro-2-quinolone with phosphorus oxychloride alone,[361] or mixed with phosphorus pentachloride,[362] yields 2-chloro-5,6,7,8-tetrahydroquinoline. The fused 2-quinolone–α-pyrone system (**171**) yields the 2-chloro-derivative (**172**) on treatment with phosphorus oxychloride.[363]

2,3-Dichloro-,[364] 2,4-dichloro-,[365] and 2,7-dichloro-quinoline[366] have been prepared from the appropriate chloro-2-quinolones, as have several alkyl- and aryl-dichloroquinolines.

Reports on the action of phosphorus halides on 2-quinolonecarboxylic acids are somewhat inconsistent in that several workers report formation of the corresponding 2-chloroquinolinecarbonyl chloride, whereas others observe formation of the

2-chlorocarboxylic acid. In general it appears that phosphorus oxychloride converts 2-quinolonecarboxylic acids into the 2-chloro-acids, while phosphorus pentachloride yields the 2-chloro-acyl chlorides. For example, 2-quinolone-4-carboxylic acid



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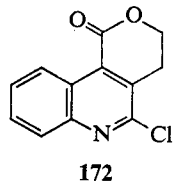

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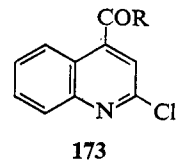

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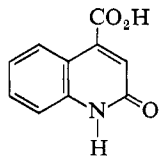
reacts with phosphorus oxychloride to give 2-chloroquinoline-4-carboxylic acid (**173**; R = OH),[346, 367] whereas with phosphorus pentachloride the 2-chloroquinoline-4-carbonyl chloride (**173**; R = Cl) is formed.[368–372] Other 2-quinolone carboxylic acids behave similarly.[373–375] Exceptions are, however, known as in the case of 2-quinolone-3-carboxylic acid which is converted into the 2-chloro-3-carbonyl chloride when heated under reflux with phosphorus oxychloride.[376] 4-Phenyl-2-quinolone-3-carboxylic acid behaves similarly.[377] Conversely, 3-phenyl-2-quinolone-4-carboxylic acid yields the 2-chloro-acid when heated with a mixture of phosphorus tri- and penta-chloride.[378] On the other hand, 6-iodo-2-quinolone-4-carboxylic acid on treatment with mixed phosphorus halides at 100 °C is reported to yield a 50 : 50 mixture of 2-chloro-6-iodoquinoline-4-carboxylic acid and the 2-quinolone acid chloride.[379] 2-Quinolonecarboxylic esters behave normally in that the 2-chloro-derivatives are readily formed in high yield.[380–382]

1,2,3,4-Tetrahydro-2-oxoquinoline-4-carboxylic acid (**160**; R = H) and the 2-quinolone-4-carboxylic acid (**174**) with phosphorus pentachloride at 120–150 °C for 1 hour yield 2-chloroquinoline-4-carboxylic acid (**173**; R = OH).[198] A similar



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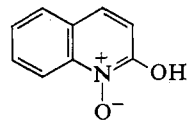

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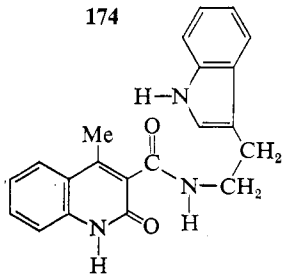

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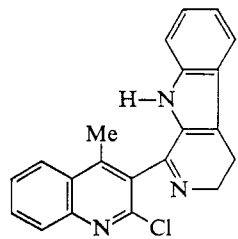

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phosphorus halide-induced dehydrogenation has been reported by Baeyer[383] who found that 1,2,3,4-tetrahydro-2-oxoquinoline with a hot mixture of phosphorus halides is converted into 2,3-dichloroquinoline.

2-Quinolones containing cyano,[384, 385] sulphone,[386–388] nitro-,[389] acetyl,[390] phenylazo-,[391] tosyloxy-,[392, 393] methylthio-,[394] and trifluoromethyl[390, 395] groups have all been

transformed successfully by phosphorus halides into the corresponding 2-chloro-derivatives. 2-Hydroxyquinoline *N*-oxide (**175**) with phosphorus oxychloride undergoes dichlorination accompanied by deoxygenation to give 2,4-dichloroquinoline.[396] In contrast, 2-hydroxy-3,6-dinitroquinoline *N*-oxide, under similar conditions, yields only the monochloro-derivative, 2-chloro-3,6-dinitroquinoline.[397]

2-Quinolones with primary[320, 398] and secondary[399, 400] amino-substituents on treatment with phosphorus halides readily yield the 2-chloro-derivatives, which are usually isolated as the hydrochlorides.

The indolyl-substituted 2-quinolone-3-carboxamide (**176**) with hot phosphorus oxychloride undergoes chlorination and cyclization of the amide side chain to give the 2-chloro-dihydro-β-carboline (**177**) in 85% yield.[385]

For further detail see Table 9.

TABLE 9. 2-Chloroquinolines by Reaction of 2-Quinolones with Phosphorus Chlorides*

2-Chloroquinoline†	Yield (%)	M.p. (°C)	References
4-Acetonyl-2-chloro-		64	401
4-Acetoxymethyl-2-chloro-	85	100	355
4-Acetyl-2-chloro-		100.5	390
3-Amino-2-chloro-		170	320
5- or 7-Amino-2-chloro-3-ethyl-4-methyl-		138	427
5- or 7-Amino-2-chloro-4-methyl-			428
6-Amino-2-chloro-4-methyl-		152	398
4-Anilino-2-chloro-	98	156, 164	399, 426
3-(Benzenesulphonyl)-2-chloro-		150	387
3-(Benzenesulphonyl)-2-chloro-8-methoxy-		195	388
5-Bromo-2-chloro-6,7-dimethoxy-4-methyl-	70	147.5	409
8-Bromo-2-chloro-5-ethyl-6-nitro-	85	146	425
3-(*p*-Bromobenzenesulphonyl)-2-chloro-		181.5	386
3-(*n*-Butyl)-2-chloro-4-methyl-6-nitro-	82	124.5	416
2-Chloro-4-(*p*-chloroanilino)-	100	175	399
2-Chloro-3-(*p*-chlorobenzenesulphonyl)-		170	387
2-Chloro-3-(*p*-chlorobenzenesulphonyl)-8-methoxy-		212	388
2-Chloro-3-cyano-4-methyl-	86	148	385
2-Chloro-3-cyano-5,6,7,8-tetrahydro-			384
2-Chloro-4-(2-diethylaminoethyl)-		82	399, 400
2-Chloro-4-(3-diethylaminopropylamino)-	68	52	399, 400
2-Chloro-4-(3-diethylaminopropylamino)-3-ethyl-		Liq.	399, 400
2-Chloro-4-(3-diethylaminopropylamino)-3-methyl-		Liq.	399, 400
2-Chloro-5,8-dimethoxy-4-methyl-	95	117.5	403
2-Chloro-6,7-dimethoxy-	96	124	408
2-Chloro-6,7-dimethoxy-4-methyl-	92	173	407
2-Chloro-7,8-dimethoxy-		95	410
2-Chloro-3,4-dimethyl-6-nitro-	100	194	416
2-Chloro-4,6-dimethyl-3-nitro-	32	157	421
2-Chloro-4,6-dimethyl-5-nitro-		162	419
2-Chloro-4,7-dimethyl-6-nitro-		164	421

* For the sake of brevity and in order to avoid undue repetition, Tables 9 and 10 contain details of only those 2- and 4-chloroquinolines that bear substituents other than alkyl, aryl, and halogen. Most 2- and 4-chloroquinolines possessing the latter type of group are accessible by the phosphorus halide route and Tables 40–60a, at the end of this Chapter, should be consulted for the physical properties of, and reference to, the preparation of these compounds.

† See footnote to Table 1, p. 340.

TABLE 9 (*cont.*)

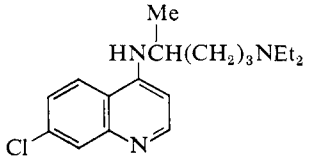
2-Chloroquinoline*	Yield (%)	M.p. (°C)	References
2-Chloro-4,7-dimethyl-8-nitro-		156	421
2-Chloro-4,8-dimethyl-6-nitro-	31	195	421
2-Chloro-5,6-dimethyl-4-carboxylic acid	93	220	375
2-Chloro-6,7-dimethyl-4-carboxylic acid	93	219	375
2-Chloro-3,6-dinitro-		162	397
Et 2-chloro-3-carboxylate		86	376
Et 2-chloro-4-methoxy-3-carboxylate		Liq.	414
Et 2-chloro-4-phenyl-3-carboxylate		106	382
Et 2-chloro-4-(*o*-tolyl)-3-carboxylate		123	382
Et 2-chloro-4-carboxylate		63	198, 381
2-Chloro-3-(*p*-ethoxybenzenesulphonyl)-		162	386
2-Chloro-6-iodo-4-carboxylic acid	50	216	379
2-Chloro-6-methoxy-		92, 107	404, 405
2-Chloro-6-methoxy-4-methyl-	98.5	148	346, 402, 403, 406
2-Chloro-7-methoxy-	76	97	253, 408
2-Chloro-7-methoxy-4-methyl-		113	412
2-Chloro-8-methoxy-3-(*p*-tosyl)-		197	388
Me 2-chloro-3-carboxylate	100	81	376
2-Chloro-3-(*o*-methoxybenzenesulphonyl)-		171	386
2-Chloro-4-methyl-6-nitro-	90	207, 213	420, 421–423
2-Chloro-8-methyl-6-nitro-		173	418
2-Chloro-4-[3-(*N*-methylindolyl)]-			429
2-Chloro-4-(*methylthio*)-	85.5	107	394
2-Chloro-3-(2-naphthalenesulphonyl)-		159	386
2-Chloro-4-methoxy-*x*-nitro-		145	415
2-Chloro-3-nitro-		119	396
2-Chloro-4-nitro-		81.5	390
2-Chloro-5-nitro-		130	175, 424
2-Chloro-5-nitro-3-(*p*-nitrophenyl)-		215	359
2-Chloro-6-nitro-		230.5	405, 417
2-Chloro-6-nitro-3-carbonyl chloride	92.5	Liq.	374
2-Chloro-4-phenylazo-		117	391
2-Chloro-3-phenyl-4-carboxylic acid		220	373, 378
2-Chloro-4-phenyl-3-carbonyl chloride		125	377
2-Chloro-3-carboxylic acid		200 d	413
2-Chloro-4-carboxylic acid	95	235	346, 367, 381
2-Chloro-4-(ethoxycarbonylmethyl)-		84	356
2-Chloro-4-carbonyl chloride	98.5	89	369, 370, 371, 372
2-Chloro-3-(*o*-tosyl)-		161	386
2-Chloro-3-(*p*-tosyl)-		179	387
2-Chloro-8-(*p*-tosyloxy)-	86	134	392, 393
2-Chloro-3,6,8-trinitro-		187	389, 396, 397
2,4-Dichloro-6,8-dinitro-		210	396
2,7-Dichloro-4-(3-diethylaminopropylamino)-		87	399, 400
Et 2,6-dichloro-4-carboxylate-		133	380
2,*x*,*x*,*x*-Tetrachloro-8-methoxy-		170	253
2,3,8-Trichloro-4-ethoxy-		63.5	411

* See footnote to Table 1, p. 340.

(*ii*) *Chloro-compounds from* 4-*Quinolones.* 4-Chloroquinoline is readily synthesized by the action of either a mixture of phosphorus pentachloride and phosphorus oxychloride[430-432]; or phosphorus oxychloride alone[433] or in benzene solution,[434] on 4-quinolone. 4-Chloro-5,6,7,8-tetrahydroquinoline results when 5,6,7,8-tetrahydro-4-quinolone is heated with a phosphorus oxychloride–pentachloride mixture.[435]

4-Hydroxyquinoline *N*-oxide on treatment with phosphorus trichloride in an inert solvent undergoes both deoxygenation and chlorination.[436] Detailed investigations show that the reaction products are dependent on the solvent used. For example, on reaction with a 3-molar excess of phosphorus trichloride in boiling chloroform, 4-quinolone (36.5%) and 4-chloroquinoline (30%) result, whereas in acetic anhydride solution with four equivalents of phosphorus trichloride only deoxygenated material (51%) is obtained. Other solvent systems have also been used: an early report indicates that 4-hydroxy-2-methylquinoline *N*-oxide on treatment with phosphorus trichloride undergoes chlorination and deoxygenation to yield 4-chloro-2-methylquinoline.[437]

Numerous examples of the conversion of alkyl- and aryl-substituted 4-quinolones to the corresponding 4-chloro-compounds have appeared in the literature. In general the reactions proceed readily with phosphorus chloride mixtures at temperatures of 100–140 °C, although in a few instances a solution of the phosphorus chloride in an inert solvent, e.g. carbon tetrachloride,[438], ethylene dichloride,[439] or toluene,[440] has been employed. The resulting 4-chloroquinolines are valuable synthetic intermediates for the preparation of 4-aminoquinolines of which several are known to possess antimalarial activity. One of the earliest and most effective antimalarials is "Chloroquine" (**178**), in whose synthesis 4,7-dichloroquinoline, prepared from 7-chloro-4-quinolone, is a key intermediate. Its industrial synthesis has been discussed in detail,[439] and a convenient laboratory preparation has been published.[441]



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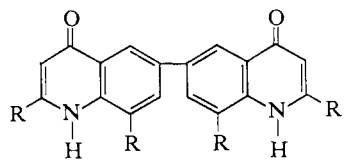

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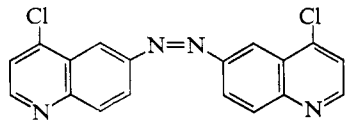
Only in a few instances has difficulty been experienced in converting a 4-quinolone into the required chloro-compound. The 6,6′-biquinolone (**179**; R = H) fails to give either the mono- or di-chloro-derivative when treated with various mixtures of phosphorus halides under a whole range of reaction conditions.[442] The corresponding tetramethyl compound (**179**; R = Me), however, reacts with a boiling mixture of phosphorus pentachloride and oxychloride to yield a monochloro-derivative.

In contrast, some earlier work[443] includes the synthesis of the 4,4′-dichloroazoquinoline (**180**) from the corresponding 4,4′-diquinolone, and the structurally



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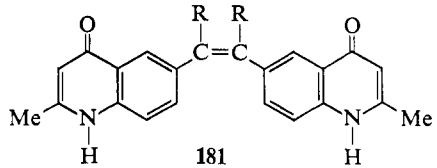
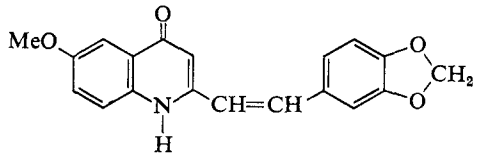


181

similar 6,6′-vinylenediquinolones (**181**; R = H and Me) readily yield the respective 4,4′-dichloro-compounds on treatment with hot phosphorus oxychloride.[444]

The styrylquinolone (**182**), prepared by condensing 6-methoxy-2-methyl-4-quinolone with piperonaldehyde, on chlorination with boiling phosphorus oxychloride yields the trichloro-derivative (**183**).[445]



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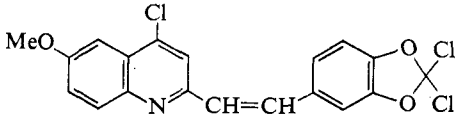
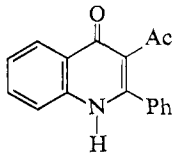


183

Other examples of the conversion of 4-quinolones which bear an unsaturated side chain, e.g. allyl, into the corresponding chloro compounds, are also known.[446, 447]

4-Quinolones bearing aryloxy-,[448] sulphonyloxy-,[392] heteroaryl,[449] nitro-,[417] aminocarbonyl,[450] alkylthio-,[451] acetamido-,[452] trifluoromethyl,[395, 453] acetyl,[454] benzoyl,[455] cyano-,[109] tertiary amino-,[456] formyl,[109] and secondary amino-substituents[457] have all been converted into their chloro derivative in high yield and are listed in Table 10. Many alkoxy-4-chloroquinolines, too numerous to mention here, have been prepared, and are also listed in Table 10.

There appear to be unexplained difficulties in preparing 3-acyl-4-chloroquinolines from the corresponding 3-acyl-4-quinolones. Singh and Nair[458] successfully prepared 3-acetyl-4-chloro-2-phenylquinoline (**185**; R = H) by heating the 4-quinolone (**184**)



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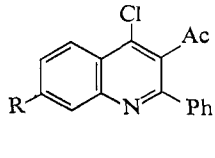
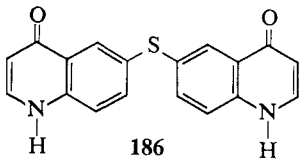


185

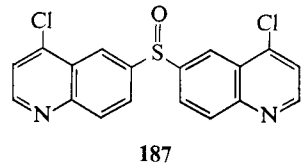
under reflux with phosphorus oxychloride for 1 hour. The 4,7-dichloro-derivative (**185**; R = Cl) has also been prepared under similar conditions.[454] Staskun,[459] however, was unable to repeat the former reaction and found that the 4-quinolone (**184**) remains unchanged even after heating with phosphorus oxychloride–pentachloride mixture at 150 °C for 2 hours. Bamberg and Johansson[460] have also experienced difficulty in preparing 3-acetyl-4-chloroquinolines.

Of interest is the observation of Price and his co-workers[461] who found that sulphide (**186**) with phosphorus pentachloride at 120 °C reacts exothermally to give, not the expected dichloro-sulphide, but the dichloro-sulphoxide (**187**).

4-Chloro-3-nitroquinoline, prepared by treating 3-nitro-4-quinolone with phosphorus oxychloride and phosphorus pentachloride at 140 °C, is reported to explode on attempted vacuum-distillation;[462] however, the melting point (122 °C) of this chloronitroquinoline is significantly lower than the value reported by other workers for this compound (see Table 10).

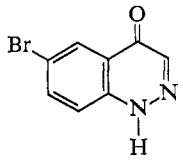


186



187

Several bromo-substituted 4-chloroquinolines have been prepared from the corresponding bromo-4-quinolones.[213, 452, 463, 464] Schofield and Swain[212] have examined these reactions in some detail since the structurally related bromo-4-cinnolones (e.g. **188**) readily undergo bromine–chlorine exchange when treated with phosphorus oxychloride–pentachloride mixture at 135 °C. The authors found, however, that the corresponding bromoquinolines do so only to a very small extent.



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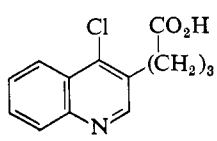

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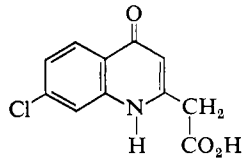


190

4-Quinolonecarboxylic acids give the 4-chloro-derivatives accompanied apparently by little, if any, of the acyl chloride.[465–467] 4-Quinolones possessing carboxyalkyl side chains are successfully converted into the 4-chloro-derivatives (e.g. **189**) by means of phosphorus halides.[468] However, the 2-quinoline acetic acid (**190**) reacts with phosphorus oxychloride to give only intractable tars.[469] The 4-chloro-derivative was finally prepared by heating the 4-quinolone (**190**) with phosphorus oxychloride in diethylene glycol diethyl ether solution.

Dehydrogenation and nuclear chlorination have been observed during the conversion of 4-quinolones into 4-chloroquinolines. Thus 2-methyl-[470] and 3-phenyl-4-quinolone,[471] on being heated with phosphorus pentachloride at 140 °C yield unidentified polychloroquinolines, while 8-chloro-1,2,3,4-tetrahydro-4-oxoquinoline reacts with phosphorus oxychloride in 1,2-dichloro-ethane in the presence of iodine at 90 °C to yield 4,8-dichloroquinoline.[472]

TABLE 10. Chloroquinolines by Reaction of 4-Quinolones and Hydroxyquinolines with Phosphorus Chlorides*

Chloroquinoline†	Yield (%)	M.p. (°C)	References
6-Acetamido-4-chloro-		157	553
6-Acetamido-4-chloro-3-(3-chlorobut-2-enyl)-2-methyl-		123	508
6-Acetamido-4-chloro-2-(*p*-chlorophenyl)-		257	551
6-Acetamido-4-chloro-3-(*p*-ethoxybenzyl)-2-methyl-	74	126	508
6-Acetamido-4-chloro-2-(*p*-methoxyphenyl)-	91	206, 241	551, 555
6-Acetamido-4-chloro-3-(*p*-methoxybenzyl)-2-methyl-	78	127	508
6-Acetamido-4-chloro-2-methyl-	75	210	452, 476, 552

* See footnote to Table 9, p. 389.
† See footnote to Table 1, p. 340.

TABLE 10 (*cont.*)

Chloroquinoline*	Yield (%)	M.p. (°C)	References
6-Acetamido-4-chloro-2-phenyl-	75	214	479, 551
Et 6-acetamido-4-chloro-2-carboxylate		231	553
6-Acetyl-4-chloro-	20	48	481
3-Acetyl-4-chloro-2-(*p*-methoxyphenyl)-		148	559
6-Acetyl-4-chloro-2-methyl-		137.5	560
3-Acetyl-4-chloro-2-phenyl-	100	140	458, 559
Et 6-allyloxy-4-chloro-3-carboxylate		174	528
2-Amino-4-chloro-	62	136	120
6-Amino-4-chloro-3-(3-chlorobut-2-enyl)-2-methyl-		97	508
6-Amino-4-chloro-3-(*p*-ethoxybenzyl)-2-methyl-	65	97	508
2-Amino-4-chloro-7-hydroxy-	97	226	120
2-Amino-4-chloro-7-methoxy-	87	200	120
6-Amino-4-chloro-3-(*p*-methoxybenzyl)-2-methyl-	63	105	508
6-(2-Amino-4-methyl-6-pyrimidyl)amino-4-chloro-		254	457
2-Anilino-4-chloro-		161	554
6-Anilino-4-chloro-	6	148	417, 484
6-Benzamido-4-chloro-3-(3-chlorobut-2-enyl)-2-methyl-		114	508
6-Benzoyl-4-chloro-	86	117	455
3-Benzoyl-4-chloro-2-methyl-		124	458, 559
Et 7-benzyloxy-4-chloro-3-carboxylate		121	528
Me 7-benzyloxy-4-chloro-3-carboxylate		120	528
7-Bromo-4-chloro-6-methoxy-		200	505
Et 6-(*n*-butoxy)-4-chloro-3-carboxylate		92	528
Me 6-(*n*-butoxy)-4-chloro-3-carboxylate		86	528
6-(*n*-Butoxy)-4-chloro-2-(*p*-methoxyphenyl)-	74.5	107	486
3-(*n*-Butyl)-4-chloro-6-methoxy-2-methyl-	74.5	86	507
3-(*n*-Butyl)-4-chloro-8-methoxy-2-methyl-		97	318, 506
4-Chloro-2-carboxylic acid		171	465
Et 4-chloro-2-carboxylate	74	86	518, 532
Et 4-chloro-3-carboxylate	92	46	124, 450, 460, 516, 517, 519–522
8-Chloro-5-carboxylic acid		231	531
3-(4-Chloro-3-quinolyl)butanoic acid		150	468
6-(4-Chloro-3-quinolyl)heptanoic acid		127	468
5-(4-Chloro-3-quinolyl)hexanoic acid		114	468
7-(4-Chloro-3-quinolyl)octanoic acid		143	468
4-(4-Chloro-3-quinolyl)pentanoic acid		147	468
4-Chloro-3-(3-chlorobut-2-enyl)-6-ethoxy-2-methyl-		69	508
Et 4-chloro-2-(*o*-chlorophenyl)-3-carboxylate	79	116	526
4-Chloro-3-(3-chlorobut-2-enyl)-6-methoxy-2-methyl-		78	508
4-Chloro-5-cyano-	24	156	533
4-Chloro-7-cyano-	27	167	533
4-Chloro-3-cyano-6-methoxy-	51	227	109
4-Chloro-6-cyano-2-methyl-	60	142	476
Et 4-chloro-6-cyano-3-methyl-2-carboxylate		123	532
4-Chloro-3-cyano-2-(methylthio)-	30	133	561
6-Di-(*n*-butylamino)-4-chloro-2-methyl-	40	179	456
4-Chloro-3-(3,3-dichloroallyl)-6-methoxy-		119	509

* See footnote to Table 1, p. 340.

TABLE 10 (*cont.*)

Chloroquinoline*	Yield (%)	M.p. (°C)	References
4-Chloro-6-diethylamino-2-methyl-	87	34	456
Me 4-chloro-6,7-di-isopropoxy-3-carboxylate		110	512
4-Chloro-5,8-dimethoxy-	78	111	502
4-Chloro-6,7-dimethoxy-	40	134	481
Et 4-chloro-6,7-dimethoxy-2-carboxylate		167	532
Et 4-chloro-6,7-dimethoxy-3-carboxylate		161	529
4-Chloro-5,8-dimethoxy-2-methyl-	69	123	503
Et 4-chloro-6,7-dimethoxy-3-methyl-2-carboxylate		112	532
4-Chloro-6,8-dimethoxy-2-methyl-		142	504
4-Chloro-5,8-dimethoxy-2-methyl-6-nitro-		193	545
4-Chloro-5,8-dimethoxy-2-methyl-7-nitro-		156.5	503
Et 4-chloro-6,7-dimethyl-3-carboxylate		87	529
4-Chloro-6-ethoxy-2,3-dimethyl-	97	116	511
4-Chloro-7-ethoxy-2,3-dimethyl-	100	96.5	511
4-Chloro-8-ethoxy-2,3-dimethyl-	97	110	511
4-Chloro-3-ethyl-2,8-dimethyl-6-nitro-	95	167	511
4-Chloro-5-methoxy-2,3-dimethyl-	100	150.5	511
4-Chloro-6-methoxy-2,3-dimethyl-	42	111, 285 ?	500, 501
4-Chloro-7-methoxy-2,3-dimethyl-	100	118	511
4-Chloro-8-methoxy-2,3-dimethyl-		133	506
4-Chloro-8-methoxy-2,3-dimethyl-6-nitro-	96	199	511
4-Chloro-2,3-dimethyl-6-nitro-	96	169	511
4-Chloro-2,8-dimethyl-6-nitro-	95	179	511
4-Chloro-6,7-di-(2-methylallyloxy)-		85	513
4-Chloro-6-dimethylamino-	60	230 d	481
4-Chloro-6-dimethylamino-2-methyl-	89	93	456, 476
5-Chloro-6,8-dinitro-		145.5	548
Et 3-chloro-6-ethoxy-3-carboxylate		99	517
4-Chloro-7-ethoxy-	53	76	484
4-Chloro-6-ethoxy-3-ethyl-2-methyl-	97	87	511
4-Chloro-8-ethoxy-3-ethyl-2-methyl-	98	79	511
4-Chloro-6-ethoxy-2-(*p*-methoxyphenyl)-	72.5	125	486
4-Chloro-8-ethoxy-2-(*p*-methoxyphenyl)-	70.5	93	486
4-Chloro-6-ethoxy-2-methyl-	85	64, 80	474, 497–499
4-Chloro-6-ethoxy-3-methyl-	89	72	464
4-Chloro-7-ethoxy-3-methyl-	84	94	485
4-Chloro-8-ethoxy-3-methyl-	99	64	482
4-Chloro-6-ethoxy-2-phenyl-	86	130	480
Et 4-chloro-3-(*p*-ethoxybenzyl)-2-methyl-6-carboxylate	85	90	527
4-Chloro-3-(*p*-ethoxyphenylamidocarbonyl)-	33	158	450
4-Chloro-3-ethyl-5-methoxy-2-methyl-	100	72.5	511
4-Chloro-3-ethyl-6-methoxy-2-methyl-	97	72	511
4-Chloro-3-ethyl-7-methoxy-2-methyl-	100	73	511
4-Chloro-3-ethyl-8-methoxy-2-methyl-		115	506
4-Chloro-3-ethyl-8-methoxy-2-methyl-6-nitro-	92	199	511
4-Chloro-3-ethyl-2-methyl-6-nitro-	96	135	511
Et 4-chloro-7-fluoro-3-carboxylate		65	529
4-Chloro-7-fluoro-6-methoxy-	59	154	510
4-Chloro-3-formyl-6-methoxy-	75	> 300	109
4-Chloro-2-furyl-6-methoxy-		77	449
4-Chloro-3-(*n*-heptyl)-7-methoxy-		Liq.	483
4-Chloro-3-(*n*-hexyl)-6-methoxy-2-methyl-	25	305 ?	507

TABLE 10 (*cont.*)

Chloroquinoline*	Yield (%)	M.p. (°C)	References
4-Chloro-3-(*n*-hexyl)-8-methoxy-2-methyl-		97, 103	318, 506
4-Chloro-4′-hydroxy-2,2′,8,8′-tetramethyl-6,6′-biquinoline	40	>360	442
4-Chloro-6-hydroxy-	60	77	494
4-Chloro-8-hydroxy-2-carboxylic acid		205	467
4-Chloro-8-hydroxy-2-methyl-	76	54.5	144
4-Chloro-8-hydroxy-2-methyl-5-nitro-		162	545
Et 4-chloro-7-iodo-3-carboxylate		113	522
4-Chloro-3-(isopentyl)-6-methoxy-2-methyl-	31	65	507
4-Chloro-6-(isopentyloxy)-2-(*p*-methoxyphenyl)-	67.5	109	486
4-Chloro-6-(isopropoxy)-2-(*p*-methoxyphenyl)-	63	105	486
4-Chloro-6-methoxy-	89	78, 81	405, 488–491
Et 4-chloro-6-methoxy-2-carboxylate		86, 94	515, 516
4-Chloro-7-methoxy-		83, 91	412, 487, 493
4-Chloro-8-methoxy-		81	58, 487
Et 4-chloro-8-methoxy-3-carboxylate		78	525
4-Chloro-6-methoxy-2-(*p*-methoxyphenyl)-	68	138	486
4-Chloro-8-methoxy-2-(*p*-methoxyphenyl)-	72	102	486
4-Chloro-6-methoxy-2-methyl-	83	93, 100	473, 474–476, 492
Et 4-chloro-6-methoxy-3-methyl-2-carboxylate		83	532
4-Chloro-6-methoxy-3-methyl-	92	88	464
4-Chloro-7-methoxy-2-methyl-		90	483
4-Chloro-7-methoxy-3-methyl-	78	78	321
4-Chloro-8-methoxy-2-methyl-		89	318
4-Chloro-8-methoxy-3-methyl-	90	84	482
4-Chloro-8-methoxy-5-methyl-	45	78	484
4-Chloro-8-methoxy-2-methyl-5-nitro-		116	545
4-Chloro-8-methoxy-2-methyl-6-nitro-	93	195 d	511
4-Chloro-8-methoxy-2-methyl-3-(*n*-pentyl)-		98, 102	318, 506
4-Chloro-8-methoxy-2-methyl-3-(*n*-propyl)-		123	506
β-(4-Chloro-6-methoxy-2-methyl-3-quinolyl)-propanoic acid		142	509
4-Chloro-6-methoxy-8-nitro-	82	178, 188	417, 481, 540
5-Chloro-6-methoxy-8-nitro-	95	205	547
4-Chloro-6-methoxy-2-phenyl-	90	110	477, 478–480
4-Chloro-6-methoxy-3-phenyl-		138.5	471
4-Chloro-7-methoxy-2-phenyl-	43	101.5	477
4-Chloro-8-methoxy-2-phenyl-	84	95, 179	479, 480
4-Chloro-6-methoxy-2-(trifluoromethyl)-	97	107	453
4-Chloro-6-methoxy-7-(trifluoromethyl)-	88	155	510
4-Chloro-3-(*p*-methoxyphenylamidocarbonyl)-	75	192	450
4-Chloro-3-(*p*-methoxybenzoyl)-2-methyl-		140	559
4-Chloro-2-(*p*-methoxyphenyl)-6-(*n*-propoxy)-	69.5	97	486
4-Chloro-2-(*p*-methoxyphenyl)-8-(*n*-propoxy)-	67.5	82	486
Et 4-chloro-2-methyl-6-carboxylate	95	114	476
Et 4-chloro-3-methyl-2-carboxylate		61	532

* See footnote to Table 1, p. 340.

TABLE 10 (*cont.*)

Chloroquinoline*	Yield (%)	M.p. (°C)	References
Et 4-chloro-8-methyl-3-carboxylate	94	41	530
Et 4-chloro-3-methyl-6-(methylthio)-2-carboxylate		88	532
4-Chloro-2-methyl-3-nitro-	90	94	470, 542
4-Chloro-2-methyl-6-nitro-	92	142, 148	423, 452, 476, 511, 541
4-Chloro-3-methyl-6-nitro-		171.5	543
4-Chloro-3-methyl-8-nitro-	92	125	543
4-Chloro-2-methyl-6-(*n*-propylethylamino)-	93	57	456
4-Chloro-2-methyl-6-(2-thiazolylamino)-3-(piperidinylmethyl)-		>300	558
4-Chloro-2-methyl-6-(2-thiazolylamino)-		207	557
4-Chloro-7-(*p*-tolylthio)-	83.8	60	514
Et 4-chloro-2-(methylthio)-3-carboxylate		42	451
Et 4-chloro-7-(methylthio)-3-carboxylate		82	529
4-Chloro-3-nitro-	90	120.5	462, 534–536
4-Chloro-6-nitro-	70	145	417, 534, 537,† 538, 539
4-Chloro-7-nitro-		175.5	390
Et 4-chloro-7-nitro-3-carboxylate		167	522
4-Chloro-8-nitro-	70	127	54, 481
7-Chloro-8-nitro-		185	549
8-Chloro-5-nitro-		145	546
4-Chloro-6-nitro-2-phenyl-		169	544
4-Chloro-6-nitro-3-phenyl-		172	471
Et 4-chloro-2-(*o*-nitrophenyl)-3-carboxylate	83	129	526
4-Chloro-6-nitro-2,3,8-trimethyl-	98	161	511
4-Chloro-6-phenoxy-	71	51	481
4-Chloro-7-phenoxy-	76	52.5	448, 481
Et 4-chloro-2-phenyl-3-carboxylate	53.5	103	440
Me 4-chloro-6-(*n*-propoxy)-3-carboxylate		149	528
4-Chloro-3-(*p*-tosyloxy)-		119	392
Et 4-chloro-7-(trifluoromethyl)-3-carboxylate	80	71	460
Et 4-chloro-3,6,8-trimethyl-2-carboxylate		81	532
4-Chloro-3,6,8-trinitro-		191	550
3,4-Dichloro-8-methoxy-	61	115.5	58
4,4′-Dichloro-6,6′-azoquinoline	42	274	443
Di-(4-chloro-6-quinolyl) sulphoxide	22.5	198	461
3-Acetyl-4,5- or 4,7-dichloro-2-phenyl-		125	454
4,5-Dichloro-8-methoxy-	6	127	484
4,5-Dichloro-3-nitro-	65	121	534
4,6-Dichloro-2-quinolone		138	411
Et 4,6-dichloro-2-carboxylate		112	532
Et 4,6-dichloro-3-carboxylate	89	77, 87	460, 519, 524
4,6-Dichloro-8-methoxy-2,3-dimethyl-	96	126	511
4,6-Dichloro-3-ethyl-8-methoxy-2-methyl-	93	139.5	511
4,6-Dichloro-8-methoxy-2-methyl-	99	142	511
Et 4,6-dichloro-3-methyl-2-carboxylate		70	532

† Reported in this paper as 4-chloro-3-nitroquinoline, but see, however, references 534 and 538.

TABLE 10 (*cont.*)

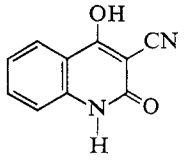
Chloroquinoline*	Yield (%)	M.p. (°C)	References
3-Acetyl-4,7-dichloro-	55	100	460
2-Amino-4,7-dichloro-	81	202	120
6-(Benzylthio)-4,7-dichloro-	90	137	481
4,7-Dichloro-2-carboxylic acid	70	183	466
Et 4,7-dichloro-2-carboxylate		81	466, 522
Et 4,7-dichloro-3-carboxylate	80	82	466, 522, 523
4,7-Dichloro-3-ethoxy-		97	493
4,7-Dichloro-5-methoxy-		135	495
4,7-Dichloro-6-methoxy-	36	162.5	494–496
4,7-Dichloro-8-methoxy-		91.5	487
4,7-Dichloro-3-nitro-	85	152	534
4,8-Dichloro-5-ethoxy-2,3-dimethyl-	100	106	511
4,8-Dichloro-5-methoxy-2,3-dimethyl-	100	131	511
4,8-Dichloro-3-ethyl-5-methoxy-2-methyl-	100	88.5	511
4,8-Dichloro-5-methoxy-2-methyl-	100	126.5	511
Et 2-(6-acetamido-4-chloro-2-methyl-3-quinolyl)-propanoate	92		556
Et 2-(4-chloro-3-quinolyl)acetate	86	53	460
Et 2-(4-chloro-6-methoxy-2-quinolyl)acetate	79	65	469
Et 2-(4-chloro-6-methyl-2-quinolyl)acetate	66	69.5	469
Et 2-[4-chloro-7-(trifluoromethyl)-3-quinolyl]-acetate	35	81	460
Et 2-(4,6-dichloro-3-quinolyl)acetate		56	460
Et 2-(4,7-dichloro-2-quinolyl)acetate	69	66	469
Me 2-(6-benzoyl-4-chloro-2-quinolyl)acetate	43	118	469
Me 3-(4-chloro-6-methoxy-2-methyl-3-quinolyl)-propanoate		104	509
Et 4,5,6-trichloro-3-methyl-2-carboxylate		98	532

* See footnote to Table 1, p. 340.

(*iii*) *Chloro-compounds from 4-Hydroxy-2-quinolones.* In the majority of cases 4-hydroxy-2-quinolones can be converted directly into the corresponding 2,4-dichloroquinolines by hot phosphorus halides and a list of 2,4-dichloroquinolines so prepared is given in Table 11.

2,4-Dichloroquinoline can be prepared by treating 4-hydroxy-2-quinolone with hot phosphorus oxychloride, whereas if the reaction is carried out by using an excess of phosphorus pentachloride then a trichloroquinoline (m.p. 105 °C) of unknown composition is obtained.[562]

Dichlorination of 4-hydroxy-2-quinolones is presumably a stepwise reaction but only in a few instances has this been demonstrated. Gabriel[563] found that 3-cyano-4-hydroxy-2-quinolone (**191**) yields the 2,4-dichloro-derivative (**192**) on treatment with boiling phosphorus pentachloride–oxychloride mixture for 1.5 hours. However, when



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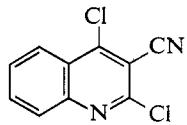

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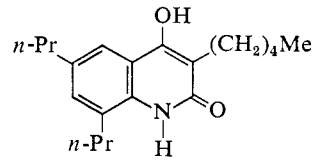
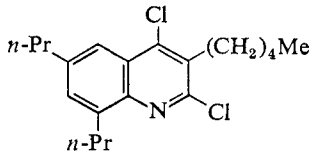


193

the reaction is interrupted after 30 minutes an uncharacterized monochlorocyanoquinolone (m.p. > 280 °C) can be isolated. The highly substituted 4-hydroxy-2-quinolone (**193**) gives a mixture of the required 2,4-dichloro-compound (20%) (**194**) and an unidentified monochloroquinolone, when treated with phosphorus oxychloride–pentachloride mixture at 100 °C.[564]



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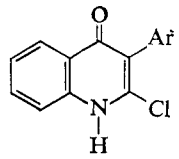

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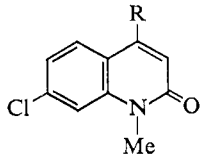
Another example of monochlorination is apparent in the work of de Diesbach and his co-workers[343] who found that 4-hydroxy-3-(*o*-nitrophenyl)-2-quinolone with phosphorus oxychloride either in dry benzene or mixed with phosphorus pentachloride gives the 2-chloro-4-quinolone (**195**; Ar = *o*-$NO_2C_6H_4$); however, with the latter mixture at 200 °C the 2,4-dichloro-derivative is produced. 7-Chloro-4-hydroxy-1-methyl-2-quinolone (**196**; R = OH) reacts with boiling phosphorus oxychloride to give the 4-chloro-2-quinolone (**196**; R = Cl).[565]



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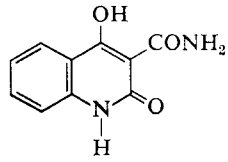

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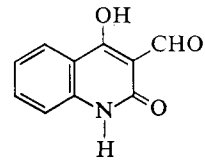

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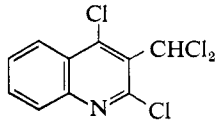
4-Hydroxy-2-quinolone-3-carboxamide (**197**) with phosphorus oxychloride at 100 °C in a sealed tube suffers dichlorination, and dehydration of the amide, to yield the dichloro-nitrile (**192**).[566] Other examples involving modification of a substituent group during the preparation of 2,4-dichloroquinolines have been noted. For example, 3-formyl-4-hydroxy-2-quinolone (**198**) reacts with hot phosphorus oxychloride to yield the 2,4-dichloro-3-(dichloromethyl)quinoline (**199**), together with a small amount of 4-chloro-3-(dichloromethyl)-2-quinolone;[567, 568] this result is in contrast to the behaviour of 3-formyl-6-methoxy-4-quinolone which under similar conditions yields only the 4-chloro-derivative.[109]



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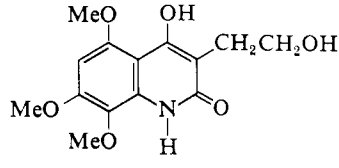
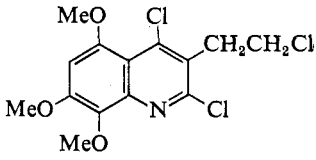


200

The 4-hydroxy-2-quinolone (**200**) reacts with boiling phosphorus oxychloride to give the trichloro-derivative (**201**).[569]

During studies on the synthesis of dictamnine (**202**) and related alkaloids several 2,4-dichloroquinolines have been synthesised.[570–574] In most cases the dichloro-compounds are obtained by treating furanoquinolones of type (**203**) with boiling



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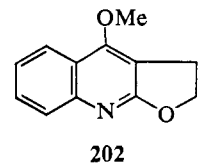

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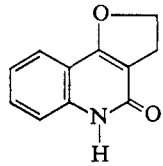

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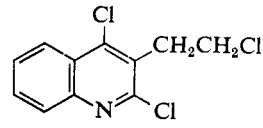
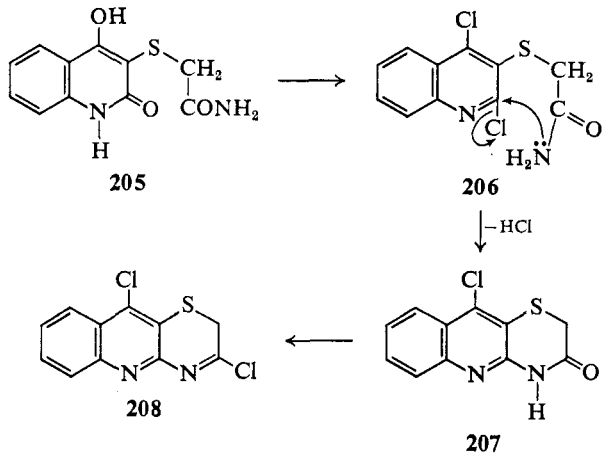


204

phosphorus oxychloride. Under these conditions cleavage of the dihydrofuran ring occurs and good yields of trichloroquinolines (e.g. **204**) are formed.

Treatment of the 4-hydroxy-2-quinolone (**205**) with phosphorus oxychloride in hot tetrachloroethane leads to formation of the dichlorothiazinoquinoline (**208**).[262] The reaction involves initial formation of the 2,4-dichloroquinoline (**206**) which then suffers intramolecular nucleophilic displacement of the 2-chloro-substituent by the

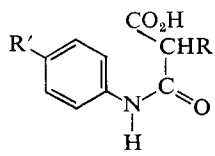


SCHEME 10

amide nitrogen as outlined in Scheme 10. The resulting lactam (**207**), with phosphorus oxychloride, undergoes chlorination to yield the final product (**208**).

The greater reactivity of the 2-chloro- over that of the 4-chloro-substituent (see Section II.2.C.b) ensures that none of the angular isomeric thiazinoquinoline is formed.

Monoanilides of malonic acid (e.g. **209**; R = R′ = H) undergo cyclization and trichlorination on treatment with phosphorus pentachloride in benzene.[575, 576] Presumably the reaction involves initial formation of a 4-hydroxy-2-quinolone which, under the reaction conditions, yields the 2,3,4-trichloroquinoline (e.g. **210**).



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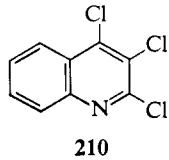

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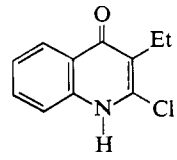


211

Substituted anilides (e.g. **209**; R = H, R′ = Me) behave similarly,[577, 578] whereas the anilide (**209**; R = Et, R′ = H) yields only 2-chloro-3-ethyl-4-quinolone (**211**).[579, 580]

Aromatic primary amines condense with malonic acid in the presence of phosphorus oxychloride to give 4-hydroxy-2-quinolones;[581, 582] however, prolonged treatment with the oxychloride leads to formation of the 2,4-dichloroquinoline.

TABLE 11. 2,4-Dichloroquinolines by Reaction of 4-Hydroxy-2-quinolones with Phosphorus Chlorides

2,4-Dichloroquinoline*	Yield (%)	M.p. (°C)	References
2,4-Dichloro-	93	67	562, 583–586
Et 2,4-dichloro-3-carboxylate	95	104	414
3-Benzyl-2,4-dichloro-5,8-dimethyl-	43	95	589
3-Benzyl-2,4-dichloro-6,8-dimethyl-	48	92	589
3-Benzyl-2,4-dichloro-7,8-dimethyl-		97	589
6-Bromo-2,4-dichloro-3-(3-chlorobut-2-enyl)-	68	152	596
6-Bromo-2,4-dichloro-3-(*p*-methoxybenzyl)-	70	126	596
3-(*n*-Butyl)-2,4-dichloro-6-methoxy-	77	76	274
6-(*n*-Butyl)-2,4-dichloro-3,8-di-(*n*-propyl)-			564
3-(*n*-Butyl)-2,4-dichloro-6,8-di-(*n*-propyl)-			564
2,4-Dichloro-3-(2-chloroethyl)-	59	112	414, 572, 573
2,4-Dichloro-3-(2-chloroethyl)-7,8-dimethoxy-		118	571
2,4-Dichloro-3-(2-chloroethyl)-6-methoxy-		118	590
2,4-Dichloro-3-(2-chloroethyl)-7-methoxy-		121	574, 590, 591
2,4-Dichloro-3-(2-chloroethyl)-8-methoxy-	58	109	570, 573
2,4-Dichloro-3-(2-chloroethyl)-5,7,8-trimethoxy-		140	569
2,4-Dichloro-3-(3-chlorobut-2-enyl)-6-carboxylic acid	69	135	592
Et 2,4-dichloro-3-(3-chlorobut-2-enyl)-6-carboxylate	73	103	592
2,4-Dichloro-3-cyano-		169	563, 566
2,4-Dichloro-3-(dichloromethyl)-		126	567, 568
2,4-Dichloro-3-(2-ethoxyethyl)-6,7-dimethoxy-		139	588
2,4-Dichloro-5,8-dimethyl-		80.5	581
2,4-Dichloro-6,8-dimethyl-	87	115.5	589
2,4-Dichloro-7,8-dimethyl-		73	589

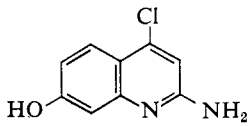
* See footnote to Table 1, p. 340.

TABLE 11 (*cont.*)

2,4-Dichloroquinoline*	Yield (%)	M.p. (°C)	References
2,4-Dichloro-8-(*n*-pentyl)-3,6-di-(*n*-propyl)-			564
2,4-Dichloro-6-(*n*-pentyl)-3,8-di-(*n*-propyl)-			564
2,4-Dichloro-3-(*n*-pentyl)-6,8-di-(*n*-propyl)-	20		564
2,4-Dichloro-3-(*p*-ethoxybenzyl)-	72	106	596
2,4-Dichloro-3-(*p*-ethoxybenzyl)-6-methyl-	69	112	596
2,4-Dichloro-3-(2-ethoxyethyl)-8-methoxy-	99	74	573
2,4-Dichloro-3-ethyl-	88		399
2,4-Dichloro-6-methoxy-		175	582
2,4-Dichloro-8-methoxy-		92	411, 586
2,4-Dichloro-8-methoxy-3-(3-methylbutyl)-	98	74	587
2,4-Dichloro-3-(*p*-methoxybenzyl)-	76	87	596
2,4-Dichloro-3-methyl-		84, 91	399, 437
2,4-Dichloro-5-methyl-		132	595
2,4-Dichloro-6-methyl-	70	95	582, 589
2,4-Dichloro-7-methyl-		134	582
2,4-Dichloro-8-methyl-	72	86	582, 589
2,4-Dichloro-3-nitro-		102	563
2,4-Dichloro-3-(*o*-nitrophenyl)-		142	343
2,4-Dichloro-3-phenyl-		94	357
2,4,5,8-Tetrachloro-		134	582
2,3,4-Trichloro-		107.5	575, 576
2,3,4-Trichloro-6-methyl-		134	577, 578
2,3,4-Trichloro-8-methyl-		112.5	577
2,4,*x*-Trichloro-		105	562
2,4,6-Trichloro-		126	582, 593
2,4,6-Trichloro-3-(3-chlorobut-2-enyl)-	73	148	596
2,4,6-Trichloro-3-(*p*-methoxybenzyl)-	66	84	596
2,4,7-Trichloro-	84	107.5	582, 585, 593, 594
2,4,8-Trichloro-		104	593

(*iv*) *Chloro-compounds from Various Hydroxyquinolines.* As expected hydroxyquinolines in which the hydroxyl group is borne at the 3-position, or in the carbocyclic ring, of the quinoline nucleus yield chloroquinolines on treatment with phosphorus halides only when an electron-withdrawing group is present at the *ortho*- and/or the *para*-position to the hydroxyl function. For example, 2-amino-7-hydroxy-4-quinolone yields only the 4-chloro-derivative (**212**) when treated with hot phosphorus oxychloride.[120] Other examples of this type have also been recorded.[144, 467]

8-Hydroxy-5-nitroquinoline and 7-hydroxy-8-nitroquinoline, however, react readily with phosphorus pentachloride to give 8-chloro-5-nitro-[546] and 7-chloro-8-nitro-quinoline,[549] respectively, and other hydroxynitroquinolines behave similarly.[547, 548] One instance of the replacement of a hydroxyl group *para* to a carboxylic



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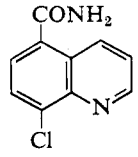

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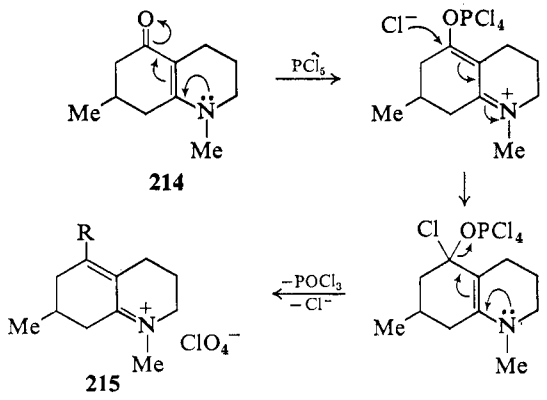
* See footnote to Table 1, p. 340.

acid has been reported:[531] the reaction, which requires forcing conditions (phosphorus oxychloride–pentachloride mixture under reflux for 5 hours), involves the conversion of 8-hydroxyquinoline-5-carboxylic acid into 8-chloroquinoline-5-carboxylic acid which is isolated as the amide (**213**). In a like manner 8-hydroxyquinoline-5-sulphonic acid is converted by phosphorus pentachloride into 8-chloroquinoline-5-sulphonyl chloride.[158] Melting points for these chloroquinolines are given in Table 10 (p. 393).

The octahydro-1-methyl-5-quinolone (**214**) behaves as a typical enamine and on treatment with phosphorus pentachloride in boiling benzene undergoes chlorination,



SCHEME 11

as indicated in Scheme 11, to give the 5-chloro-compound, which is isolated as the perchlorate (**215**; R = Cl).[597]

(*v*) *Addendum.* Amongst the 4-chloroquinolines prepared by the methods described in the preceding sections are several for which large discrepancies are apparent in the reported melting points. These anomalies are spread throughout the literature and an attempt has been made to gather together in this Section these conflicting values.

3,4-Dichloro-2-methylquinoline is cited[598] as melting at 67 °C, whereas an earlier report[599] lists its melting point as 322 °C. The former workers emphasize that such a high melting point is completely uncharacteristic of dichloroalkyl quinolines (see Table 50, p. 727), but they offer no alternative structure for the higher-melting compound. It must be pointed out, however, that the chlorine analysis figure quoted by the early workers is some 1.3% higher than that required for a compound having the dichloromethylquinoline structure.

Other examples of variations in melting point are to be found with (*a*) ethyl 4-chloroquinoline-3-carboxylate for which melting points of 37 °C[516] and 51 °C[517] have been reported; (b) 4-chloro-6-ethoxy-2-methylquinoline, m.p. 64 °C[474] and 78 °C;[497] (c) 2-benzyl-4-chloroquinoline, m.p. 51 °C[600] and 135 °C;[601] and (d) 6-acetamido-4-chloroquinoline, m.p. 224 °C[602, 603] and 157 °C.[553]

A series of 2,3-dialkyl-4-chloro-6-methoxyquinolines have been reported[501, 507] some of which exhibit anomalously high melting points. For example, one of the compounds, 4-chloro-6-methoxy-2,3-dimethylquinoline, is stated to have a melting point of 285 °C as against the value of 111 °C reported by other workers.[500] Surprisingly in none of these examples do the later authors comment on the large difference.

3,4,7-Trichloroquinoline (m.p. 84.4 °C) as reported in a patent[604] appears, on the basis of comparison of the melting points of 3,4,5-trichloro- (m.p. 85 °C) and 3,4,7-trichloroquinoline (m.p. 114.5 °C) (as reported by Surrey and Cutler[122]), to be in fact the 3,4,5-trichloro-isomer. However, in the absence of definite structural proof no firm decision as to which isomer is which can be made.

c. Bromoquinolines by Reaction of Quinolones with Phosphorus Bromides. Examples of the formation of bromoquinolines by the action of phosphorus bromides on quinolones are far less numerous than for the corresponding chloro-compounds.

An early example involves heating 2-quinolone with phosphorus pentabromide at 130 °C under an atmosphere of carbon dioxide, whereupon 2-bromoquinoline is obtained.[605] Alternatively 2-bromoquinoline may be prepared by heating 2-quinolone with phosphorus tribromide at 180 °C.[606] Quinoline is also formed in this reaction, and at 200 °C appears to be the major product. 4-Bromoquinoline has been prepared by the action of phosphorus pentabromide on 4-quinolone at 130 °C, but in this case nuclear bromination also occurs and 3,4-dibromoquinoline is isolated as a by-product.[171] Kaslow and Marsh,[607] however, prepared several 2- and 4-bromoquinolines from the 4-quinolones using phosphorus pentabromide and only in one instance, with 2-methyl-4-quinolone, was dibromination observed; the dibromo-compound was tentatively identified as 3,4-dibromo-2-methylquinoline.

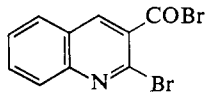
4-Hydroxyquinoline *N*-oxide with an excess of phosphorus tribromide at 100 °C yields mainly 4-quinolone.[608] This is in direct contrast to the action of phosphorus trichloride which brings about deoxygenation and chlorination to give 4-chloroquinoline in 30% yield.[436]

Nakano and his co-workers in a series of papers[609–614] report the synthesis of a host of 2-bromoquinolines by treating substituted 2-quinolones with phosphorus oxybromide at temperatures of around 140 °C. Substituents include alkoxy-, alkyl, and aryl, and in every case high yields of the 2-bromoquinoline are obtained. Alkyl- and aryl-substituted 2-bromoquinolines have also been synthesized by treating the quinolone with phosphorus tribromide–oxybromide mixtures.[615–617] Several dibromoquinolines have been prepared similarly from bromo-2-quinolones.[118, 284, 618]

4-Hydroxy-2-quinolone reacts with phosphorus pentabromide to give what is thought to be, 2,4-dibromoquinoline.[127] Similar reactions have also been recorded with 3-bromo-4-hydroxy-2-quinolone, and with the unknown bromo-compound obtained by brominating 4-hydroxy-2-quinolone in cold formic acid. The structure of these products, however, must remain in doubt since the melting points given for the dibromoquinolines are vastly different from those recorded previously. For example, 2,4-dibromoquinoline is reported to melt at 265 °C, whereas other workers[619] quote a melting point of 93 °C, a figure in accord with the melting points of many other known dibromoquinolines (see Table 48, p. 725).

Little study has been carried out on the relative merits of phosphorus penta-, tri-, and oxy-bromide as agents for the conversion of quinolones into bromoquinolines. Kaslow and Lawton,[213] however, report that whereas phosphorus oxybromide converts 2-phenyl-4-quinolones into the corresponding 4-bromoquinolines, the use of phosphorus pentabromide causes nuclear bromination. The orientation of these polybromo-compounds has not been elucidated, but bromination is presumed to have taken place at the 3-position. An instance of bromination at the 3-position was noted earlier by Claus and his co-workers,[131, 165] who isolated 3,5,7-tribromo-8-hydroxyquinoline from the reaction of 5,7-dibromo-8-hydroxyquinoline with phosphorus pentabromide.

2-Quinolone-3-carboxylic acid with phosphorus oxybromide gives the expected 2-bromoquinoline-3-carbonyl bromide (**216**).[620, 621] 8-Methoxy-4-quinolone-2-carboxylic acid, however, behaves differently with boiling phosphorus oxybromide in



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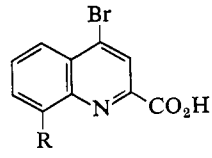

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that a mixture of 4-bromo-8-methoxyquinoline-2-carboxylic acid (**217**; R = MeO) and the unexpected demethylated product 4-bromo-8-hydroxyquinoline-2-carboxylic acid (**217**; R = OH) is formed.[304]

The octahydro-5-quinolone (**214**) reacts with phosphorus tribromide in an identical manner to that described earlier for the preparation of 5-chloro-compound (**215**; R = Cl), to give the corresponding 5-bromo-derivative (**215**; R = Br).

Further detail is given in Table 12.

TABLE 12. Bromoquinolines by Reaction of Quinolones with Phosphorus Bromides

Bromoquinoline	Yield (%)	M.p. (°C)	References
2-BROMO-			
2-Bromo-	81	49	605, 606, 622
2-Bromo-3-carbonyl bromide		Liq.	621
2-Bromo-3-carboxamide		208	620
Et 2-bromo-3-carboxylate	64	77.5	621
Me 2-bromo-3-carboxylate		94.5	621
2-Bromo-4-carboxylic acid		176	621
2-Bromo-6-chloro-4-methyl-	60	167	614
2-Bromo-7-chloro-4-methyl-	75	123	614
2-Bromo-8-chloro-4-methyl-	80	99	614
2-Bromo-5,8-dimethoxy-4-methyl-	51.5	125	611
2-Bromo-3,4-dimethyl-		139	610
2-Bromo-4,6-dimethyl-		113	610
2-Bromo-4,7-dimethyl-		38	610
2-Bromo-4,8-dimethyl-	81	65.5	610
2-Bromo-4,6-diphenyl-	66	168.5	614
2-Bromo-6-ethoxy-4-methyl-	63	149	611
2-Bromo-6-ethoxy-4-phenyl-	61	126	613
2-Bromo-7-ethoxy-4-methyl-	76	116	611
2-Bromo-7-ethoxy-4-phenyl-	81	96.5	613
2-Bromo-8-ethoxy-4-methyl-	64	72	612
2-Bromo-8-ethoxy-4-phenyl-	94	125	613
2-Bromo-4-ethyl-	67.5	81	612
2-Bromo-4-ethyl-6-methyl-	67.5	117	612
2-Bromo-4-ethyl-7-methyl-	75	76	612
2-Bromo-4-ethyl-8-methyl-	92	53	612
2-Bromo-8-ethyl-	80	27	617
2-Bromo-6-methoxy-4-methyl-	86	147	607, 609

TABLE 12 (*cont.*)

Bromoquinoline	Yield (%)	M.p. (°C)	References
2-Bromo-6-methoxy-4-phenyl-	80	111	613
2-Bromo-7-methoxy-4-methyl-	79	114	611
2-Bromo-7-methoxy-4-phenyl-	84	128	613
2-Bromo-8-methoxy-4-methyl-	82	126	611
2-Bromo-8-methoxy-4-phenyl-	80	130	613
2-Bromo-4-methyl-	72	81.5	607, 610
2-Bromo-4-methyl-5-phenyl-	26	165	612
2-Bromo-6-methyl-		118	616
2-Bromo-6-methyl-4-phenyl-	94	101	609
2-Bromo-7-methyl-4-phenyl-	82	67	609
2-Bromo-8-methyl-	65	79	617
2-Bromo-8-methyl-4-phenyl-	58	70.5	609
2-Bromo-4-phenyl-		95	609, 615
2-Bromo-8-phenyl-	81	Liq.	617
4-BROMO-			
4-Bromo-			171
2-Benzyl-4-bromo-3-phenyl-		126.5	625
Et 4-bromo-2-carboxylate	58	92	607
4-Bromo-3-(2-bromoethyl)-8-hydroxy-2-methyl-		115	624
4-Bromo-3-(2-bromoethyl)-2-methyl-		96	624
4-Bromo-2-(*p*-bromophenyl)-	91	120.5	213
4-Bromo-6-chloro-2-(trifluoromethyl)-	90	120	627
4-Bromo-6,8-dichloro-2-(trifluoromethyl)-	97	76	627
4-Bromo-6,8-dimethyl-2-(trifluoromethyl)-	95	116	627
4-Bromo-8-hydroxy-2-carboxylic acid		200	304
4-Bromo-6-methoxy-2-methyl-		118	626
4-Bromo-6-methoxy-2-(trifluoromethyl)-	92	125	627
4-Bromo-8-methoxy-2-carboxylic acid		135	304
4-Bromo-2-methyl-	25	Liq.	607
4-Bromo-6-methyl-2-(trifluoromethyl)-	91	71	627
4-Bromo-2-phenyl-	83.5	90.5	213
4-Bromo-2-(trifluoromethyl)-	80	39	627
DIBROMO-			
2,3-Dibromo-		97	284
2,4-Dibromo-		93, 265 ?	127, 619
2,5-Dibromo-		86	618
2,6-Dibromo-		167	618
2,7-Dibromo-		134	618
3,4-Dibromo-	76	82	118, 171
3,4-Dibromo-2-(*p*-bromophenyl)-	91	223	623
3,4-Dibromo-2-phenyl-	88	150	623
4,6-Dibromo-2-phenyl-	70	122	213
TRIBROMO-			
2,3,*x*-Tribromo-		174	284
2,3,4-Tribromo-		288 ?	127
2,4,*x*-Tribromo-		276 ?	127
3,5,7-Tribromo-8-hydroxy-		169	131, 165

d. HALOQUINOLINES BY THE ACTION OF PHOSPHORUS HALIDES ON 1-ALKYLQUINOLONES. The preparation of haloquinolines by treating a 1-alkylquinolone, usually 1-methyl, with phosphorus halides was developed mainly by Fischer. The method is particularly useful for the synthesis of 2-haloquinolines, whereas only isolated examples of 4-haloquinoline formation by this route have appeared.[124, 129]

1-Methyl-2-quinolones are readily prepared by potassium ferricyanide oxidation of the 1-methylquinolinium iodide. Although no comparative work has been carried out, the method, in general appears to be inferior,[418, 425] as a preparative route to haloquinolines, to the action of phosphorus halides on unsubstituted quinolones.

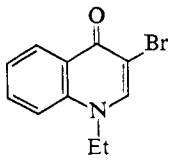
In his early investigations Fischer obtained 2-chloroquinoline by heating 1-methyl- or 1-ethyl-2-quinolone with phosphorus oxychloride–pentachloride mixture at 140 °C for 8 hours.[628] Later workers have shown,[629] however, that the reaction proceeds more readily and in higher yield (90%) at higher temperatures (175 °C). Fischer found[630] that a solution of phosphorus halide in a high-boiling inert solvent is effective in shortening the reaction time. For example, 1-methyl-2-quinolone with phosphorus pentachloride in boiling *p*-dichlorobenzene (4 hours) gives 2-chloroquinoline in good yield (90%). 4,7-Dichloro-1-methyl-2-quinolone is recovered unchanged after being heated (1.5 hours) with phosphorus pentachloride in *p*-dichlorobenzene at 170 °C;[565] however, the reaction is successful with an excess of phosphorus halide in *p*-dichlorobenzene in a sealed tube at 225 °C for 6 hours. Similar difficulties were experienced with 4-chloro-1-methyl-2-quinolone. 4-Hydroxy-1-methyl-2-quinolone reacts under reflux with phosphorus oxychloride–pentachloride mixture to give mainly 4-chloro-1-methyl-2-quinolone plus a small amount of 2,4-dichloroquinoline.[565]

Beyond these few examples little variation in the reaction conditions have been recorded, and many examples of the formation of alkyl-,[259, 631] halo-,[632, 633] nitro-,[424, 630, 632] alkoxy-,[633, 634] carboxy-[635] and ethoxycarbonyl-[636] substituted 2-chloroquinolines have been reported. A list of chloroquinolines prepared by this method is given in Table 13.

1,6,8-Trimethyl-2-quinolone reacts normally with a 1 : 3 phosphorus pentachloride–oxychloride mixture at 140 °C to yield 2-chloro-6,8-dimethylquinoline.[259] However, in the presence of an excess of phosphorus pentachloride an unidentified dichloro-compound (m.p. 109 °C) is formed.

Bromoquinolines are accessible by treating 1-methyl-2-quinolones with phosphorus bromide either alone or in an inert solvent. 1-Methyl-2-quinolone reacts at 140 °C with phosphorus pentabromide to give 2-bromoquinoline;[631] 1,6-dimethyl-2-quinolone reacts with phosphorus pentabromide in boiling *p*-dibromobenzene to give 2-bromo-6-methylquinoline,[630] while 3-bromo-1-ethyl-4-quinolone (**218**) with boiling phosphorus tribromide yields 3,4-dibromoquinoline.[124]

It has been shown that 3-dimethylamino-4-hydroxy-1-methyl-2-quinolone (**219**; R = OH) when heated under reflux with a six-fold excess of phosphous oxychloride, yields only the monochloro-derivative (**219**; R = Cl).[129] Other 1-alkyl-4-hydroxy-2-quinolones behave in a similar manner.



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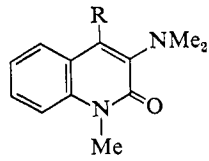

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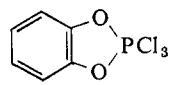

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Balli and Schelz[637] have prepared a series of 2-chloroquinolines by treating the corresponding 1-methyl-2-quinolone with a solution of 2,2,2-trichloro-2,2-dihydro-1,3,2-benzodioxaphosphole (**220**) in boiling *o*-dichlorobenzene. The use of this reagent as a method of converting phenols into aryl halides has been described by Gross and Gloede.[638]

TABLE 13. Haloquinolines by Reaction of 1-Alkylquinolones with Phosphorus Halides

Haloquinoline*	Method of preparation (yield)	References
BROMO-		
2-Bromo-	1-Me-2-Q'one; PBr_5 at 140 °C	631
2-Bromo-6-methyl-	1,6-diMe-2-Q'one; PBr_5 in *p*-diBrC_6H_4 under reflux for 2 h	630
6-Bromo-2-chloro-	1-Me-6-Br-2-Q'one; $POCl_3/PCl_5$ for 4 h at 180 °C	633
6-Bromo-2-chloro-8-ethyl-	1-Me-6-Br-8-Et-2-Q'one; $PCl_5/POCl_3$ at 135 °C for 3 h	653
6-Bromo-2-chloro-8-ethyl-5-nitro-	1-Me-6-Br-8-Et-5-NO_2-2-Q'one; $PCl_5/POCl_3$ at 135 °C for 3 h	653
6-Bromo-2-chloro-8-methyl-	1-Me-6-Br-8-Me-2-Q'one; $POCl_3/PCl_5$ at 175 °C for 4.5 h (76%)	647
6-Bromo-2-chloro-8-methyl-5-nitro-	1-Me-6-Br-8-Me-5-NO_2-2-Q'one; $PCl_5/POCl_3$ at 150 °C for 1.75 h (69%)	647
8-Bromo-2-chloro-5-ethyl-	1-Me-8-Br-5-Et-2-Q'one; $POCl_3/PCl_5$ at 130 °C for 2 h (5.9%)	425
8-Bromo-2-chloro-5-ethyl-6-nitro-	1-Me-8-Br-5-Et-6-NO_2-2-Q'one; as above (1.1%)	425
8-Bromo-2-chloro-6-ethyl-	1-Me-8-Br-6-Et-2-Q'one; $PCl_5/POCl_3$ under reflux (31%)	644
8-Bromo-2-chloro-6-ethyl-5-nitro-	1-Me-8-Br-6-Et-5-NO_2-2-Q'one; as above (87%)	644
8-Bromo-2-chloro-6-methyl-	1-Me-8-Br-6-Me-2-Q'one; $PCl_5/POCl_3$ at 125 °C for 1.25 h (43%)	650
8-Bromo-2-chloro-6-methyl-5-nitro-	1-Me-8-Br-6-Me-5-NO_2-2-Q'one; as above (88%)	650
2-Chloro-	1-Me- or 1-Et-2-Q'one; (i) $PCl_5/POCl_3$ at 140 °C for 8 h (90%); (ii) PCl_5/*p*-diClC_6H_4 under reflux for 4 h	628, 629, 630, 634
2-Chloro-4-carboxylic acid	1-Me-2-Q'one-4-CO_2H; PCl_5 at 120 °C	635
Et 2-chloro-4-carboxylate	1-Me-2-Q'one-4-CO_2Et; $PCl_5/POCl_3$ at 160 °C for 4 h (83%)	368, 636
2-Chloro-3,4-diethyl-	1,3,4-triEt-2-Q'one; PCl_5	643
2-Chloro-6,8-dimethyl-	1,6,8-triMe-2-Q'one; $POCl_3/PCl_5$ for 45 min at 140 °C	259
2-Chloro-6-ethoxy-8-nitro-	1-Me-6-EtO-8-NO_2-2-Q'one; $PCl_5/POCl_3$ at 135 °C for 3 h (77%)	654
CHLORO-		
2-Chloro-6-methoxy-	1-Me-6-MeO-2-Q'one; $POCl_3/PCl_5$ at 175 °C for 9 h	634
2-Chloro-6-methoxy-8-nitro-	1-Me-6-MeO-8-NO_2-2-Q'one; $PCl_5/POCl_3$ at 135 °C for 3 h (71%)	654
2-Chloro-8-methoxy-	1-Me-8-MeO-2-Q'one; $POCl_3/PCl_5$ for 4 h at 180 °C	633

* See footnote to Table 1, p. 340.

TABLE 13 (*cont.*)

Haloquinoline*	Method of preparation (yield)	References
2-Chloro-6-methyl-	1,6-diMe-2-Q'one; (i) as above at 175 °C for 8 h; (ii) PCl_5/*p*-diClC_6H_4 at 140 °C for 2 h	637, 640–642
2-Chloro-6-methyl-8-nitro-	1,6-diMe-8-NO_2-2-Q'one; PCl_5 at 180 °C	641, 649
2-Chloro-7-methyl-	1,7-diMe-2-Q'one; $PCl_5/POCl_3$ at 140 °C for 4 h	652
2-Chloro-7-methyl-8-nitro-	1,7-diMe-8-NO_2-2-Q'one; $PCl_5/POCl_3$ at 125 °C for 1.25 h	652
2-Chloro-8-methyl-	1,8-diMe-2-Q'one; $POCl_3/PCl_5$ for 1 h at 150 °C or PCl_5 at 130 °C	259, 633
2-Chloro-8-methyl-6-nitro-	1,8-diMe-6-NO_2-2-Q'one; $PCl_5/POCl_3$ at 140 °C for 4 h	418
2-Chloro-5-nitro-	1-Me-5-NO_2-2-Q'one; PCl_5 in *p*-diClC_6H_4 at 170 °C for 2 h	424
2-Chloro-6-nitro-	1-Me-6-NO_2-2-Q'one; PCl_5 in *p*-diClC_6H_4 at 150 °C for 3 h	630
2-Chloro-8-nitro-	1-Me-8-NO_2-2-Q'one; PCl in *p*-diClC_6H_4 at 170 °C for 2 h	651
4-Chloro-3-dimethylamino-6-methoxy-1-methyl-2-quinolone	1-Me-4-HO-3-Me_2N-6-MeO-2-Q'one; $POCl_3$ under reflux for 1 h	129
4-Chloro-3-dimethylamino-1-methyl-2-quinolone	1-Me-4-HO-3-Me_2N-2-Q'one; $POCl_3$ under reflux for 1 h	129
4-Chloro-3-dimethylamino-1-(*n*-propyl)-2-quinolone	1-(*n*-Pr)-4-HO-3-Me_2N-2-Q'one; $POCl_3$ under reflux for 1 h	129
DIHALO-		
2,6-Dibromo-	1-Me-6-Br-2-Q'one; PBr_5 at 160 °C	633
3,4-Dibromo-	1-Et-3-Br-4-Q'one; PBr_3 under reflux for 1 h	124
2,4-Dichloro-	1-Me-4-Cl-2-Q'one; PCl_5 at 175 °C	565
2,5-Dichloro-[a]	1-Me-5-Cl-2-Q'one; $POCl_3/PCl_5$ for 4 h at 180 °C	633
2,6-Dichloro-	1-Me-6-Cl-2-Q'one; $POCl_3/PCl_5$ for 4 h at 180 °C	633
2,6-Dichloro-8-ethyl-	1-Me-6-Cl-8-Et-2-Q'one; $POCl_3/PCl_5$ at 135 °C for 3 h (41%)	632
2,6-Dichloro-8-ethyl-5-nitro	1-Me-6-Cl-8-Et-5-NO_2-2-Q'one; as above	632
2,6-Dichloro-8-methyl-	1-Me-6-Cl-8-Me-2-Q'one; $POCl_3/PCl_5$ at 175 °C for 4.5 h (78%)	647
2,6-Dichloro-8-methyl-5-nitro-	1-Me-6-Cl-8-Me-5-NO_2-2-Q'one; as above at 135 °C for 3.5 h (73%)	647
2,8-Dichloro-	1-Me-8-Cl-2-Q'one; $POCl_3/PCl_5$ for 4 h at 180 °C (77%)	639
2,8-Dichloro-6-ethyl-	1-Me-8-Cl-6-Et-2-Q'one; PCl_5 at 165 °C for 2.5 h (57%)	645
2,8-Dichloro-6-ethyl-5-nitro-	1-Me-8-Cl-6-Et-5-NO_2-2-Q'one; as above (61%)	645

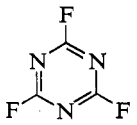
[a] Listed as the 2,7-dichloro-isomer, but see reference 366.

TABLE 13 (*cont.*)

Haloquinoline*	Method of preparation (yield)	References
2,8-Dichloro-6-methyl-	1-Me-8-Cl-6-Me-2-Q'one; $POCl_3/PCl_5$ at 175 °C for 4.5 h (62.5%)	646
2,8-Dichloro-6-methyl-5-nitro-	1-Me-8-Cl-6-Me-5-NO_2-2-Q'one; as above (19%)	646
TRIHALO-		
2,6,8-Tribromo-	1-Me-6,8-diBr-2-Q'one; PBr_5 at 130 °C for 1 h (90%)	655
2,3,6-Trichloro-	1-Me-3,6-diCl-2-Q'one; PCl_5 heat under reflux for 15 min	55
2,4,7-Trichloro-	1-Me-4,7-diCl-2-Q'one; PCl_5/p-diClC_6H_4 at 225 °C for 6 h	565
2,6,8-Trichloro-	1-Me-6,8-diCl-2-Q'one; PCl_5	648
2,6,8-Trichloro-5-nitro-	1-Me-6,8-diCl-5-NO_2-2-Q'one; as above	648

* See footnote to Table 1, p. 340.

e. Reactions of Quinolones with Various Halogenating Agents. What appears to be the only report of the preparation of a fluoroquinoline by the action of a fluorinating agent on a quinolone is contained in a British patent,[656] which indicates that 4-methyl-2-quinolone and 2-methyl-4-quinolone with 2,4,6-trifluoro-1,3,5-triazine (cyanuric fluoride) **221**) at 175 °C give 2-fluoro-4-methyl- and 4-fluoro-2-methyl-quinoline, respectively. Under the same conditions 4-hydroxy-2-quinolone undergoes difluorination to yield 2,4-difluoroquinoline (**222**).



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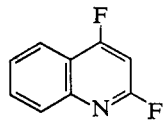

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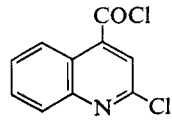

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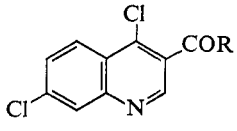
Thionyl chloride has been used on occasions to bring about the conversion of quinolones into chloroquinolines. Early work[657] shows that 2-quinolone-4-carboxylic acid on treatment with thionyl chloride at 100 °C yields the chloro-acid chloride (**223**) (80%). 3-Methyl-2-quinolone-4-carboxylic acid[658] and 3-benzyl-4-quinolone-7-carboxylic acid[659] behave similarly, whereas 3-ethyl-2-quinolone-4-carboxylic acid yields only the acid chloride.[657] The reaction time, however, in the latter example is much shorter (15 minutes) than in the former cases (5 hours). The anilide (**224**; R = *m*-ClC_6H_4NH) can be prepared by treating the corresponding 4-quinolone-carboxylic acid with thionyl chloride and then allowing the acyl chloride (**224**; R = Cl) so formed to react with *m*-chloroaniline.[660]



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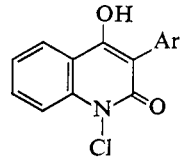

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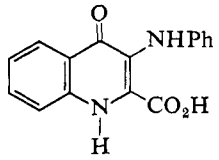
4-Hydroxy-3-(*o*-nitrophenyl)-2-quinolone with thionyl chloride gives the *N*-chloro-derivative (**225**; Ar = *o*-$NO_2C_6H_4$),[343] while boiling sulphuryl chloride converts 2,6-dimethyl-4-quinolone into the 4-chloro-derivative.[661]

Phosgene reacts with 1-methyl-2-quinolone in either ether[662] or toluene[663] solution to give 1-methyl-2-chloroquinolinium chloride, which was originally thought[662] to be 2,2-dichloro-1,2-dihydro-1-methylquinoline, since on hydrolysis[664] 1-methyl-2-quinolone is regenerated. If the 1-methyl-2-quinolone is heated at 180 °C in a sealed tube with a toluene solution of phosgene, then 2-chloroquinoline (70%) is obtained.[665]

An early report indicates that 4-quinolone with benzoyl chloride at 200 °C yields, not the expected 4-benzoyloxy-derivative, but 4-chloroquinoline.[666] 4-Methyl-2-quinolone behaves similarly, whereas 2-methyl-4-quinolone yields only traces of the 4-chloro-derivative. More recently a related reaction has been observed during the treatment of 3-anilino-4-quinolone-2-carboxylic acid (**226**) with benzoyl chloride;[667] in this instance chlorination at the 4-position is accompanied by benzoylation of the



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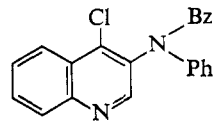

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anilino-group and loss of the carboxylic acid function. The structure of the product (**227**) was confirmed by synthesis from 3-anilino-4-quinolone and hot benzoyl chloride.

The use of *p*-toluenesulphonyl chloride in diethylaniline as a means of converting nitrophenols into chloronitro-compounds, as described by Ullmann and Nadai,[668] has been applied[669] to 8-hydroxy-5,7-dinitroquinoline. However, in this case the expected 8-chloro-5,7-dinitroquinoline was obtained in only low yield.

The use of phosphorus halides as a means of chlorodehydroxylating heterocyclic compounds has been criticized by Robison.[670] He points out that high temperatures, and hence sealed tubes, are often necessary with reactions involving phosphorus oxychloride, while the less volatile phosphorus pentachloride frequently causes further unwanted nuclear chlorination. As an alternative chlorinating agent, he suggests the use of phenylphosphorus dichloride ($PhPOCl_2$). Robison has carried out a series of comparative chlorinations on a wide variety of "hydroxy" heterocycles and in almost every case this reagent compares favourably with the more traditional phosphorus compounds. 2-Quinolone, the only quinoline compound tried, gave, when boiled with a 2-molar excess of phenylphosphorus dichloride at 160 °C for 30 minutes, a 98% yield of 2-chloroquinoline. Similar chlorinations have been achieved[637, 638] by using the chloro-phosphorus compound, 2,2,2-trichloro-2,2-dihydro-1,3,2-benzodioxaphosphole (**220**) mentioned on p. 407.

*E. Preparation from Aminoquinolines by way of Diazonium Compounds**

a. FLUOROQUINOLINES. The introduction of fluorine onto the aromatic nucleus via decomposition of diazonium borofluorides constitutes the classical Balz–Schiemann reaction.[671] This has been applied with great effect to heterocyclic systems and serves as the main method for introducing fluorine into the quinoline nucleus.

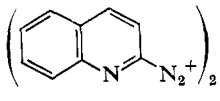
* See also Addenda, p. 679.

The first attempt to prepare a fluoroquinoline by this reaction appears to have been reported by Elderfield and his co-workers[90] during their work on the antimalarials "Pamaquine" and "Plasmochin". It was thought that the relatively high toxicity of these drugs may be due to oxidation of the molecule at the 5-position, and various blocking groups (e.g. chloro and methyl) were introduced but in each case antimalarial activity dropped drastically. Attempts were, therefore, made to introduce the hitherto untried fluoro-group at the suspect position. However, all their efforts to obtain 5-fluoro-6-methoxyquinoline from the corresponding quinoline-5-diazonium borofluoride resulted only in tar formation. Three years later, however, Roe and Hawkins[672] successfully synthesized all the monofluoroquinolines, with the possible exception of 4-fluoroquinoline, by the Balz–Schiemann reaction. 4-Fluoroquinoline proved troublesome, in that it showed a tendency to undergo self-quaternization; however, a product thought to be 4-fluoroquinoline is reported by Roe and Hawkins but so far no further attempts at its preparation appear to have been made.

Fluoroquinolines bearing hydroxy-,[230, 261, 673, 674] alkyl,[675–677] alkoxy-,[677] and sulphonic acid[69] groups have since been prepared by the Balz–Schiemann procedure.

Traditionally aryl fluorides are prepared by thermolysis of the diazonium borofluoride. However, an American patent[678] describes the synthesis of fluoroarenes by photolytic decomposition of the arenediazonium salt. High yields of product are claimed in cases where often the Schiemann reaction fails or gives the desired product only in low yield. Amongst the less successful examples cited is 8-fluoroquinoline, which is obtained in 19% yield by irradiating quinoline-8-diazonium borofluoride for 54 hours with light of wavelength 350 nm. In comparison, Roe and Hawkins[672] report a yield of 25% from the thermolysis of quinoline-8-diazonium borofluoride.

Since the discovery of the Schiemann reaction many attempts have been made to replace the borofluoride ion by other fluorine-containing anionic species, e.g. SiF_6^{2-},[679] and PF_6^-.[680, 681] So far, however, in all such variations the yields of fluoro-compound have proved to be inferior to those obtained by the borofluoride route. For example, 2-fluoroquinoline is obtained in 21% yield[679] from the thermolysis of the diazonium silicon hexafluoride salt (**228**) (28% by the Balz–Schiemann method[672]), while 3-fluoroquinoline (48%) results from the thermolysis of quinoline-3-diazonium hexafluorophosphate (**229**)[681] (74% by the Balz–Schiemann method[672]).



SiF_6^{2-}

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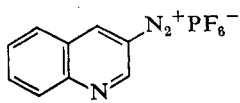

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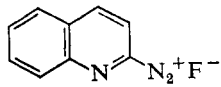

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Beaty and Musgrave[679] have shown that the yield (17%) of 2-fluoroquinoline obtained by decomposing quinoline-2-diazonium fluoride (**230**) in anhydrous hydrogen fluoride (Ferm–Vanderwerf method[682]) is inferior to that attained by the classical method, but comparable to that obtained by pyrolysis of the hexafluorosilicate (**228**).

A list of fluoroquinolines prepared by the Balz–Schiemann reaction is given in Table 14.

b. CHLOROQUINOLINES. Many chloroquinolines have been prepared by diazotization of aminoquinolines and treatment of the resulting diazonium compound under either Sandmeyer or Gattermann conditions. Claus and Schedler[281] indicate that the Gattermann reaction is more successful in the quinoline series than the Sandmeyer

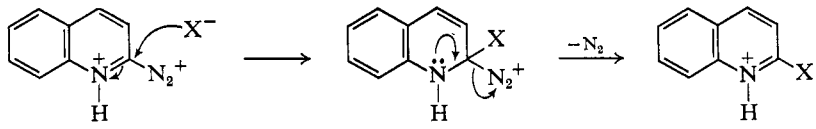
TABLE 14. Fluoroquinolines by the Balz–Schiemann Reaction

Fluoroquinoline	Yield (%)	B.p. (°C/mm) (M.p.) (°C)	References
2-Fluoro-	28	133/30	672, 679
2-Fluoro-4-methoxy-	26.5	(52)	677
3-Fluoro-	74	102/15	672, 681, 683, 684
3-Fluoro-2-methyl-		(56)	675
4-Fluoro- ?		119/15	672
4-Fluoro-2,8-dimethyl-	18	(41)	677
4-Fluoro-2-methoxy-		69/1	677
4-Fluoro-2-methyl-, monohydrate		(40)	676
5-Fluoro-	59	123/30	672, 685
5-Fluoro-8-hydroxy-	39	(112)	230, 673, 674
6-Fluoro-	57	124/30	672
7-Fluoro-	27	129/30	672
7-Fluoro-8-hydroxy-	22	(110.5)	261
7-Fluoro-8-hydroxy-5-sulphonic acid		(320)	69
8-Fluoro-	25	148/30	672, 678
8-Fluoro-2-methyl-			675

process, an observation later confirmed by Roberts and Turner.[91] However, no quantitative comparison has been carried out and both procedures have been used with success.

In a large majority of the reported reactions the amino-group undergoing diazotization is located on the carbocyclic ring and relatively few examples of 2-, 3-, and 4-chloroquinoline formation by this method are to be found in the literature.

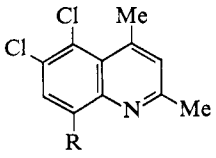
In general, as with 2- and 4-aminopyridines, diazotization of the corresponding aminoquinolines in hydrochloric acid leads to direct formation of the chloroquinoline without recourse to a copper catalyst. In such cases attack by chloride ion with accompanying loss of nitrogen is facilitated by the adjacent protonated heteroatom as indicated in Scheme 12.



SCHEME 12

Occasionally[119, 686] hydroxyquinoline formation accompanies the production of the chloroquinolines but in the great majority of cases a pure chloroquinoline is obtained. Chloroquinolines substituted by alkyl,[401, 543, 687] aryl,[477, 688, 689] halo,[690, 691] alkoxy-,[583, 692] sulphonic acid,[69] hydroxy-,[533] acyl,[693] and alkylthio-groups[394] have been prepared in high yield by the Gattermann–Sandmeyer procedure.

Roberts and Turner[91] have prepared several polyhalodimethylquinolines from the corresponding aminohalodimethylquinolines. They found, however, that the amino-chloro-compounds (**231** and **232**; R = NH_2) are difficult to diazotize and could not be converted into their respective trichloro-compounds (**231** and **232**; R = Cl).



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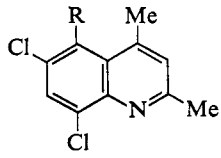

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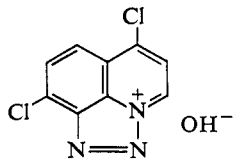

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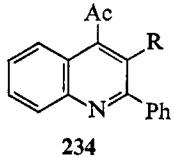
In contrast, several other 8-aminoquinolines have been converted into 8-chloroquinolines with no apparent difficulty. However, in one instance[694] an intermediary triazoloquinolinium hydroxide (**233**) has been isolated; decomposition of the triazole in dilute hydrochloric acid in the presence of copper powder yielded the desired 4,7,8-trichloroquinoline.

Another instance of cyclization accompanying diazotization is to be found in the work of Atkinson and Mattocks[693] who observed that diazotization of the 4-acyl-3-aminoquinoline (**234**; R = NH_2) in hydrochloric acid followed by heating at 60 °C for 4 hours leads to a mixture of 4-acetyl-3-chloro-2-phenylquinoline (**234**; R = Cl) (50%) and the 1,2,9-triazaphenanthrene (**235**) (10%); in alkaline media the latter compound is the major product (80%).



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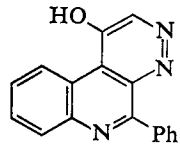

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Ochiai and Naito[695] found that 4-aminoquinoline *N*-oxide is converted into 4-chloroquinoline *N*-oxide under normal Sandmeyer–Gattermann conditions. Naito[696] has shown that 4,6-diaminoquinoline and its *N*-oxide undergo preferential diazotization of the 6-amino-group, and thus was able to prepare 4-amino-6-chloroquinoline and its *N*-oxide.

2,8-Dichloro-4-methylquinoline, prepared either from 8-amino-2-chloro-4-methylquinoline by a Gattermann reaction, or from 8-chloro-4-methyl-2-quinolone and phosphorus oxychloride, is reported[420] to melt at 105 °C, whereas earlier workers[697] starting from the latter material report a melting point of 88 °C. The compounds originally formulated[268, 698] as 5- and 7-chloroquinoline have been shown[699] by unambiguous synthesis from the corresponding amines to be the 7- and 5-chloro-isomers, respectively.

A list of chloroquinolines prepared by Gattermann and Sandmeyer reactions is given in Table 15.

TABLE 15. Chloroquinolines via Diazonium Compounds

Chloroquinoline	Yield (%)	M.p. (°C)	References
MONOCHLORO-			
4-(*n*-Butoxy)-2-chloro-	19	89	119
3-Chloro-	34	Liq.	704
4-Acetyl-3-chloro-2-phenyl-	50	101	693
3-Chloro-2-phenyl-		92	686
4-Chloro-	85	26	700, 701

TABLE 15 (*cont.*)

Chloroquinoline	Yield (%)	M.p. (°C)	References
4-Chloro *N*-oxide		134	695
4-Chloro-2-ethoxy-	67	44	583
4-Chloro-2-iodo-		108	713
4-Chloro-6-methoxy-2-phenyl-		109	712
4-Chloro-3-methyl-2-phenyl-		97	688
4-Chloro-2-(methylthio)-	50	53.5	394
4-Chloro-2-phenyl-		64	689
5-Chloro-		45	268, 690, 698, 699, 702
5-Chloro-2,6-dimethyl-	89	45	687, 710, 711
5-Chloro-4,6-dimethyl-2-quinolone		264	419
5-Chloro-6,8-dimethyl-		44	705
5-Chloro-8-hydroxy-		126.5	674
5-Chloro-8-hydroxy-2-methyl-		61	674
5-Chloro-6-iodo-		141	690
5-Chloro-8-iodo-		138	690
5-Chloro-4-methyl-	59	106.5	347
5-Chloro-6-methyl-		46	419, 707, 708
5-Chloro-2,4,6-trimethyl-	94	50	419
5-Chloro-2,6,8-trimethyl-		64	705
4-Amino-6-chloro-		226	696
4-Amino-6-chloro *N*-oxide			696
6-Chloro-2,5,8-trimethyl-	88	94	687
7-Chloro-	59	30	268, 698, 699, 709
7-Chloro-4-quinolone	36	276	533
7-Chloro-8-hydroxy-5-sulphonic acid	93	300	69
8-Chloro-4,6-dimethoxy-2-methyl-		98	475
8-Chloro-2,4-dimethyl-		74	91
8-Chloro-2,7-dimethyl-	88	65.5	687
8-Chloro-6-fluoro-		102.5	714
8-Chloro-5-iodo-		118	690
8-Chloro-6-methoxy-	82	60	692
8-Chloro-4-methyl-	20	107	401
DICHLORO-			
2,5-Dichloro-4-methyl-		105	347
2,8-Dichloro-4-methyl-	20	105	420
3,6-Dichloro-	58	113	55
4,5-Dichloro-3-methyl-		71	543
4,6-Dichloro-3-methyl-		119	543
4,7-Dichloro-2-phenyl-	10	101.5	477
4,8-Dichloro-2-methyl-		82	541
4,8-Dichloro-3-methyl-		98	543
5,6-Dichloro-		85	281
5,6-Dichloro-2,4-dimethyl-		120	91
5,8-Dichloro-		93	268
5,8-Dichloro-2,4-dimethyl-		118	91
5,8-Dichloro-2,6-dimethyl-	76	84	687
5,8-Dichloro-2,7-dimethyl-		97	687

TABLE 15 (*cont.*)

Chloroquinoline	Yield (%)	M.p. (°C)	References
6,8-Dichloro-		104	281
7,8-Dichloro-2,4-dimethyl-		104.5	91
7,8-Dichloro-2-methyl-		71	706
TRICHLORO-			
4,7,8-Trichloro-		126	691, 694
5,6,8-Trichloro-2,4-dimethyl-		112.5	91
5,7,8-Trichloro-		150	703

c. BROMOQUINOLINES. Bromoquinolines are accessible by methods similar to those employed for the preparation of chloroquinolines, i.e. Sandmeyer and Gattermann reactions. Claus and his co-workers, in particular, have prepared several mono-,[171, 709, 715] di-,[94, 282, 716–718] and tri-bromoquinolines[96, 217, 296, 298] by these procedures, and bromoquinolines substituted by alkyl,[347, 711, 719] aryl,[686, 720] fluoro-,[271, 721] alkoxy-,[722, 723] hydroxy-,[133, 169, 674] and nitro-groups[288] have also been prepared.

Musgrave and his co-workers[271, 721] have synthesized 7-bromo-5,6,8-trifluoroquinoline by diazotizing 7-amino-5,6,8-trifluoroquinoline in hydrofluoric acid at −10 °C and then treating the diazonium solution with cuprous bromide in hydrobromic acid.

4-Aminoquinoline *N*-oxide under Gattermann conditions yields 4-bromoquinoline *N*-oxide.[695] However, attempts to prepare 2-bromoquinolines by diazotization of the corresponding 2-aminoquinolines failed;[617] in each case 2-quinolones were produced. Claus and his co-workers[171, 314] observed that 4-aminoquinoline failed to diazotize on treatment with sodium nitrite in hydrobromic acid but instead underwent bromination to yield 4-amino-3-bromoquinoline; 3-bromoquinoline is also isolated from the reaction mixture, but whether this arises by deamination of the aminobromo-compound or by initial deamination followed by bromination is not clear. 4-Aminoquinoline does, however, undergo diazotization in concentrated sulphuric acid, and on treatment of the diazonium solution with cuprous bromide 4-bromoquinoline is obtained in good yield.[171]

A list of bromoquinolines prepared by the Gattermann and Sandmeyer procedures is given in Table 16.

TABLE 16. Bromoquinolines via Diazonium Compounds

Bromoquinoline	Yield (%)	M.p. (°C)	References
MONOBROMO-			
3-Bromo-2-phenyl-		86	686
4-Bromo-		30	171, 314
4-Bromo *N*-oxide		136	695
4-Bromo-6-methoxy-2-phenyl-		157	712
4-Bromo-2-phenyl-		91	720
5-Bromo-	48	48	669, 699, 715, 724, 725
5-Bromo-8-hydroxy-	36	126.5	133, 169, 674

TABLE 16 (*cont.*)

Bromoquinoline	Yield (%)	M.p. (°C)	References
5-Bromo-8-hydroxy-2-methyl-		64	674
5-Bromo-4-methyl-	72	113.5	347
6-Bromo-5,8-dimethoxy-2-methyl-	51	137	723
7-Bromo-	45	35	699, 709, 715, 725
7-Bromo-1,2,3,4-tetrahydro-2-(isopropylaminomethyl)-6-methyl hydrochloride		241	711
7-Bromo-5,6,8-trifluoro-		99	271, 721
8-Bromo-		Liq.	669
8-Bromo-6-methoxy-		66	722
8-Bromo-6-methyl-		58	719
8-Bromo-6-nitro-		164	288
DIBROMO-			
3,5-Dibromo-		85	94, 282
3,6-Dibromo-		130	177
3,8-Dibromo-		108	717
5,6-Dibromo-		95	176, 177, 217, 716
5,8-Dibromo-		127	175, 717, 718
7,8-Dibromo-		112	725
TRIBROMO-			
3,5,6-Tribromo-		149	177
5,6,7-Tribromo-		124	298
5,6,8-Tribromo-		175, 159	96, 175, 217, 296, 298
5,7,8-Tribromo-		141	175, 283
6,7,8-Tribromo-		84	298

d. IODOQUINOLINES. Iodoquinolines are readily obtained from quinoline diazonium compounds by the standard method, i.e. warming the diazonium chloride solution with a solution of potassium iodide or tri-iodide (KI_3) in the presence of copper powder. Several mono- and di-iodo-compounds have been so prepared[690] and iodoquinolines substituted by alkyl,[337] chloro-,[713] trifluoromethyl,[726] alkoxy-,[712] hydroxy-[674, 727] and arsonic acid[333] groups have been prepared by this method. As expected diazotized 4-aminoquinoline *N*-oxide, on treatment with potassium iodide, yields 4-iodoquinoline *N*-oxide.[695] 4-Aminoquinoline, however, is reported[314] to undergo anomalous reactions with sodium nitrite in hydriodic acid in that iodination at the 3-position is observed; as with bromination, however, the diazotization proceeds normally with sodium nitrite in concentrated sulphuric acid, and subsequent treatment of the diazonium sulphate with potassium iodide yields 4-iodoquinoline.

8-Amino-7-(trifluoromethyl)quinoline diazotizes normally in 6N-sulphuric acid and on treatment with potassium iodide yields 8-iodo-7-(trifluoromethyl)quinoline.[726] 8-Iodo-5-(trifluoromethyl)quinoline was prepared in a similar manner except that diazotization was carried out using preformed nitrosylsulphuric acid.

Gershon and MacNeil[727] have examined the effect of iodide ion on diazotized 5-amino-8-hydroxyquinoline, following an unpublished report by Irving[66] that the product does not appear to be the expected 5-iodo-derivative. Gershon and MacNeil found in fact that the main product is 8-hydroxy-7-iodoquinoline (56%) together with the 5-iodo- (3%) and 5,7-di-iodo- (4%) derivatives; they also found that 7-amino-8-hydroxyquinoline under similar conditions yields 8-hydroxyquinoline and no iodinated derivatives. The results are explained by the authors on the basis of a heterolysis of the diazonium compound to give an aryl cation which undergoes a 1,3-hydride ion shift to yield a cationic species with the positive charge localized at the 7-position (see Section II.2.J, Scheme 79).

A list of iodoquinolines prepared by diazonium reactions is given in Table 17.

TABLE 17. Iodoquinolines via Diazonium Compounds

Iodoquinoline	Yield (%)	M.p. (°C)	References
3-Iodo-	52	62	233
4-Iodo-		100	314
4-Iodo *N*-oxide		166	695, 731
2-Chloro-4-iodo-		109	713
4-Iodo-6-methoxy-2-phenyl-		178	712
5-Iodo-		101	728, 729
6-Chloro-5-iodo-	28	136	730
8-Chloro-5-iodo-		118	690
8-Hydroxy-5-iodo-		130	674, 727
8-Hydroxy-5-iodo-2-methyl-		153	674
6-Iodo-		88	729
5-Chloro-6-iodo-		141	690
7-Iodo-		103	729
8-Hydroxy-7-iodo-		113	727
8-Hydroxy-7-iodo-5-arsonic acid			333
8-Iodo-	60	36	690
5-Chloro-8-iodo-		138	690
8-Iodo-6-methyl-		66	337
8-Iodo-5-(trifluoromethyl)-		63	726
8-Iodo-7-(trifluoromethyl)-		112	726
5,6-Di-iodo-		125	690
5,8-Di-iodo-	50	162	690

*F. Preparation by Halogen–Halogen Exchange Reactions**

The halogen in 2- and 4-haloquinolines is susceptible to replacement by a variety of nucleophiles. Use has been made of this property for the synthesis of haloquinolines since it is possible, generally under mild conditions, to bring about the exchange of one halogen atom for another by a nucleophilic process. However, as will be seen in the following section, such halogen-exchange reactions are not limited solely to the "activated" 2- and 4-haloquinolines.

a. REPLACEMENT OF CHLORINE BY IODINE. Friedlander and Weinberg[732] showed that when 2-chloroquinoline is heated with hydriodic acid in the presence of red phosphorus, chlorine–iodine exchange, rather than reductive dechlorination, takes place. More recently Japanese workers[733] have confirmed this result.

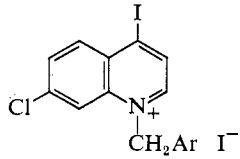
* See also Addenda, p. 679.

Alkyliodoquinolines have been prepared by Wöhnlich,[643] and by Byvanck[427] by heating the alkylchloroquinoline with a mixture of hydriodic acid, potassium iodide, and red phosphorus. Byvanck,[427] however, found that under vigorous conditions (reflux for 18 hours rather than 100 °C for 1 hour), reductive dechlorination rather than halogen exchange occurs. Thielepape[368, 636] has prepared ethyl 2-iodoquinoline-4-carboxylate from the 2-chloro-compound under similar conditions.

Roser[734] tried to prepare the methiodide of 2-chloroquinoline by heating the base with methyl iodide in a sealed tube but found that halogen exchange occurred and only 2-iodoquinoline methiodide was isolable. This exchange reaction has since been investigated in some detail by Bradlow and Vanderwerf[735] who have shown that quaternization of the quinoline ring is a prerequisite for replacement of chlorine. It appears, not unexpectedly, that quaternization enhances the lability of the chlorine group towards nucleophilic displacement by iodide ion. Several examples of chlorine–iodine exchange accompanying methiodide formation have been reported,[634, 663, 736] and the reaction forms a valuable synthetic method for the production of quinoline-cyanine dyestuff intermediates.[586, 642, 701]

2,4-Dichloroquinoline, heated with methyl iodide in a sealed tube at 100 °C for 3 days, undergoes a double halogen exchange to yield 2,4-di-iodoquinoline methiodide (49%).[586] 2-Chloroquinoline with iodine in a mixture of hydriodic acid and aqueous ethyl methyl ketone under reflux yields 2-iodoquinoline (72%).[737]

Quaternization of 4,7-dichloroquinoline with 2-chlorobenzyl chloride in hot acetone and in the presence of sodium iodide leads to the formation of the chloro-iodoquinolinium iodide (**236**; Ar = *o*-ClC_6H_4) which has use as an anthelmintic agent.[738]



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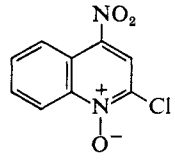
4-Chloro-2-iodoquinoline readily yields 2,4-di-iodoquinoline when heated under reflux with 57% hydriodic acid,[713] while under similar conditions 4,7-dichloroquinoline yields 7-chloro-4-iodoquinoline (75%).[739] Nógrádi[740] has found that 5-chloro-8-hydroxy-7-iodoquinoline in boiling aqueous dioxan undergoes halogen exchange to give a mixture of 8-hydroxy-5,7-di-iodo- and 5,7-dichloro-8-hydroxyquinoline.

b. Replacement of Chlorine by Bromine. Replacement of chlorine by bromine is not a common process and only a few examples have been recorded. Boiling 4,7-dichloroquinoline in hydrobromic acid for 50 minutes yields 4-bromo-7-chloroquinoline (77%).[739] A similar exchange is observed with 4,7-dichloro-3-methylquinoline, but under more forcing conditions (under reflux for 15 hours). Japanese workers have shown[741] that chlorine–bromine exchange occurs when 2-chloro-4-nitroquinoline *N*-oxide (**237**) is treated with phosphorus tribromide in chloroform at room temperature.

c. Replacement of Bromine by Chlorine. Elderfield and Claflin[49] have shown that halogen exchange occurs during the diazotization and subsequent deamination



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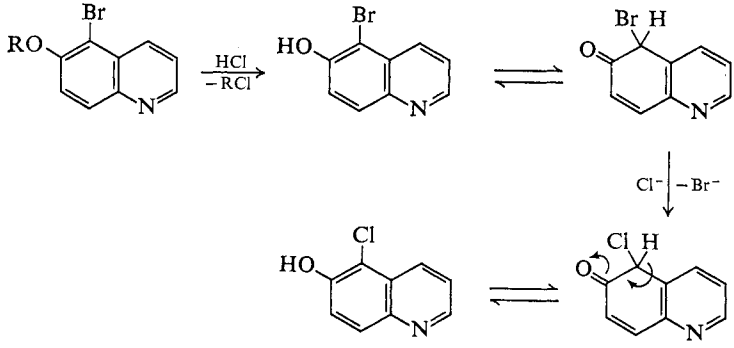
of 8-amino-5,7-dibromoquinoline in hydrochloric acid, which yields 5,7-dichloroquinoline; under these conditions the normally unreactive 5- and 7-bromo-substituents are activated towards nucleophilic substitution by the initially formed diazonium group. Such activation of halogen *ortho* and *para* to a diazonium cation is well known and constitutes the so-called "nuisance effect".[742] The activating influence of the diazonium group on the replacement is indicated by the fact that the dibromoamine does not undergo halogen exchange even on prolonged boiling with concentrated hydrochloric acid. Deamination without halogen exchange was accomplished by carrying out the diazotization directly in hypophosphorous acid.

Other examples of bromine–chlorine exchange are known, but curiously only one example appears to involve an activated bromine substituent, viz., the reaction of 2-bromo-4-nitroquinoline *N*-oxide with phosphorus trichloride in chloroform at room temperature to give the corresponding 2-chloro-compound (**237**) in 64% yield.[741]

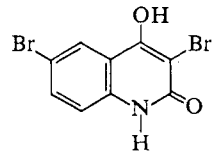
In each of the other examples of bromine–chlorine exchange, the bromine undergoing replacement is adjacent to a hydroxy-function. Howitz and his co-workers[743–745] have treated a number of 5- and 7-bromo-substituted 6-alkoxyquinolines and 1-alkylquinolones with concentrated hydrochloric acid at 160–170 °C and have obtained the corresponding chlorohydroxyquinolines or quinolones. Mechanistically these exchanges may involve keto–enol participation (see Scheme 13) such as is found in



SCHEME 13

the Bucherer reaction[746] and, since all these reactions appear to have been carried out in hot concentrated hydrochloric acid in a sealed tube, bromine–chlorine exchange is not surprising.

Unlike the reactions mentioned above, the dibromo-compound (**238**) undergoes bromine–chlorine exchange at the 3-position under relatively mild conditions, namely concentrated hydrochloric acid and hydrogen peroxide in dioxan solution.[128] Halogen exchange is also accompanied by further chlorination to give the dichloro-compound (**239**).



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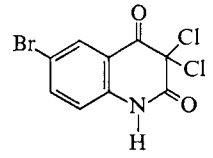

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Schofield and Swain[212] have shown that bromine–chlorine exchange can occur when various 3- and 6-bromoquinolines are heated with phosphorus pentachloride. The amount of halogen exchange detected, however, is insignificant compared with the corresponding bromocinnolines, which under similar conditions undergo halogen exchange to a high degree.

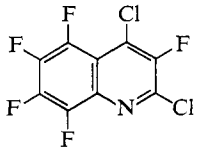
d. Replacement of Chlorine by Fluorine. Generally, in protic solvents, fluoride ion is highly solvated and behaves as a weak nucleophile. In aprotic solvents, however, the nucleophilicity of fluoride ion is much increased and many examples of halogen exchange involving fluoride ion are known.[747] For example, 2,7-dichloroquinoline and potassium fluoride in hot dimethylformamide[748] give 7-chloro-2-fluoroquinoline, and 2-chloroquinoline and potassium fluoride in hot dimethyl sulphone give 2-fluoroquinoline in 60% yield.

The preparation of heptafluoroquinolines by heating the corresponding heptachloroquinolines with anhydrous potassium fluoride at 450–500 °C for several hours has been described;[35, 36] the resulting mixture of two isomeric monochlorohexafluoroquinolines and 2,3,4,5,6,7,8-heptafluoroquinoline, formed in the ratio 3 : 12 : 85, can be separated by fractional distillation, followed by preparative-scale gas–liquid chromatography.

e. Replacement of Fluorine by Chlorine, Bromine, or Iodine. Several polyfluoroquinolines have been reported[271, 721] to undergo fluorine–chlorine exchange when heated with phosphorus chlorides. Thus 5,6,7,8-tetrafluoroquinoline, heated with phosphorus pentachloride at 235 °C for 4 hours in an autoclave, suffers not only replacement of fluorine by chlorine but also further mono- and di-chlorination to yield a mixture of unidentified penta- and hexachloroquinolines.

The relative reactivity of heptafluoroquinoline, heptafluoroisoquinoline, and pentafluoropyridine towards hydrogen halides has been investigated;[750] perfluoroquinoline proves to be by far the most reactive of the compounds studied, a result which is in contrast to the almost equal reactivity shown by the three systems towards nucleophilic replacement of halogen under neutral or basic conditions.[751] With an excess of dry hydrogen chloride in anhydrous tetrahydrothiophen dioxide (sulpholane) solution heptafluoroquinoline yields 2,4-dichloro-3,5,6,7,8-pentafluoroquinoline (**240**) in high yield (80%). In the same solvent, but with one equivalent of hydrogen chloride and in a sealed tube, a mixture of 2-chlorohexafluoro- (60%) and 2,4-dichloropentafluoro-quinoline (20%) is obtained, together with starting material, in the ratio 3 : 1 : 1; no 4-chlorohexafluoroquinoline was detected in the reaction products. The reaction appears to be very water-sensitive since even under super-dry conditions traces of polyfluoro-2- and -4-quinolone are always obtained. Although optimum yields of dichloro-compound are obtained on using a solvent of high dielectric constant, e.g. sulpholane, the reaction is also successful in acetone, diethyl ether, and (in low yield) hexane. The nucleophilic displacements are thought to occur at the quinolinium species (**241**) and, since no 4-chlorohexafluoroquinoline has been isolated, exchange is thought to proceed initially at the 2-position.

Perfluoroquinoline reacts in an analogous manner with dry hydrogen bromide in sulpholane solution to give 2-bromohexafluoro- and 2,4-dibromo-3,5,6,7,8-pentafluoroquinoline. As expected, with aqueous hydrogen bromide only polyfluoroquinolones are obtained. A somewhat different reaction is observed with hydrogen



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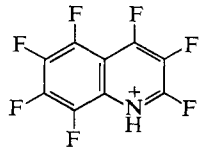

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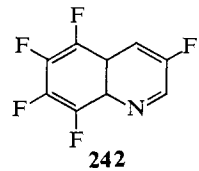

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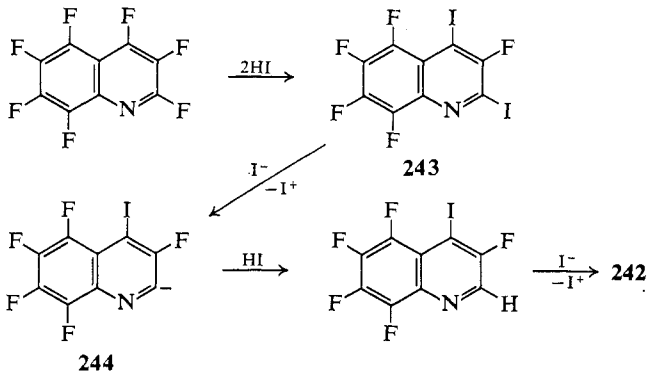
iodide and perfluoroquinoline in that the expected 2,4-di-iodopentafluoroquinoline is formed along with 3,5,6,7,8-pentafluoroquinoline (**242**).

A mixture of pentafluoro- and pentafluoro-di-iodo-quinoline also results when perfluoroquinoline is heated with concentrated hydriodic acid. The formation of pentafluoroquinoline is explained on the basis of the reactions illustrated in Scheme 14. The di-iodo-derivative (**243**), initially formed by halogen exchange in the presence



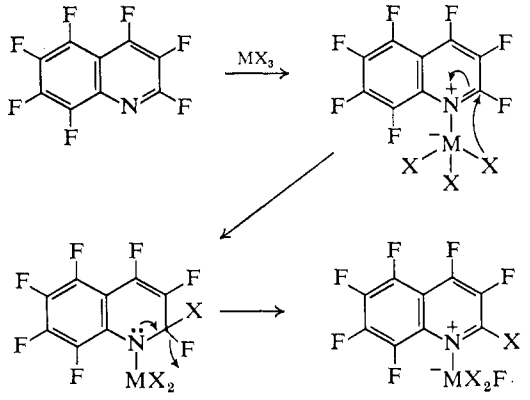
SCHEME 14

of an excess of iodide ion, suffers loss of iodonium ion and concomitant formation of the carbanion (**244**). The carbanion subsequently abstracts a proton from a convenient source (solvent or hydriodic acid) to yield the monoiodoquinoline which by a repeat process yields the pentafluoroquinoline (**242**).

Formation of the pentafluorodi-iodoquinoline (**243**) even under aqueous conditions, which in the case of hydrobromic acid and hydrochloric acid leads to quinolone formation, is explicable in terms of the superior nucleophilicity of iodide ion in aqueous solution, as this makes feasible the successful competition of iodide ion with water molecules for replacement of fluorine.

The above reactions are of particular value for the synthesis of substituted polyfluoroquinolines since the introduced chloro- and bromo-groups are more readily replaced by other nucleophiles than is fluorine itself. For example, 2-bromo- and 2,4-dibromo-polyfluoroquinoline react smoothly with sodium iodide in hydriodic acid to give hexafluoro-2-iodo- and pentafluoro-2,4-di-iodoquinoline, respectively, in good yield.

Some intriguing fluorine–halogen exchanges are observed on treating perfluoroquinoline with Lewis acids.[752] Reaction of polyfluoroquinoline with an excess of boron tribromide at 150 °C in a sealed tube for 55 hours leads to 2,4-dibromo-3,5,6,7,8-pentafluoroquinoline (88%). Similar treatment with boron trichloride at 140 °C for 128 hours yields 2,4-dichloropentafluoroquinoline (**240**) (91%). Boron tri-iodide, however, leads only to the formation of tar. With aluminium halides the reactions follow a different course: for example, perfluoroquinoline with an excess of aluminium chloride or bromide at 150 °C for several days yields 2-chloro- (90%) and 2-bromo-hexafluoroquinoline (74%), respectively. In contrast, at temperatures above 150 °C perfluoroquinoline with an excess of aluminium bromide gives 2,8-dibromo-3,4,5,6,7-pentafluoroquinoline (95%), while with aluminium iodide at 150 °C a low yield (27%) of 3,4,5,6,7-pentafluoro-2,8-di-iodoquinoline is obtained. The authors suggest that 2-substitution, as observed with both boron and aluminium halides, may proceed by means of an intramolecular process involving a metal halide–quinoline



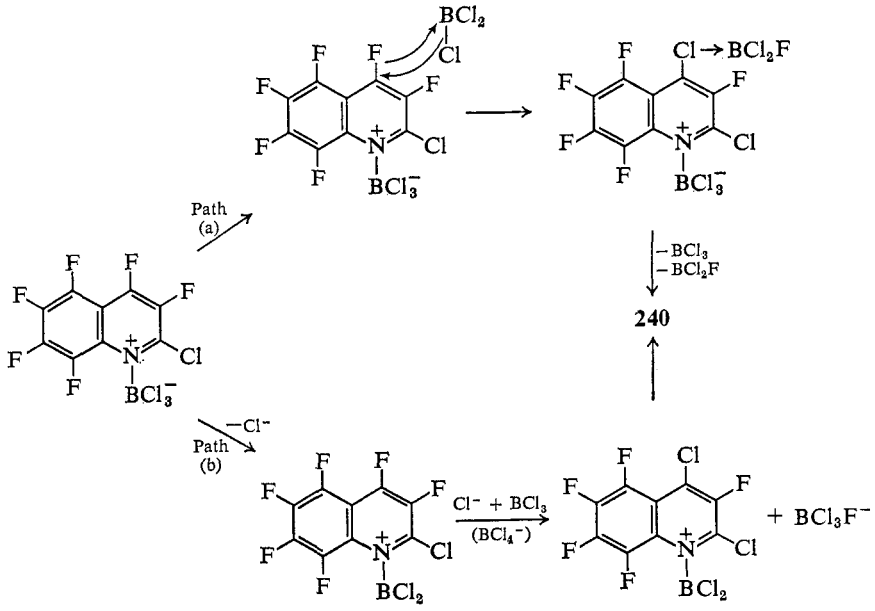
SCHEME 15

complex as indicated in Scheme 15. They also suggest that substitution at the 8-position is occurring by a similar intramolecular process. Substitution at the 4-position must, however, occur via an intermolecular reaction, and a reaction scheme involving either attack by BCl_4^- (Scheme 16; pathway b) or an exchange process (pathway a) is suggested.

f. MISCELLANEOUS REPLACEMENTS. During a study of the pharmacological effects of antimalarials Counsell and his co-workers[753] synthesized the radio-isotopically labelled iodine compounds (**245**; R = ^{125}I and R = ^{131}I) by a halogen-exchange process that involved heating a solution of the iodo-substituted amine (**245**; R = ^{127}I) under reflux in ethylene glycol solution with iodine-125 or sodium iodide (^{131}I). The labelled iodo-compounds had activity of 2.03 mc/mmol and 1.42 mc/mmol, respectively.

Later studies[754] indicate that, of the several labelled iodine compounds prepared by this method, the dimethylaminopropylamino-derivative (**245**; R = ^{125}I) shows a marked affinity for melanotic tumours in animals.

Halogen-exchange reactions mentioned in the preceding Sections are listed, in greater detail, with others, in Table 18.



SCHEME 16

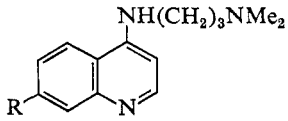


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TABLE 18. *Haloquinolines by Halogen–Halogen Exchange Reactions*

Haloquinoline* produced	Method of preparation (yield)	References
SINGLE HAL–HAL EXCHANGES		
2-Bromo-3,4,5,6,7,8-hexafluoro-	(i) 2,3,4,5,6,7,8-heptaF-Q; 1 mol of HBr at room temp. for 10 days (60%); (ii) excess of $AlBr_3$ at 150 °C for 120 h (74%)	750, 752
2-Bromo-4-nitro *N*-oxide	2-Cl-4-NO_2-Q *N*-oxide; $PBr_3/CHCl_3$ at 20 °C	741
4-Bromo-7-chloro-	4,7-diCl-Q; HBr reflux 50 min (77%)	739
4-Bromo-7-chloro-3-methyl-	4,7-diCl-3-Me-Q; HBr reflux 15 h	739
6-Bromo-3,3-dichloro-1,2,3,4-tetrahydro-2,4-dioxo-	3,6-diBr-4-HO-2-Q'one; conc. HCl/dioxan/H_2O_2 (96.5%)	128
2-Chloro-4-nitro *N*-oxide	2-Br-4-NO_2-Q *N*-oxide; $PCl_3/CHCl_3$ at 20 °C (64%)	741

* See footnote to Table 1, p. 340.

TABLE 18 (*cont.*)

Haloquinoline* produced	Method of preparation (yield)	References
2-Chloro-3,4,5,6,7,8-hexafluoro-	2,3,4,5,6,7,8-heptaF-Q; dry sulpholane/HCl gas in a sealed tube for 10 days (60%); (ii) excess of $AlCl_3$ at 150 °C for 200 h in a sealed tube (90%)	750, 752
2-Chloro-3,5,6,7,8-pentafluoro-4-quinolone	2,3,4,5,6,7,8-heptaF-Q; sulpholane/HCl gas in wet solvent at 100 °C for 50 h (23%); hexafluoro-2-quinolone also isolated	750
4-Chloro-3,5,6,7,8-pentafluoro-2-quinolone	2,3,4,5,6,7,8-heptaF-Q; dry sulpholane/HCl gas for 50 h at room temp.	750
5-Chloro-1-ethyl-6-hydroxy-2-quinolone	1-Et-5-Br-6-HO-2-Q'one; conc. HCl in sealed tube at 170 °C	744
5-Chloro-6-hydroxy-	5-Br-6-HO-Q; conc. HCl in sealed tube at 170 °C	743
5-Chloro-6-hydroxy-1-methyl-2-quinolone	5-Br-6-MeO-1-Me-2-Q'one; conc. HCl in sealed tube at 170 °C	745
5-Chloro-8-hydroxy-	5-Br-8-HO-Q; conc. HCl in sealed tube at 170 °C	743
7-Chloro-1-(*o*-chlorobenzyl)-4-iodoquinolinium iodide	4,7-diCl-Q; *o*-$ClC_6H_4CH_2Cl$/NaI/Me_2CO under reflux for 24 h	738
2-Fluoro-	2-Cl-Q; KF/Me_2SO_2 at 200 °C for 120 h (60%)	749
7-Chloro-2-fluoro-	2,7-diCl-Q; KF/DMF at 160 °C for 96 h	748
7-Chloro-8-hydroxy-	7-Br-8-HO-Q; conc. HCl in sealed tube at 170 °C	743
7-Chloro-8-hydroxy-1-methyl-2-quinolone	7-Br-8-HO-1-Me-2-Q'one; conc. HCl in sealed tube at 170 °C	743
7-Chloro-4-iodo-	4,7-diCl-Q; HI reflux 20 min (75%)	739
4-Iodo-2-ethyl-3-methyl-	4-Cl-2-Et-3-Me-Q; HI/KI/red P	643
2-Iodo-	2-Cl-Q; (i) HI/red P at 140–150 °C for 3 h; (ii) KI/HI/red P heat for 3 h (78%); (iii) I_2/HI/MEK/H_2O reflux for 30 h (72%)	732, 733, 737
2-Iodo-4-methyl-	2-Cl-4-Me-Q; KI/HI/red P at 100 °C for 1 h	111, 427
4-Ethyl-2-iodo-3-methyl-	2-Cl-4-Et-3-Me-Q; HI/KI/red P	643
Et 2-iodo-4-carboxylate	2-Cl-Q-4-CO_2Et; KI/HI/red P at 100 °C for 3 h (92%)	368, 636
2-Ethyl-4-iodo-3-methyl-	4-Cl-2-Et-3-Me-Q; HI/KI/red P	643
DOUBLE HAL–HAL EXCHANGE		
2,4-Dibromo-3,5,6,7,8-pentafluoro-	2,3,4,5,6,7,8-heptaF-Q; (i) excess of HBr for 10 days at room temp. (61%); (ii) excess of BBr_3 at 150 °C for 55 h in sealed tube (88%). 2-Br-3,5,6,7,8-pentaF-4-quinolone also isolated	750, 752
2,8-Dibromo-3,4,5,6,7-pentafluoro-	2,3,4,5,6,7,8-heptaF-Q; excess of $AlBr_3$ at > 150 °C for 120 h (95%)	752
2,4-Dichloro-3,5,6,7,8-pentafluoro-	2,3,4,5,6,7,8-heptaF-Q; (i) dry sulpholane/HCl gas for 50 h at room temp. (80%); (ii) excess of BCl_3 at 140 °C for 28 h in a sealed tube (91%)	750, 752
5,7-Dichloro-	5,7-diBr-8-NH_2-Q; $NaNO_2$/HCl, then H_3PO_2 (60%)	49

TABLE 18 (*cont.*)

Haloquinoline* produced	Method of preparation (yield)	References
5,7-Dichloro-8-hydroxy-	5,7-diBr-8-HO-Q; conc. HCl in sealed tube at 170 °C	743
5,7-Dichloro-8-hydroxy-1-methyl-2-quinolone	5,7-diBr-8-MeO-1-Me-2-Q'one; conc. HCl in sealed tube at 170 °C	743
2,4-Di-iodo-	2,4-diCl-Q; HI (57%) under reflux 15 min	713
3,5,6,7,8-Pentafluoro-2,4-di-iodo-	(i) 2,3,4,5,6,7,8-heptaF-Q; HI/sulpholane for 10 days at room temp. in a sealed tube (28%); (ii) 2,4-diBr-3,5,6,7,8-pentaF-Q; NaI/HI dry Me_2CO under reflux for 12 h (68%)	750
3,4,5,6,7-Pentafluoro-2,8-di-iodo-	2,3,4,5,6,7,8-heptaF-Q; excess of AlI_3 at 150 °C for 160–170 h (27%)	752
8-Hydroxy-5,7-di-iodo-	5-Cl-7-I-8-HO-Q; boil for 30 min in H_2O/dioxan + 5,7-diCl-8-HO-Q	740
MULTIPLE HAL–HAL EXCHANGES		
x,*x*,5,6,7,8-Hexachloro-	5,6,7,8-tetraF-Q; PCl_5 at 235 °C for 4 h in an autoclave	271, 721
2,3,4,5,6,7,8-Heptafluoro-	2,3,4,5,6,7,8-heptaCl-Q; KF at 470 °C for 17 h in an autoclave	36
Cl→I WITH QUATERNIZATION		
2-Iodo-, ethiodide	2-Cl-Q; EtI boil for 10 days (81%)	642, 735
2-Iodo-, methiodide	2-Cl-Q; MeI/H_2O in sealed tube or under reflux for 10 days (92%); or at 90 °C for 12 h	634, 642, 663, 734, 735
2-Iodo-4-methyl-, ethiodide	2-Cl-4-Me-Q; EtI under reflux for 8 days in the dark	586
2-Iodo-6-methyl-, methiodide	2-Cl-6-Me-Q; MeI at 100 °C for 2 days	642
4-Iodo-, ethiodide	4-Cl-Q; EtI at 100 °C for 2 days (84%)	701
4-Iodo-, methiodide	4-Cl-Q; MeI at 100 °C in sealed tube for 2 days (62%)	701
4-Iodo-2-methyl-, methiodide	4-Cl-2-Me-Q; MeI at 100 °C for 26 h	736
2,4-Di-iodo-, methiodide	2,4-diCl-Q; MeI (excess) at 100 °C for 3 days in sealed tube (49%)	586
2,4-Di-iodo-, ethiodide	2,4-diCl-Q; EtI at 100 °C for 3 weeks (47%)	586

G. Preparation from Quinoline N-*Oxides*†

The chemistry of *N*-oxides, particularly heterocyclic *N*-oxides, has seen great advances during the post-war years and two excellent books[755, 756] on the subject are available. Of the many reactions undergone by *N*-oxides two are of use in the synthesis of haloquinolines, namely the reaction with phosphorus or sulphur halides, as considered in the following Section, and the reaction of 2- and 4-substituted quinoline *N*-oxides with acylating agents. The latter reactions involve replacement of the substituent by halogen and as such are considered in a later Section (II.1.H.b). In

* See footnote to Table 1, p. 340.

† See also Addenda, p. 679.

general, halogenation is accompanied by deoxygenation of the *N*-oxide function, particularly when phosphorus halides are used as the halogenating agent.

a. Reaction with Phosphorus Halides. Bachman and Cooper,[757] following earlier work of Meisenheimer[241] and Bobranski,[758, 759] have shown that quinoline *N*-oxide reacts with chlorinating agents to give 2- and 4-chloroquinoline. They also showed that, whereas solvent has little effect on the relative amounts of 2- and 4-chloroquinoline formed, the ratio of these products is affected by substituents. For example, 6-methoxy-, 6-nitro-, and 6-chloro-quinoline *N*-oxide react with phosphorus oxychloride to give a mixture of the 2- and 4-chloroquinolines in the ratios of 1 : 0.6, 1 : 3.5, and 1 : 1.38, respectively.[757] Quinoline *N*-oxide itself yields 2- and 4-chloroquinoline in the ratio 1 : 1.7.

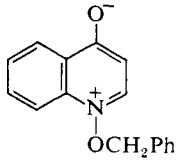
From 6-nitroquinoline *N*-oxide is obtained a mixture of 2- (16%) and 4-chloro-6-nitroquinoline (56.5%), together with a third isomer (3.5%), thought by the authors to be 3-chloro-6-nitroquinoline. Simpson and Wright[760] confirmed these results, although the products were obtained in substantially lower yields (5.6%, 33.2%, and 2.8%, respectively). More recently the reaction has been repeated by Japanese researchers[405] who obtained the 2- and 4-chloro-6-nitro-isomers in yields of 18.8% and 51%, respectively; no reference is made, however, to the formation of the 3-chloro-6-nitro-derivative.

Bachman and his co-workers[761] report that 5-nitroquinoline *N*-oxide undergoes a similar reaction to yield a mixture of 2- (44.5%), 3- (13.1%), and 4-chloro-5-nitroquinoline (9.4%), when heated under reflux with phosphorus oxychloride. Shortly afterwards virtually identical results were published by Mosher and his co-workers[537] who confirmed the structure of the 3-chloro-5-nitro-isomer.

Quinoline *N*-oxides substituted at the 4-position by groups other than nitro (for which, see Section II.1.H.b) generally undergo chlorination at the 2-position accompanied by deoxygenation, and by this method 2-chloroquinolines bearing carboxylic acid,[762] alkyl,[763] aryl,[764] phenylazo-,[391] styryl-,[765] alkylamino-,[766] and amino-substituents[767] have been prepared. Similarly, if the 2-position of the *N*-oxide is blocked by a substituent other than nitro, then 4-chloroquinolines result, and several 2-alkyl-[768] and 2-aryl-substituted[769–771] 4-chloroquinolines have been prepared by this route. The latter compounds were required as intermediates in the synthesis of "open-model" "Atabrin"-type antimalarials.[769]

4-(Hydroxyamino)quinoline *N*-oxide on treatment with phosphorus oxychloride undergoes reduction of both the *N*-oxide and the hydroxylamine function, to yield 4-amino-2-chloroquinoline.[767] In the case of the zwitterion (**246**) treatment with hot phosphorus oxychloride brings about, not only 2-chlorination, but also chlorodebenzyloxylation, to give 2,4-dichloroquinoline in high yield (91%).[772]

3-Substituted quinoline *N*-oxides appear to be halogenated at either the 2- or the 4-position. For example, 3,6-dinitroquinoline *N*-oxide suffers only deoxygenation on treatment with phosphorus trichloride in chloroform solution, whereas with phosphorus oxychloride at 100 °C 2-chloro-3,6-dinitroquinoline is obtained.[773] Under similar conditions 3-nitroquinoline *N*-oxide yields the 2-chloro-derivative, whereas 3-bromoquinoline *N*-oxide gives 3-bromo-4-chloroquinoline.[396]



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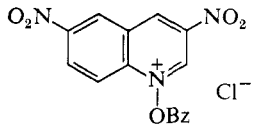

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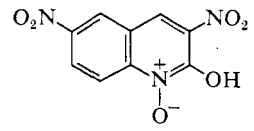

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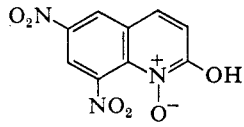
Both the *N*-(benzoyloxy)dinitroquinoline (**247**)[397] and the 2-hydroxy-3,6-dinitroquinoline *N*-oxide (**248**)[774] are reported to yield uncharacterized tetrachloro-derivatives on treatment with phosphorus oxychloride and phosphorus pentachloride at 180 °C. Conversely, with hot phosphorus oxychloride the dinitro-compound (**248**) yields 2-chloro-3,6-dinitroquinoline,[397] whereas the 6,8-dinitro-isomer (**249**) gives 2,4-dichloro-6,8-dinitroquinoline.[396]



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In the absence of substituents at the 2-, 3-, and 4-positions quinoline *N*-oxides generally yield a mixture of 2- and 4-chloroquinolines on treatment with phosphorus halides. Thus, 7-chloroquinoline *N*-oxide yields a mixture of 2,7-dichloro-, 4,7-dichloro-, and 2,4,7-trichloro-quinoline,[775] whereas under similar conditions 6-methoxyquinoline *N*-oxide yields the 2-chloro- and 4-chloro-derivatives in a ratio of 11 : 7.[405, 776] This ratio, however, is reversed if a solution of phosphorus oxychloride in chloroform is employed.[405] 7-Methylquinoline *N*-oxide with hot phosphorus oxychloride yields roughly equal amounts of the 2- and 4-chloro-compounds,[777] whereas under similar reaction conditions 7-methyl-8-nitroquinoline *N*-oxide undergoes monochlorination specifically at the 2-position.[778] Both 6-acetamido-,[405] and 8-acetamido-6-methoxy-quinoline *N*-oxide[537] react with hot phosphorus oxychloride to yield only resinous products; 6-nitroquinoline *N*-oxide, however, gives a mixture of 2- (17.8%) and 4-chloro-6-nitroquinoline (51%).[405]

Relatively little work has been published on the action of phosphorus bromides on quinoline *N*-oxides. 4-Bromoquinoline *N*-oxide is reported[619] to yield a mixture of 2,4-dibromoquinoline (40%) and 4-bromo-2-quinolone (24%) when treated with boiling phosphorus oxybromide in chloroform solution. 4-Iodoquinoline *N*-oxide undergoes deoxygenation on treatment with phosphorus tri-iodide in chloroform at room temperature.[731]

During their researches into the synthesis of cinchona alkaloids Ochiai and his co-workers[779-782] prepared several 2-chloroquinolines by treating the *N*-oxides of the various alkaloids with hot phosphorus oxychloride.

b. Reaction with Sulphur Halides. The use of sulphur halides for the conversion of quinoline *N*-oxides into chloroquinolines is not as well documented as the corresponding reaction employing phosphorus halides, despite the fact that the first recorded reaction of this type, i.e. the conversion of quinoline *N*-oxide into 4-chloroquinoline, was achieved by Meisenheimer[241] using sulphuryl chloride as the halogenating agent. Later studies by Bobranski[758, 759] showed that the above reaction does in fact yield a mixture of 2- (38%) and 4-chloro-quinoline (62%) together with a trace of an unidentified tetrachloroquinoline. Polychlorination appears to be a typical consequence of using sulphuryl chloride as the chlorinating agent. For example, while 6-methoxyquinoline *N*-oxide reacts with phosphorus oxychloride to give only the 2- and 4-chloro-derivatives,[405,776] with sulphuryl chloride a mixture of three dichloroquinolines and a trichloroquinoline is obtained.[776]

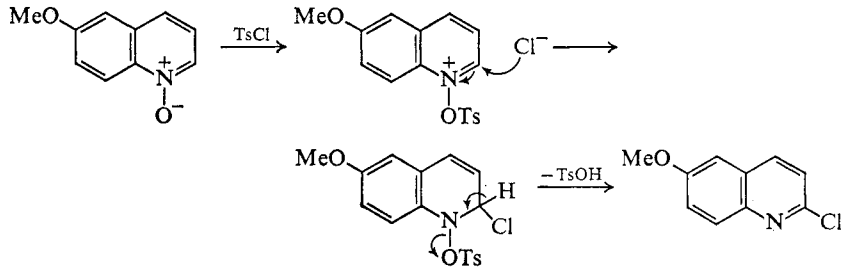
Other examples of the use of sulphuryl chloride involve the synthesis of 4-chloro-2-methylquinoline from 2-methylquinoline *N*-oxide,[783] and 2-chloro-5-nitroquinoline and 2-chloro-8-nitroquinoline from the corresponding nitroquinoline *N*-oxides.[784]

In the latter reactions no reference is made to the formation of any isomeric 4-chloronitroquinolines (see previous section).

c. Reaction with Acyl Halides. Great interest is in evidence in the literature concerning the reaction of quinoline *N*-oxides with acyl halides, particularly *p*-toluenesulphonyl chloride. Murakami and Matsumura[785] were the first to demonstrate that quinoline *N*-oxide with *p*-toluenesulphonyl chloride in benzene gives a mixture of 2-quinolone and 4-chloroquinoline. However, subsequent work by Tanida[786] indicates that in the presence of boron trifluoride at 180 °C the reaction becomes more complex and yields, besides the above products, 3-(*p*-tosyloxy)-quinoline. Tanida[787] has also found that 2- and 4-methylquinoline *N*-oxide with a mixture of *p*-toluenesulphonyl chloride and boron trifluoride in dimethylformamide solution give products chlorinated at the methyl group rather than on the quinoline nucleus; for example, 4-methylquinoline *N*-oxide yields 4-(chloromethyl)quinoline (50%). 2-Methylquinoline *N*-oxide reacts with *p*-toluenesulphonyl chloride in the presence of the enamine, *N*-cyclohex-1-enylmorpholine and an acid catalyst, to give a mixture that includes 3-chloro-2-methylquinoline, albeit in low yield (2.7%).[788]

6-Acetamidoquinoline *N*-oxide and *p*-toluenesulphonyl chloride in chloroform give 6-acetamido-2-chloroquinoline (30%) and 6-acetamido-2-quinolone (40%).[405] 6-Methoxyquinoline behaves similarly although in this instance a 62% yield of the 2-chloroquinoline (**251**) is realized.

In all the above-mentioned reactions chlorination is thought[405] to involve initial tosylation of the *N*-oxide function followed by nucleophilic attack of chloride ion mainly at the 2-position to give adduct (**250**) (Scheme 17), although 4-chlorination has also been observed.[789]



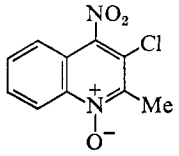
250 **251**

Scheme 17

In the presence of *p*-toluenesulphonyl chloride and a tertiary amine, quinoline *N*-oxide reacts at room temperature to give a complex mixture.[790] In the presence of *N*,*N*-dimethylaniline there are formed 2-(*p*-dimethylaminophenyl)quinoline (37.6%), 2-chloroquinoline (4.8%), 4-chloroquinoline (12.2%), and 4-quinolone (13.7%). At higher temperatures (96–98 °C) the yield of 2- and 4-chloroquinolines is raised to 31% and 22%, respectively, while 3-(*p*-tosyloxy)quinoline (6.8%) and 2-quinolone (2%) are also formed. Buchmann[791] reports that 2-methyl-4-nitroquinoline *N*-oxide and acetyl chloride give 3-chloro-2-methyl-4-nitroquinoline *N*-oxide (**252**).

The reactions of quinoline *N*-oxides with benzimidoyl chloride (PhCCl=NPh) have been investigated. Abramovitch and Rogers[792] have shown that quinoline *N*-oxide with benzimidoyl chloride in hot 1,2-dichloroethane solution gives 2-(*N*-benzoylanilino)quinoline (27.8%), 2-anilinoquinoline (35.8%), benzanilide (17.8%), and 3-quinolyl benzoate (33.5%). These products are explained on the basis of initial formation of the oxadiazole intermediate (**253**). 4-Nitroquinoline *N*-oxide, however,

reacts in a far more complicated manner to yield a host of products of which, as yet, only four, viz benzanilide, 4-chloro-3-quinolyl benzoate (**254**), 4-chloroquinoline



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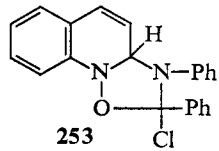

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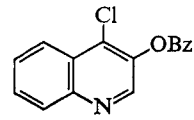

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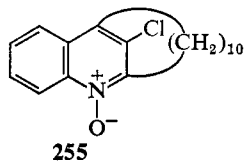
N-oxide, and 2-anilino-4-chloroquinoline, have been identified. The mechanism of this reaction has still to be resolved.

Parham and Sloan[793] have carried out similar reactions but on more complicated quinoline *N*-oxide systems. They have treated the metacyclophanes (**255** and **256**) with benzimidoyl chloride to give the di- and tri-chloroquinolines (**257** and **258**),



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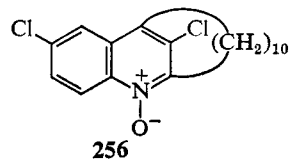

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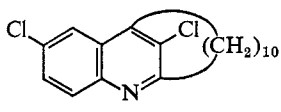

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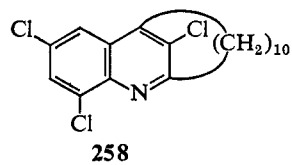

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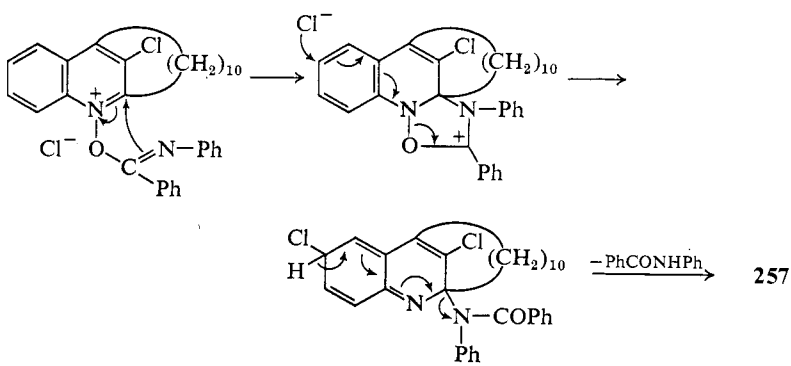
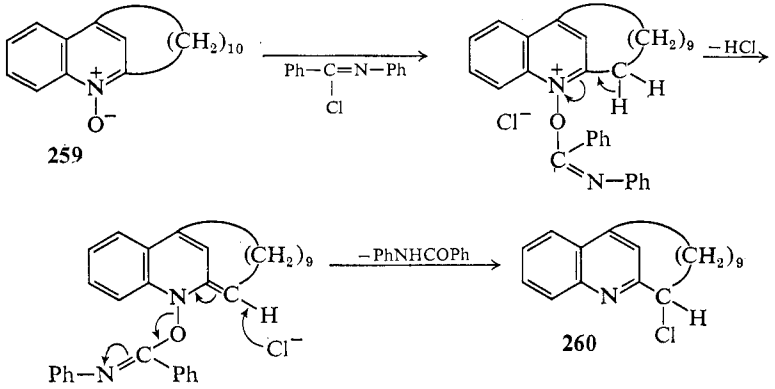
respectively, in yields of 80 and 69%. The unsubstituted metacyclophane *N*-oxide (**259**), however, behaves differently in that halogenation of the methylene chain occurs to yield the chloro-compound (**260**) (16%). The structure of the product was confirmed in each case by both analytical and spectral measurements. Formation of the di- and tri-chloro-derivatives (**257** and **258**) is as visualized in Scheme 18.



SCHEME 18

In the case of the unsubstituted *N*-oxide (**259**) the authors claim that inspection of molecular models reveals that removal of halogen from the 3-position relieves constraint on the methylene bridge, thus allowing easier formation of an sp^2-carbon centre. Hence, chlorination occurs at the α-carbon of the bridging methylene chain (as outlined in Scheme 19) rather than at the quinoline nucleus.



SCHEME 19

Further detail about haloquinolines obtained from *N*-oxides are presented in Table 19.

TABLE 19. Haloquinolines from Quinoline *N*-oxides

Product*	Yield (%)	M.p. (°C)	References
2-Chloro-			759, 790
6-Acetamido-2-chloro-	30	207	405
4-Amino-2-chloro-		198	767
2-Chloro-4-carboxylic acid		192	762
2-Chloro-4-carbonyl chloride		90	762
2-Chloro-4-(*p*-chlorophenylazo)-		169	391
2-Chloro-4-(2,4-dichlorophenylazo)-		165	391
2-Chloro-3,6-dinitro-		162	397, 773
2-Chloro-6-methoxy-	55	107	405, 757, 769, 776
2-Chloro-4-methyl-8-nitro-			763
2-Chloro-7-methyl-		81	777
2-Chloro-7-methyl-8-nitro-	40	134	778
2-Chloro-3-nitro-		119	396
2-Chloro-5-nitro-	44.5	134	537, 761, 784
2-Chloro-6-nitro-	16	230	405, 757, 760
2-Chloro-8-nitro-		149	784
2-Chloro-4-phenyl-	83	89	764
2-Chloro-4-phenylazo-		115	391
2-Chloro-4-(2-pyridylmethyl)-		151	766
2-Chloro-4-styryl-		121	765
3-Chloro-2-methyl-	2.7	66	788

* See footnote to Table 1, p. 340.

TABLE 19 (*cont.*)

Product*	Yield (%)	M.p. (°C)	References
3-Chloro-2-methyl-4-nitro *N*-oxide	63	205	791
3-Chloro-5-nitro-	13.1	129	537, 761
3-Chloro-6-nitro-	3.5	145	757, 760
4-Chloro-			241, 758, 759, 785, 786, 789, 790
3-Bromo-4-chloro-		68.5	396
4-Chloro-2-(*m*-chlorophenyl)-6-methoxy-	64	154	769
4-Chloro-2-(*p*-chlorophenyl)-6-methoxy-	76.5	164	769
4-Chloro-2-(*m*-chlorophenyl)-6-methyl-	78	116	771
4-Chloro-2-(*p*-chlorophenyl)-6-methyl-	47	139	771
4-Chloro-2-(*p*-chlorophenyl)-7-methyl-	50	135.5	771
4-Chloro-6-methoxy-	35	79	405, 757, 769, 776
4-Chloro-6-methoxy-2-phenyl-	91	111	769
4-Chloro-2-(*o*-methoxyphenyl)-	56.5	98	769
4-Chloro-2-(*p*-methoxyphenyl)-6-methyl-	75	109	770
4-Chloro-2-(*p*-methoxyphenyl)-7-methyl-	76.5	91	770
4-Chloro-2-methyl-		43	783
4-Chloro-7-methyl-		Liq.	777
4-Chloro-5-nitro-	9.4	150	537, 761
4-Chloro-6-nitro-	56.5	142.5	405, 757, 760
4-Chloro-2-phenyl-		63	764, 794
2,4-Dibromo-	40.5	93	619
x,*x*,-Dichloro-6-methoxy-		98	776
x,*x*-Dichloro-6-methoxy-		116	776
x,*x*,-Dichloro-6-methoxy-		124	776
2,4-Dichloro-	91	66	396, 772
2,4-Dichloro-6,8-dinitro-		210	396
2,6-Dichloro-	49	161.5	757
2,7-Dichloro-		120	775
4,4′-Dichloro-2,2′-biquinoline	24	307	795
4,5-Dichloro-2-methyl-	50	89	768
4,6-Dichloro-	35	104	757
4,7-Dichloro-		85	775
4,7-Dichloro-2-methyl-	63	103	768
x,*x*,*x*,*x*-Tetrachloro-		158	759
x,*x*,*x*,*x*-Tetrachloro-3,6-dinitro-		168	397, 774
x,*x*,*x*-Trichloro-6-methoxy-		191	776
2,4,7-Trichloro-		100	775
3,6-Dichloro-2,4[10]quinolinophane (**257**)	80	79	793
3,6,8-Trichloro-2,4[10]quinolinophane (**258**)	69	160	793

H. Preparation by Displacement of Substituents Other than Halogen†

In a previous Section (II.1.F) the preparation of haloquinolines by halogen–halogen exchange has been discussed. In the present Section the preparation of haloquinolines by displacement of substituents other than halogen is considered.

* See footnote to Table 1, p. 304.

† See also Addenda, p. 679.

a. Sulphonic Acids and Other Sulphur-containing Groups. The displacement of sulphonic acid groups during halogenation, especially bromination, of aromatic compounds is well known, and this reaction has been utilized in the quinoline series for the preparation of bromoquinolines.

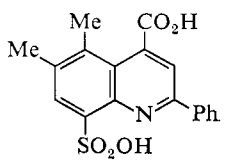
Quinoline-7-sulphonic acid reacts with aqueous bromine to yield initially an unstable bromine adduct that, when heated at 100 °C, undergoes loss of the sulphonic acid group and yields a dibromoquinoline of unknown constitution.[796] With an excess of aqueous bromine a tribromoquinoline, m.p. 199 °C, is formed, again with loss of the sulphonic acid group.

Quinoline-6-sulphonic acid reacts with cold aqueous bromine (2 equivalents) to give 3,6-dibromoquinoline, whereas 3,6,8-tribromoquinoline is produced by an excess of aqueous bromine under reflux.[797] 3,6,8-Tribromoquinoline is also obtained by heating quinoline-8-sulphonic acid[297, 796, 797] or 6-bromoquinoline-8-sulphonic acid[297, 716] with aqueous bromine. 5-Bromoquinoline-8-sulphonic acid also reacts with two equivalents of bromine in aqueous solution to give 3,5,8-tribromoquinoline, whereas with an excess of halogen a tetrabromo-derivative, m.p. 198 °C, possibly 3,5,6,8-tetrabromoquinoline, is obtained.[297] Quinoline-5-sulphonic acid behaves somewhat differently in that with bromine in acetic acid bromination occurs at the 3-position without loss of the sulphonic acid group;[798] however, with neat bromine, or in chloroform solution, a mixture of 3,5,8-tribromo- and 3,5,6,8-tetra-bromoquinoline is formed.

Heating 5- or 7-bromoquinoline-8-sulphonic acid with potassium bromide at 300 °C yields 5,8- and 7,8-dibromoquinoline, respectively.[725] Bromine or phosphorus pentabromide converts 8-hydroxyquinoline-5-sulphonic acid into 5,7-dibromo-8-hydroxyquinoline,[158] whereas with phosphorus pentabromide at 170 °C in a sealed tube 3,5,7-tribromo-8-hydroxyquinoline is formed.[158, 165, 297] In contrast, 6-hydroxyquinoline-5-sulphonic acid suffers only monobromination when treated with bromine and yields 5-bromo-6-hydroxyquinoline.[330]

1,2,3,4-Tetrahydroquinoline-8-sulphonic acid reacts with bromine water to give as the main product 3,6,8-tribromo-quinoline;[189] also formed are an unidentified monobromoquinoline, a dibromo-compound (m.p. 101 °C; possibly 6,8-dibromoquinoline), and a tetrabromo-derivative, m.p. 255 °C. In chloroform solution, however, the sole bromination product appears to be 6-bromo-1,2,3,4-tetrahydroquinoline-8-sulphonic acid, which, with aqueous bromine, yields 3,6,8-tribromoquinoline. 1,2,3,4-Tetrahydroquinoline-5-sulphonic acid reacts with neat bromine or with bromine in acetic acid or chloroform solution to give what was thought to be 7-bromo-1,2,3,4-tetrahydroquinoline-5-sulphonic acid;[798] however, with an excess of aqueous bromine a mixture of products including 3,5,6-tribromoquinoline is formed.

The 8-sulphoquinoline-4-carboxylic acid (**261**) with bromine and potassium bromide in 0.2N-potassium hydroxide solution at 75 °C gives, as major product, the



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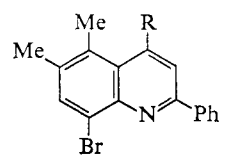

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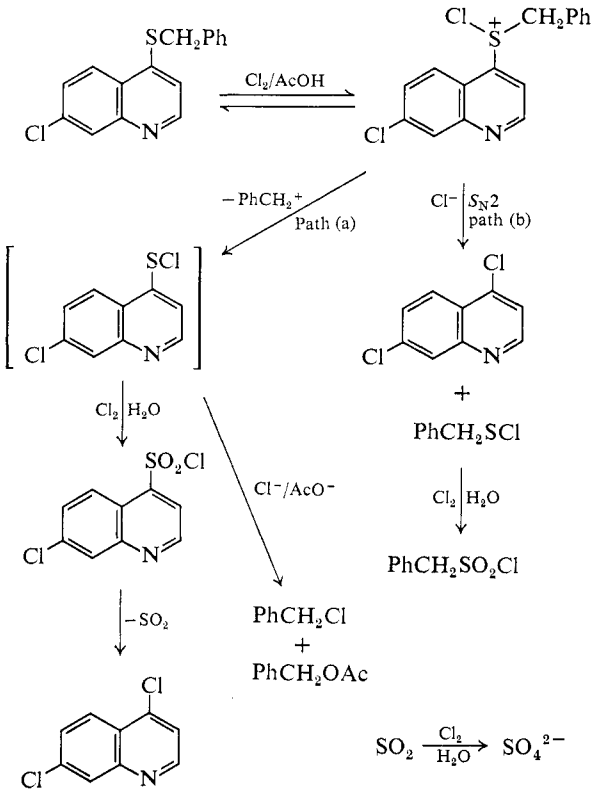
8-bromo-derivative (**262**; R = CO_2H) together with the decarboxylated material (**262**; R = H).[375]

Instances of the replacement of sulphonic acid groups by chlorine have also been recorded. Quinoline-4-sulphonic acid reacts with phosphorus pentachloride or oxychloride at 140 °C to give 4-chloroquinoline.[799] 8-Hydroxyquinoline-5-sulphonic acid with phosphorus pentachloride at 170 °C yields 5-chloro-8-hydroxyquinoline, whereas, with chlorine, 5,7,-dichloro-8-hydroxyquinoline is produced[165] An unidentified trichloroquinoline is obtained from the treatment of the uncharacterized 2-methoxyquinoline-*x*-sulphonic acid with phosphorus pentachloride at 200 °C.[800]

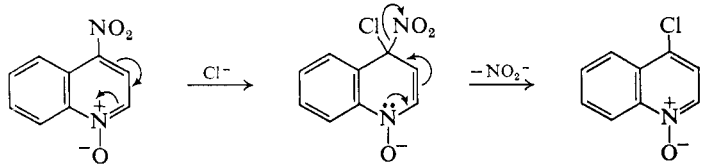
Oxidative cleavage of alkyl aryl sulphides to the corresponding arenesulphonyl chlorides is a well-documented process and can be conveniently carried out by using chlorine in "wet" acetic acid solution.[801] The method has proved successful for the synthesis of several quinolinesulphonyl chlorides,[802] but in certain cases replacement of the alkylthio-group by chlorine rather than oxidative cleavage occurs. For example, 4-(benzylthio)-7-chloroquinoline yields 4,7-dichloroquinoline (86%), and 4-(benzylthio)-8-nitroquinoline gives the corresponding 4-chloro-8-nitroquinoline (77%); the displaced benzyl group was, in each case, found in the reaction mixture as benzyl chloride, but no account of the fate of the sulphur residue was given. This omission prompted Kwart and Miller[803] to reinvestigate the chlorinolysis of carbon–sulphur bonds; they showed that phenylmethanesulphonyl chloride (8.5–12%) and sulphate ion (75–83%) account for the missing sulphur fragment, and also that benzyl acetate is present among the products. On the basis of some mechanistic studies Kwart and



SCHEME 20

his co-workers[803, 804] concluded that approximately 80% of the reaction resulting in 4-chloroquinoline formation proceeds via a carbonium ion mechanism (Scheme 20, path a), whereas 14% of the chloro-compound arises by an S_N2-type process involving displacement of phenylmethanesulphonyl chloride by chloride ion, as indicated in Scheme 20 (path b). They observed that the so-called abnormal chlorinolysis, i.e. the S_N2-process, occurs only with those compounds in which the sulphur is bonded to an unsaturated system "conjugated with an imino-nitrogen, as in R—S—$(C{=}C)_n$—C=N—", and convincing detailed arguments leading to this conclusion are given.[804]

b. Nitro and Other Nitrogen-containing Groups. As mentioned in a previous Section (II.1.G) chloroquinolines are available by treatment of quinoline *N*-oxides with phosphorus, sulphur, or acyl halides. However, if a nitro-substituent is present at the 4-position of the quinoline *N*-oxide then the nitro-group is readily replaced and 4-chloroquinolines may be obtained in good yield. Mechanistically the reaction may be viewed simply as a nucleophilic displacement (by chloride ion) of an activated nitro-group as outlined in Scheme 21.



Scheme 21

4,6-Dinitroquinoline *N*-oxide reacts with boiling phosphorus oxychloride to yield 2,4-dichloro-6-nitroquinoline.[805] Other 4-nitroquinoline *N*-oxides behave similarly on treatment with phosphorus oxychloride or oxybromide,[405, 764, 795] although in most cases only monohalogenation (resulting from displacement of the nitro-group) is observed. 4-Nitroquinoline *N*-oxide with phosphorus oxychloride at room temperature gives a mixture of 4-chloro- and 2,4-dichloroquinoline *N*-oxide together with some 4-chloro-2-quinolone;[806] little reaction is observed when phosphorus pentachloride is used. 4-Nitroquinoline *N*-oxide also reacts with phosphorus trichloride in cold chloroform solution to give a mixture of 4-chloroquinoline and the expected deoxygenated product 4-nitroquinoline;[807] in contrast, phosphorus tribromide in cold chloroform solution yields only deoxygenated material, although under reflux a mixture of nitroquinoline and 4-bromoquinoline is formed.[608, 807]

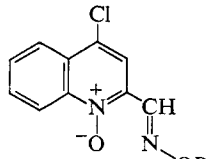
The reaction between 4-nitroquinoline *N*-oxide and phosphorus halides has been investigated in great detail by Hamana,[608, 808] who concludes that (a) 4-nitroquinoline *N*-oxide, unlike quinoline *N*-oxide, undergoes chlorination by loss of the nitro-group when treated with phosphorus trichloride, and (b) chloroquinolines are obtained in greatest yield when chloroform or carbon tetrachloride is employed as the reaction solvent. In ethyl acetate solution a mixture of products, including 4-chloroquinoline *N*-oxide and 2,4-dichloroquinoline, results. Under optimum conditions (4-nitroquinoline *N*-oxide 1 mol; phosphorus trichloride 4 mol, in chloroform solution at 100 °C for 1 hour), 4-chloroquinoline is obtained in 81.5% yield. The reaction of 4-nitroquinoline *N*-oxide with phosphorus tribromide and oxybromide has also been studied exhaustively by Hamana and his co-workers;[608, 619] with phosphorus oxybromide in hot ethyl acetate 2,4-dibromoquinoline (64%) is obtained,[619] whereas with phosphorus tribromide deoxygenation without accompanying bromination occurs to a large degree, regardless of the solvent or temperature employed.

4,4′-Dinitro-2,2′-biquinoline 1,1′-dioxide reacts with boiling phosphorus trichloride or tribromide to give 4,4′-dichloro- and 4,4′-dibromo-2,2′-biquinoline in 19% and 7% yield, respectively.[614, 795]

Replacement of a 4-nitro-substituent can also be brought about by boiling the nitroquinoline *N*-oxide with hydrochloric acid, and in this case the *N*-oxide function is retained. By this method 4-chloroquinoline *N*-oxides bearing methoxy-,[809] styryl,[810] alkyl,[791, 811–814] nitro-,[815, 816] halo-,[816] and carboxylic acid[817] groups have been synthesized. In a similar manner 4-bromoquinoline *N*-oxides may be obtained by heating 4-nitroquinoline *N*-oxides with 30% hydrobromic acid.[816]

In neutral or basic media the fluorine atom in 3-fluoro-4-nitroquinoline *N*-oxide is more reactive than the nitro-substituent towards nucleophilic displacement.[684] However, under acid conditions the order of reactivity is reversed and 4-chloro-3-fluoroquinoline *N*-oxide is obtained on warming the fluoro-nitro-*N*-oxide with concentrated hydrochloric acid.

Acid chlorides, particularly acetyl chloride, have also proved effective reagents for the replacement of nitro-groups in heterocyclic *N*-oxides by chlorine.[756] 4-Nitroquinoline *N*-oxide reacts with acetyl chloride at 45 °C to give 4-chloroquinoline *N*-oxide (83%), whereas with benzoyl chloride the chief product is 4-chloro-2-quinolone.[806] Complications, however, can arise during these reactions. For example, 2-methyl-4-nitroquinoline *N*-oxide and acetyl chloride at room temperature give 4-chloro-2-methylquinoline *N*-oxide (3.2%) together with a complex mixture of products which are thought to arise by attack of acetyl nitrate, formed *in situ*, on the reactive 2-methyl substituent;[813] amongst the products isolated are the oxime (**263**; R = H), its *O*-acetyl derivative (**263**; R = Ac), and the amide (**264**).



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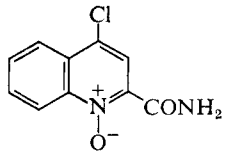

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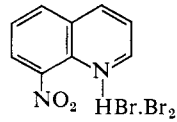

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Under Reissert reaction conditions, i.e. benzoyl chloride and potassium cyanide, 4-nitroquinoline *N*-oxide yields 4-chloro-2-cyanoquinoline.[813]

2-Chloro-4-nitroquinoline *N*-oxide is thought[741] to react with acetyl or benzoyl chloride, under reflux, to give initially 2,3-dichloroquinoline *N*-oxide. However, further reaction takes place and the isolated products are 1-acetoxy- and 1-benzoyloxy-4-chloro-2-hydroxyquinoline, respectively.

Chloroquinoline formation is reported during the photolysis of 4-nitroquinoline *N*-oxide in nitrosyl chloride solution.[818] This reaction, which is thought by the authors to be free radical in nature, is offered as evidence to show that the 4-position in 4-nitroquinoline *N*-oxide is reactive towards free-radical attack.

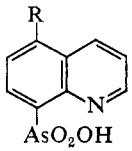
No reaction occurs when 4-nitroquinoline *N*-oxide is boiled with stannic chloride,[806] and, as expected, 5- and 6-nitro-quinoline *N*-oxide are unaffected by boiling hydrochloric acid.[816] 4-Nitroquinoline, however, when boiled with either hydrochloric acid or phosphorus oxychloride, yields 4-chloroquinoline.[807]

Schultz and his co-workers[245] find that 6-methoxy-8-nitroquinoline with sulphuryl chloride yields a mixture of chlorinated products amonst which are 3,5,7,8-tetrachloro- and 5,7,8-trichloro-6-methoxyquinoline. Loss of a nitro-group is also observed when the $HBr.Br_2$ complex (**265**) of 8-nitroquinoline is heated at 200 °C,[95] 3,8-dibromoquinoline being the product.

A similar loss of an 8-nitro-substituent occurs when 1-methyl-8-nitro-2-quinolone is heated with phosphorus pentabromide at 150 °C.[651] The resulting uncharacterized tribromo-derivative is possibly 2,6,8-tribromoquinoline.

During the preparation of some quinolinearsonic acids Slater[819] found that 8-amino-5-nitroquinoline, on diazotization and subsequent reaction with sodium arsenite and copper sulphate, yields the 5-chloroquinoline-8-arsonic acid (**266**; R = Cl) rather than the expected 5-nitro-compound (**266**; R = NO_2); it appears that the nitro-group is labilized towards nucleophilic displacement by the *para*-diazonium group formed initially in the reaction.

Elks and Hey[820] have shown that the diazoamino-compound (**267**) on treatment with hydrochloric acid in boiling benzene undergoes homolysis to 5-chloroquinoline,



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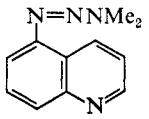

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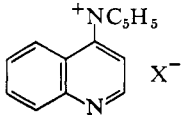


268

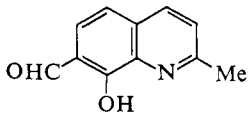
5-phenylquinoline, nitrogen, and dimethylamine. 4-Anilino-2-ethyl-3-methylquinoline is reported[599] to suffer replacement of the anilino-group on being heated with concentrated hydrochloric acid at 155 °C, and yields the 4-chloro-derivative; at 190 °C, however, the 4-quinolone is formed.

The quaternary pyridinium salts (**268**; X = Cl^- or TsO^-) with hot phosphorus pentachloride yield 4-chloroquinoline (56%).[821]

c. Carboxylic Acid and Other Carbonyl-containing Groups. Quinolinecarboxylic acids readily undergo decarboxylation and the method has been used as a preparative route to haloquinolines (see Section II.1.P). However, a few examples of the direct displacement of a carboxylic acid group and other carbonyl-containing functions by halogen are known.

Lippmann and Fleissner[266] report that 8-hydroxyquinoline-5-carboxylic acid on treatment with bromine in dilute hydrochloric acid undergoes 5,7-dibromination with loss of the 5-carboxylic acid group. 8-Hydroxyquinoline-7-carboxylic acid behaves similarly with bromine in acetic acid, and yields 5,7-dibromo-8-hydroxyquinoline.[164]

Replacement of a formyl group during bromination has also been observed. 5-Formyl-8-hydroxyquinoline with bromine in hot acetic acid gives 5,7-dibromo-8-hydroxyquinoline,[155] while 5,7-dichloro-8-hydroxy-2-methylquinoline can be prepared by treating the quinoline aldehyde (**269**) with chlorine in acetic acid.[159]



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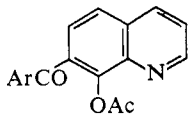

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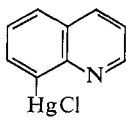
Replacement of a ketonic side chain by bromine has been reported by Matsumura[143] who isolated 7-bromo-8-hydroxyquinoline from the reaction of 8-acetoxy-7-(*o*-carboxybenzoyl)quinoline (**270**; Ar = *o*-$HO_2CC_6H_4$) with bromine in glacial acetic

acid; with an excess of bromine in dilute hydrochloric acid, 5,7-dibromo-8-hydroxyquinoline was formed.

3-Amino-2-phenylquinoline-4-carboxylic acid on treatment with thionyl chloride yields a red sticky solid, which slowly loses sulphur dioxide to deposit 3-amino-4-chloro-2-phenylquinoline.[693] The mechanism of this reaction remains obscure.

d. Miscellaneous Groups. In a series of publications Ukai has shown[99] that mercurichloride (HgCl) and mercuriacetate (HgOAc) groups are readily displaced from the quinoline nucleus by bromine. For example, 8-mercurichloroquinoline (**271**) reacts with bromine to give 8-bromoquinoline in good yield,[822, 823] while the 3-mercuriacetate (**272**) with boiling potassium bromide solution yields 3-bromoquinoline.



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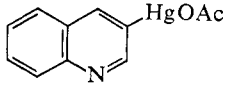

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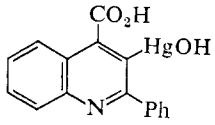

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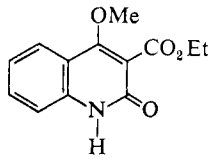
The reaction is also successful with the mercury derivatives of various methylquinolines but the orientation of the substituents in the resulting bromomethylquinolines is not always obvious since the site of initial mercuriacetoxylation is not known.[99] For example, 6-methylquinoline on mercuration followed by treatment with bromine yields a mixture of bromomethylquinolines. The isomer of m.p. 53 °C was assumed to be the 8-bromo-derivative and this has been confirmed by Capps and his co-workers.[650] The other product, m.p. 51 °C, is probably 3-bromo-6-methylquinoline. More recently Ukai has extended the reaction to the synthesis of bromoquinoline *N*-oxides.[719, 824] For example, 8-mercurichloroquinoline *N*-oxide, with bromine, yields 8-bromoquinoline *N*-oxide. 3-Bromo-2-phenylquinoline-4-carboxylic acid can be prepared by treating the mercurihydroxide derivative (**273**) with bromine in aqueous sodium bromide solution.[825]

Replacement of alkoxy-groups by halogen has been noted on a few occasions. Grundon, McCorkindale, and Rodger[414] during their studies on the synthesis of the alkaloid dictamnine, found that the ethyl ester (**274**) reacts with phosphorus oxychloride to give ethyl 2,4-dichloroquinoline-3-carboxylate (**275**; R = Cl) as well as the expected 2-chloro-4-methoxy-compound (**275**; R = OMe).



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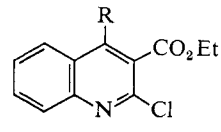

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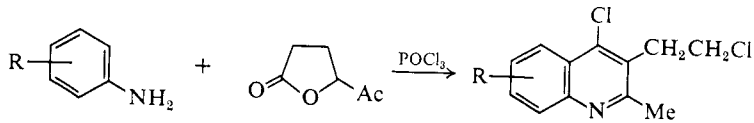
In related studies Japanese workers[166, 624, 826–831] have shown that aromatic amines condense with the acetyl-γ-butyrolactone (**276**) in the presence of phosphorus oxychloride to give 4-chloro-3-(2-chloroethyl)quinaldines (**277**). At low temperatures[624, 832] or with nitroanilines[826] it is possible to isolate the dihydrofuro[3,2-*c*]-quinoline intermediate (e.g. **278**), which on treatment with phosphorus oxychloride undergoes ring cleavage and chlorination to give the 4-chloro-3-(2-chloroethyl)



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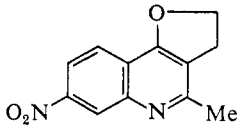
derivative (**277**; R = 7-NO_2). The initial condensation products, anils (**279**), have been isolated,[828, 830, 833] and as expected are converted by phosphorus oxychloride into the dichloro-derivatives (**277**). Phosphorus oxybromide brings about a similar reaction to yield the corresponding bromo-derivatives.[624]



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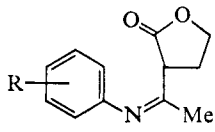

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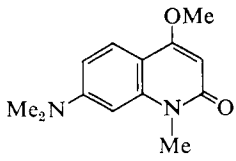
These ring-opening reactions presumably involve nucleophilic attack of chloride ion at the 4-position of the quinoline ring and hence may be considered as examples of alkoxy-displacement.

Replacement of a methoxy-group by chlorine has been observed by Harnisch and Brack[834] during formylation of the 2-quinolone (**280**) under Vilsmeier–Haack conditions. When the quinolone is treated with phosphorus oxychloride and dimethylformamide at 55 °C a 79% yield of the 3-formyl derivative (**281**) is obtained, in which the 4-methoxy-group has been replaced by chlorine.



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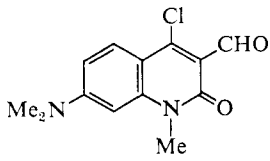

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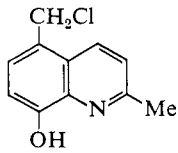

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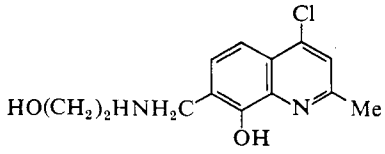
Replacement of both sulphonic acid and methoxy-groups by chlorine is observed when a 2-methoxyquinoline-*x*-sulphonic acid is heated with phosphorus pentachloride at 200 °C.[800] The product a trichloroquinoline, of indeterminate melting point (ca. 140 °C), was not identified.

Fiedler has observed the replacement of a chloromethyl group by bromine during the bromination of the 8-hydroxyquinaldine (**282**) in acetic acid.[157] 5,7-Dibromo-8-hydroxy-2-methylquinoline is obtained in 49% yield. In a similar manner the Mannich base (**283**) suffers replacement of the alkylamino side chain by bromine, when treated with bromine in acetic acid.[161]



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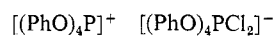

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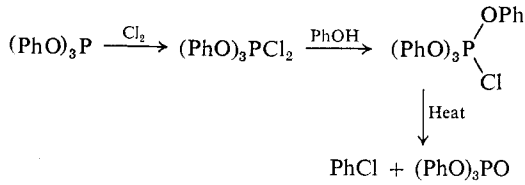
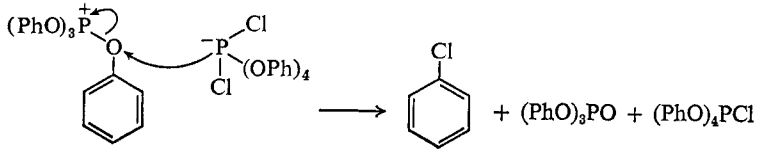
Rydon and his co-workers[835] have investigated the use of triaryl phosphite dihalides as a means of preparing aryl halides from simple phenols. The reaction, which involves chlorination of the triaryl phosphite and then reaction with the phenol (Scheme 22), is thought to proceed via a dimeric tetraphenoxyphosphorus



SCHEME 22

monohalide complex of type (**284**), which yields the chloro-compound by a process shown in Scheme 23.



SCHEME 23

The reaction, which is essentially a nucleophilic replacement of phosphate residue by chloride ion, fails when applied to 8-hydroxyquinoline, whereas 2-chloroquinoline may be prepared in 79% yield.

Reactions involving displacement are summarized in Table 20.

TABLE 20. Haloquinolines Produced by Nucleophilic Displacement of Substituents Other than Halogen

Haloquinoline* produced	Method of preparation (yield)	References
BROMO-		
3-Bromo-	Q-3-HgOAc; heat with KBr	99
3-Bromo-4-chloro *N*-oxide	4-NO_2-3-Br-Q *N*-oxide; conc. HCl at 100 °C for 30 min (79%)	816
3-Bromo-6-methyl-	6-Me-Q-3-HgOAc; Br_2	99
3-Bromo-2-phenyl-4-carboxylic acid	2-Ph-3-HgOH-Q-CO_2H; Br_2/NaBr	825
4-Bromo-	4-NO_2-Q *N*-oxide; $PBr_3/CHCl_3$ reflux for 1 h (71%)	608, 807
4-Bromo *N*-oxide	4-NO_2-Q *N*-oxide; 30% HBr at 100 °C for 30 min (60%)	731, 816
4-Bromo-6-methyl *N*-oxide	4-NO_2-6-Me-Q *N*-oxide; 48% HBr at 100 °C; heat to dryness (67%)	811, 812
5-Bromo-6-hydroxy-	6-HO-Q-SO_2OH; Br_2/H_2O	330
5-Bromo-7-methyl-	7-Me-Q-5-HgOAc; Br_2	99
5-Bromo-8-methyl-	8-Me-Q-5-HgOAc; Br_2	99

* See footnote to Table 1, p. 340.

TABLE 20 (*cont.*)

Haloquinoline* produced	Method of preparation (yield)	References
6-Bromo-4-chloro *N*-oxide	4-NO_2-6-Br-Q *N*-oxide; conc. HCl at 100 °C for 30 min (78%)	816
6-Bromo-4-chloro-5-nitro *N*-oxide	4,5-diNO_2-6-Br-Q *N*-oxide; as above (54%)	816
7-Bromo-8-hydroxy-	8-AcO-7-(*o*-$HO_2CC_6H_4CO$)-Q; Br_2/AcOH stir for 4.5 h	143
8-Bromo-	Q-8-HgCl; Br_2	822, 823
8-Bromo *N*-oxide	Q-8-HgCl *N*-oxide; Br_2	719, 824
8-Bromo-5,6-dimethyl-2-phenyl-	5,6-diMe-2-Ph-4-CO_2H-8-SO_2OH; Br_2/KBr at 75 °C for 1 h	375
8-Bromo-6-methyl-	6-Me-Q-HgOAc; Br_2	99
8-Bromo-6-methyl *N*-oxide	6-Me-Q-HgCl *N*-oxide; Br_2/KBr	719
CHLORO-		
2-Chloro-	2-Q'one; $(PhO)_3PCl_2$ heat (79%)	835
2-Chloro-4-phenyl *N*-oxide	4-NO_2-2-Ph-Q *N*-oxide; AcCl at 45 °C for 40 min	837
4-Chloro-	(i) 4-NO_2-Q *N*-oxide; $PCl_3/CHCl_3$ at 100 °C for 1 h (81.5%); (ii) Q-4-SO_2OH; PCl_5 or $POCl_3$ at 140 °C; (iii) 4-$C_5H_5N^+$-Q'ium Cl^-; PCl_5 at 140 °C (56%); (iv) 4-NO_2-Q; conc. HCl at 100 °C for 2 h or $POCl_3$ at 60 °C for 5 h	799, 807, 808, 821
4-Chloro *N*-oxide	4-NO_2-Q *N*-oxide; (i) PCl_3/AcOEt at 30 °C for 15 min (37%); (ii) conc. HCl at 100 °C for 30 min (95%); (iii) NOCl/$h\nu$; (iv) AcCl; (v) $POCl_3$ at room temp.	791, 806, 808, 816, 818
4-Chloro-2-quinolone	4-NO_2-Q *N*-oxide; PCl_3/CCl_4 at 76 °C for 1 h; or with BzCl (12.5%)	806, 808
4-Chloro-6-carboxylic acid *N*-oxide	4-NO_2-Q-6-CO_2H *N*-oxide; conc. HCl for 2 h at 100 °C	817
4-Chloro-2-cyano-	4-NO_2-Q *N*-oxide; BzCl/KCN	813
5,7-Dibromo-4-chloro-8-hydroxy-2-methyl-	4-Cl-8-HO-2-Me-7-($HOCH_2CH_2NHCH_2$)-Q; Br_2/AcOH	161
4-Chloro-7-dimethylamino-3-formyl-1-methyl-2-quinolone	1-Me-4-MeO-7-Me_2N-2-Q'one; $POCl_3$/DMF at 90 °C for 5 h (79.5%)	834
4-Chloro-2-ethyl-3-methyl-	4-PhNH-2-Et-3-Me-Q; conc. HCl at 155 °C for 2 h	599
4-Chloro-3-fluoro *N*-oxide	3-F-4-NO_2-Q *N*-oxide; HCl at 65 °C for 30 min	684
4-Chloro-2-hydroxy 1-acetoxy	2-Cl-4-NO_2-Q *N*-oxide; AcCl reflux for 30 min	741
4-Chloro-2-hydroxy 1-benzoyloxy-	As above but using BzCl	741
4-Chloro-6-methoxy *N*-oxide	4-NO_2-6-MeO-Q *N*-oxide; conc. HCl at 100 °C for 1 h	809
4-Chloro-2-(*p*-methoxystyryl) *N*-oxide	4-NO_2-2-(*p*-$MeOC_6H_4CH{=}CH$)-Q *N*-oxide; HCl/EtOH reflux 5 h (69%)	810
4-Chloro-2-methyl *N*-oxide	4-NO_2-2-Me-Q *N*-oxide; HCl/EtOH at 95 °C (73%) or with AcCl	813, 814

TABLE 20 (*cont.*)

Haloquinoline* produced	Method of preparation (yield)	References
4-Chloro-2-methyl-8-nitro *N*-oxide	4,8-diNO_2-2-Me-Q *N*-oxide; 20% HCl at 80 °C for 1.5 h (63%)	815
4-Chloro-3-methyl *N*-oxide	4-NO_2-3-Me-Q *N*-oxide; conc. HCl at 70 °C for 30 min	838
4-Chloro-5-methyl *N*-oxide	4-NO_2-5-Me-Q *N*-oxide; as above	838
4-Chloro-6-methyl *N*-oxide	4-NO_2-6-Me-Q *N*-oxide; HCl at 100 °C heat to dryness (91%)	811, 812
4-Chloro-6-methyl-5-nitro *N*-oxide	4,5-diNO_2-6-Me-Q *N*-oxide; conc. HCl at 100 °C for 30 min (78%)	816
4-Chloro-8-methyl *N*-oxide	4-NO_2-8-Me-Q *N*-oxide; as above at 70 °C for 30 min	838
4-Chloro-6-nitro-	4,6-diNO_2-Q *N*-oxide; $PCl_3/CHCl_3$ reflux for 30 min	405
4-Chloro-6-nitro *N*-oxide	4,6-diNO_2-Q *N*-oxide; conc. HCl at 100 °C for 30 min (52%)	816
4-Chloro-8-nitro-	4-$PhCH_2S$-8-NO_2-Q; Cl_2/AcOH at 30 °C (77%)	802
4-Chloro-8-nitro *N*-oxide	4,8-diNO_2-Q *N*-oxide; 15% HCl at 80 °C for 1 h	839
4-Chloro-2-phenyl-	4-NO_2-2-Ph-Q *N*-oxide; PCl_3 under reflux for 1 h	764
3-(4-Chloro-2-quinolyl)-propanoic acid *N*-oxide	4-NO_2-Q-2-$(CH_2)_2CO_2H$ *N*-oxide; AcCl at 0 °C for 30 min	817
5-Chloro-	5-Me_2N-N=N-Q; boil with HCl/C_6H_6	820
5-Chloro-8-arsonic acid	8-NH_2-5-NO_2-Q; $NaNO_2$/HCl at 15 °C then $Na_2As_2O_3/CuSO_4$ at 100 °C for 1 h	819
5-Chloro-8-hydroxy-	8-HO-Q-5-SO_2OH; PCl_5 at 170 °C	165
DIHALO-		
2,4-Dibromo-	(i) 4-Br-Q *N*-oxide; $POBr_3$ at 10 °C for 15 min; (ii) 4-NO_2-2-Br-Q; $POBr_3/CHCl_3$ under reflux for 1.5 h	619
3,8-Dibromo-	8-NO_2-Q.HBr.Br_2; heat at 200 °C	95
4,4′-Dibromo-2,2′-biquinoline	2,2′-(4,4′-diNO_2)biquinoline *N*,*N*′-dioxide; reflux with $PBr_3/CHCl_3$ for 2.5 h (12%)	614, 795
4,8-Dibromo *N*-oxide	4-Br-Q-8-HgCl *N*-oxide or 8-Br-Q-4-HgCl *N*-oxide; Br_2	719
5,7-Dibromo-8-hydroxy-	(i) 8-HO-Q-5-SO_2OH; Br_2 or PBr_5; (ii) 8-HO-5-CHO-Q; Br_2/AcOH; (iii) 8-HO-Q-5- or -7-CO_2H; Br_2/AcOH or HCl; (iv) 7-(*o*-$HO_2CC_6H_4CO$)-8-HO-Q; Br_2/dil. HCl at room temp.	143, 155, 158, 164, 266
5,7-Dibromo-8-hydroxy-2-methyl-	5-$ClCH_2$-8-HO-2-Me-Q; Br_2/AcOH (49%)	157
5,8-Dibromo-	5-Br-Q-8-SO_2OH; KBr at 300 °C in a sealed tube	725
7,8-Dibromo-	7-Br-Q-8-SO_2OH; treated as above	725
2,4-Dichloro-	4-NO_2-Q *N*-oxide; PCl_3/AcOEt at 77 °C for 1 h (18%) or with SO_2Cl_2	784, 791, 806, 808
Et 2,4-dichloro-3-carboxylate	2-Cl-4-MeO-Q-3-CO_2Et; $POCl_3$ reflux for 30 min	414

* See footnote to Table 1, p. 340.

TABLE 20 (*cont.*)

Haloquinoline* produced	Method of preparation (yield)	References
2,4-Dichloro-6,8-dinitro-	4,6,8-triNO$_2$-Q *N*-oxide; POCl$_3$/PCl$_5$ at 100 °C for 5 h	805
2,4-Dichloro-6-nitro-	4,6-diNO$_2$-Q *N*-oxide; POCl$_3$ at 100 °C for 2 h	805
3,4-Dichloro *N*-oxide	3-Cl-4-NO$_2$-Q *N*-oxide; conc. HCl at 70 °C for 30 min	838
4,4′-Dichloro-2,2′-biquinoline	2,2′-(4,4′-diNO$_2$)biquinoline *N*,*N*′-dioxide; reflux with POCl$_3$/AcCl or with POCl$_3$ (18%)	614, 795
4,5-Dichloro *N*-oxide	4-NO$_2$-5-Cl-Q *N*-oxide; conc. HCl at 70 °C for 30 min	838
4,6-Dichloro *N*-oxide	4-NO$_2$-6-Cl-Q *N*-oxide; as above (78%)	816
4,7-Dichloro-	4-PhCH$_2$S-7-Cl-Q; PCl$_5$ (86%)	802–804
4,7-Dichloro-2-methyl-	4-NO$_2$-2-Me-Q *N*-oxide; POCl$_3$	791
5,7-Dichloro-8-hydroxy-	8-HO-Q-5-SO$_2$OH; Cl$_2$/hot H$_2$O solution	165
5,7-Dichloro-8-hydroxy-2-methyl-	8-HO-2-Me-7-CHO-Q; Cl$_2$/AcOH	159
POLYHALO-		
3,5,6,8-Tetrabromo-	6-Br-Q-5- or 8-SO$_2$OH; excess of Br$_2$	836
3,5,7,8-Tetrachloro-6-methoxy-	6-MeO-8-NO$_2$-Q; SO$_2$Cl$_2$ under reflux for 15 min	245
2,6,8-Tribromo-	1-Me-8-NO$_2$-2-Q'one; PBr$_5$ at 150 °C	651
3,5,6-Tribromo-	6-Br-Q-5-SO$_2$OH; Br$_2$ warm	798, 836
3,5,7-Tribromo-8-hydroxy-	8-HO-Q-5-SO$_2$OH; PBr$_5$ at 160–170 °C in a sealed tube	158, 165, 297
3,5,8-Tribromo-	(i) 5-Br-Q-8-SO$_2$OH; Br$_2$/H$_2$O; (ii) Q-5-SO$_2$OH; 3Br$_2$ in CHCl$_3$	297, 798
3,6,8-Tribromo-	(i) 6-Br-Q-8-SO$_2$OH or Q-8-SO$_2$OH or Q-6-SO$_2$OH; heat with Br$_2$/H$_2$O; (ii) 1,2,3,4-tetraH-Q-8-SO$_2$OH; Br$_2$/H$_2$O	189, 297, 716, 797, 798, 836
2,*x*,*x*-Trichloro-	2-MeO-Q-*x*-SO$_2$OH; PCl$_5$ at 200 °C	800
4,6,7-Trichloro *N*-oxide	4-NO$_2$-6,7-diCl-Q *N*-oxide; conc. HCl at 70 °C for 30 min	838
5,8,*x*-Trichloro-	8-HO-Q-5-SO$_2$OH; heat with PCl$_5$	158
5,7,8-Trichloro-6-methoxy-	6-MeO-8-NO$_2$-Q; SO$_2$Cl$_2$ under reflux for 15 min	245

I. Deamination of Aminohaloquinolines

One of the first published syntheses of 3-bromoquinoline involved the deamination of 4-amino-3-bromoquinoline.[171] This was achieved by reduction of the diazonium compound, derived from the bromo-amine, with ethanol in sulphuric acid. In a similar manner 6-amino-3,5-dibromoquinoline yields 3,5-dibromoquinoline,[177] while under the same conditions a mixture of 5- and 7-amino-2-chloro-4-methylquinoline gives 2-chloro-4-methylquinoline in good yield.[428]

Hypophosphorous acid is a popular reagent for effecting the reductive denitrogenation of diazonium compounds and has been successfully applied for the synthesis of 6-chloro-5-nitroquinoline from the 8-amino-compound,[840] and of 3-bromoquinoline *N*-oxide from the 4-amino-derivative.[174] 5,6,8-Trifluoroquinoline is obtained by hypophosphorous acid-induced deamination of the corresponding 7-aminotrifluoroquinoline.[271, 721] Reputedly[178] the best synthesis of 5-bromoquinoline involves

deamination of 8-amino-5-bromoquinoline. Elderfield and Claflin[49] obtained 5,7-dibromoquinoline directly from 8-amino-5,7-dibromoquinoline by diazotizing the amine in 50% hypophosphorous acid.

If the amino-group is contained in the reduced ring of a hydrogenated quinoline, it behaves as an aliphatic amine and undergoes ready loss of nitrogen when treated with nitrous acid. By using this procedure Ueda[196] was able to prepare several halogenated 2-quinolones from the corresponding halogenated 3-amino-1,2,3,4-tetrahydro-2-oxoquinolines.

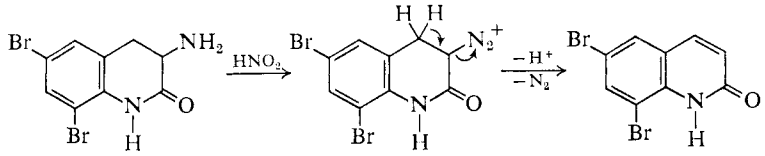


Table 21 provides a summary of such reactions.

TABLE 21. Haloquinolines by Deamination of Aminohaloquinolines

Deaminated product*	Amine (yield)	References
3-Bromo-	4-NH_2-3-Br-Q	171
3-Bromo *N*-oxide	4-NH_2-3-Br *N*-oxide	174
5-Bromo-	6-NH_2-5-Br-Q (51%)	176, 178, 841
6-Bromo-2-quinolone	3-NH_2-6-Br-1,2,3,4-tetraH-2-oxo-Q	196
6-Bromo-1,2,3,4-tetrahydro-2-oxoquinoline	7-NH_2-6-Br-1,2,3,4-tetraH-2-oxo-Q	197
2-Chloro-4-methyl-	5- or 7-NH_2-2-Cl-4-Me-Q	428
6-Chloro-5-nitro-	8-NH_2-6-Cl-5-NO_2-Q	840
3,5-Dibromo-	6-NH_2-3,5-diBr-Q	177
5,7-Dibromo-	8-NH_2-5,7-diBr-Q (40%)	49, 175
6,8-Dibromo-	5-NH_2-6,8-diBr-Q	175
6,8-Dibromo-2-quinolone	3-NH_2-6,8-diBr-1,2,3,4-tetraH-2-oxo-Q	196, 197
5,7-Dichloro-	8-NH_2-5,7-diBr-Q (60%)	49
5,6,8-Trifluoro-	7-NH_2-5,6,8-triF-Q	271, 721

J. Haloquinolines by the Skraup Reaction†

The Skraup reaction constitutes one of the classical methods for the synthesis of the quinoline ring system. A review of the reaction is available[842] which covers adequately the mechanistic aspects and the many variations that are possible in the reactants, the oxidizing agent, and the "moderator". In this Section, therefore, no attempt is made to cover all facets of the reaction and discussion will be confined to mechanistic and reactant variations in so far as they influence the synthesis of haloquinolines.

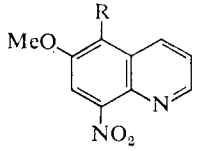
Early workers, particularly La Coste[843] and Claus,[217, 283, 287, 703, 844] utilized the Skraup reaction to great effect for the synthesis of mono-, di-, and tri-chloro- and -bromo-quinolines. Willgerodt and Arnold[845] in a like manner have synthesized several iodoquinolines, while more recently various fluoroquinolines have become available by this reaction.[271, 721, 846, 847]

* See footnote to Table 1, p. 340.

† See also Addenda, p. 680.

Haloquinolines bearing a wide variety of functional groups, viz. alkyl,[848-850] carboxyalkyl-,[851] nitro-[852-855] hydroxy-,[856-858] alkoxy-,[853, 859, 860] amino-,[861] carboxylic acid,[862, 863] and sulphonic acid,[864] have been prepared, generally in high yield, by the Skraup process. Detailed instructions for the preparation of 6-chloro-8-nitroquinoline and 5-bromo-6-methoxy-8-nitro-quinoline have been published.[853]

Most Skraup reactions appear to proceed with few attendant complications, and the resulting haloquinolines, particularly those of low molecular weight, are readily isolated by steam-distillation. Occasionally, however, anomalous results are observed. For instance, attempts to prepare 5-fluoro-6-methoxy-8-nitroquinoline (**285**; R = F)



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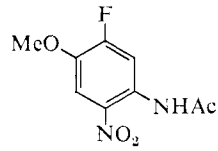

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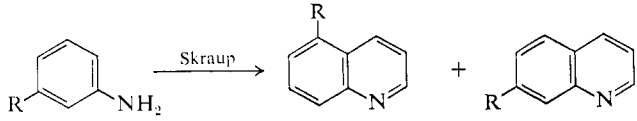
from 5-fluoro-4-methoxy-2-nitroacetanilide (**286**), using a mixture of glycerol, concentrated sulphuric acid, and arsenious oxide, failed.[90] Seemingly the 8-nitro-substituent activates the fluoro-group at position 5 towards nucleophilic displacement, and, under the reaction conditions, almost complete replacement of the fluorine by hydroxide to give the hydroxyquinoline (**285**; R = OH) takes place.

The fluoro-compound was eventually prepared, albeit in low yield (5%), by carrying out the Skraup reaction under vacuum conditions as described by Strukov.[865]

If the aromatic amine undergoing the Skraup reaction bears a substituent *meta* to the amino-function, then two isomeric quinolines are possible:



Almost invariably when the substituent (R) is halogen, a mixture of isomers is formed. Much effort has gone into devising efficient methods for the separation of these isomers, and also into the systematic investigation of reaction conditions in an attempt to determine the factors that govern isomer distribution.

Early work on *m*-chloroaniline produced a mixture of 5- and 7-chloroquinoline;[268, 698, 866] these were partially separated by fractional distillation (5-chloroquinoline, b.p. 133–135 °C; 7-chloroquinoline, b.p. 141 °C at 22 mm), then by fractional crystallization of their picrates;[269] separation has also been achieved by fractional crystallization of their dichromates.[699]

The so-called 7-chloroquinoline, m.p. 45 °C, isolated by Claus and his co-workers[268, 698] from a Skraup reaction on *m*-chloroaniline is in fact the 5-chloro-isomer.[549, 690] 7-Chloroquinoline has a melting point of 31 °C, as originally stated by La Coste and Bodewig.[866]

m-Bromoaniline similarly yields a mixture of 5- and 7-bromoquinoline, and again some confusion exists in the early literature. Claus and Tornier[287] originally gave 5-bromoquinoline as melting at 32 °C, and 7-bromoquinoline as an oil. Subsequently, however, Claus and Vis[715] showed that the solid product is in fact the 7-bromo-isomer

and that the liquid product is impure 5-bromoquinoline, which on purification yields the 5-bromo-isomer as a solid of m.p. 52 °C.[725] Separation of the bromo-isomers was effected[867] by means of their nitrates which on fractional crystallization deposited pure 7-bromoquinoline nitrate. The 5-bromo-isomer was subsequently obtained as the oxalate, and the ratio of 5- to 7-bromoquinoline was found to be 1 : 3.

Investigation[699] of the Skraup reaction of a series of *meta*-substituted anilines, including *m*-chloro- and *m*-bromo-aniline, reveals that in 60% sulphuric acid the ratio (7 : 5) of chloro-isomers formed is 1.4 : 1; this ratio increases with increasing acid strength of the reaction medium and becomes 4.4 : 1 at an acid concentration of 85%. The ratio of bromo-isomers, however, remains approximately constant at 1 : 1 under all reaction conditions examined. From their investigations the authors (Bradford *et al.*) conclude that (*a*) strongly *ortho–para*-directing groups (e.g. HO, MeO) yield only the 7-substituted quinoline, while weakly *ortho–para*-directing groups (e.g. halogen) yield mixtures in which the 7-substituted quinoline predominates; also (*b*) *meta*-directing substituents (e.g. NO_2) give mixtures of quinolines in which the 5-substituted isomer is the major component. Only in the one case (i.e. *m*-chloroaniline) is there any significant change in the isomer distribution on varying the acid concentration of the reaction mixture.

Subsequent results, however, do not corroborate these conclusions. For example, *m*-(trifluoromethyl)aniline (CF_3, a strong *meta*-director) under Skraup conditions yields predominantly 7-(trifluoromethyl)quinoline (43%) rather than the predicted 5-(trifluoromethyl) isomer.[868, 869] Such a result prompted Palmer[870] to reinvestigate the Skraup reaction for a series of *meta*-substituted and 3,4-disubstituted anilines. He found that the ratio of 7- to 5-substituted quinolines remains virtually constant regardless of the reaction conditions (i.e. acid concentration) employed. Further, in all cases, except where the substituent is nitro, the 7-substituted isomer is the main product. Thus, *m*-fluoro-, *m*-chloro-, *m*-bromo-, and *m*-iodoaniline yield a mixture of the corresponding 5- and 7-haloquinolines for which the isomer ratios are 25 : 75, 34 : 66, 46 : 54, and 49 : 51%, respectively.

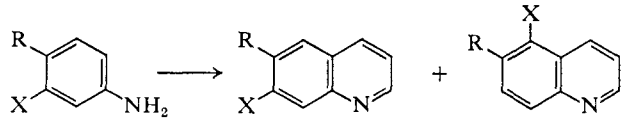
Previous conclusions arrived at by Mirek[871] have also been shown by Palmer to be suspect. Mirek on the basis, mainly of literature yields, has put forward a proportionality ratio which seemingly links the yield of haloquinoline formed in the Skraup reaction to the electronegativity of the halogen substituent. The values used by Mirek as yields are, however, somewhat inaccurate, as indicated by the more sophisticated techniques of product analysis (g.l.c. and infrared) used by Palmer. In fact, on the basis of his results, Palmer[870] could find no correlation between yield of haloquinoline and halogen electronegativity. In a later paper Mirek,[872] again on the basis of earlier published yields and some of his own findings, discusses the effect of halogen electronegativity on the course of various cyclization reactions including the Skraup synthesis. From these results he concludes that (*a*) *m*-fluoroaniline reacts to give only 7-fluoroquinoline, (*b*) the yield of haloquinoline decreases in the order F > Cl > Br, i.e. in order of decreasing electronegativity, and (*c*) iodoquinolines cannot be prepared by the Skraup synthesis since at some stage of the reaction iodine is lost. He infers from these results that the yield of haloquinoline is influenced by at least four factors, namely, the activation energy, and the *ortho*-, inductive, and conjugative (mesomeric) effects of the halogen substituent.

Again, however, the weakness of Mirek's arguments lies in the yield figures which he uses, particularly those for the 5- and 7-haloquinolines. Early work on isomer separation was in most cases carried out by fractional crystallization, generally of the dichromates. As Palmer has pointed out, such methods invariably give low results or, indeed, fail completely to isolate the generally more soluble and less easily isolable 5-halo-isomer. As a consequence there is disagreement between Mirek and Palmer

on virtually all the conclusions of the former author. Palmer has found, for instance, by gas–liquid chromatography that *m*-fluoroaniline does in fact yield a mixture of fluoroquinolines (73.5%) of which 25% is 5-fluoroquinoline. Further, the yields of haloquinoline for *m*-substituted anilines are *m*-fluoro (73.5%), *m*-chloro (73.5%), *m*-bromo (88%), and *m*-iodo (69%), i.e. there is no decrease in yield with decreasing electronegativity of the halogen substituent. The last conclusion put forward by Mirek is definitely in error since the Skraup reaction on *m*-iodoaniline using sodium *m*-nitrobenzenesulphonate, glycerol, and sulphuric acid produces a mixture of iodoquinolines (69%), of which the 5-iodo-isomer constitutes 51%. It must be mentioned, however, that Petrow and Sturgeon[147] obtained only a low yield (< 5%) of 6-iodoquinoline from a Skraup reaction on *p*-iodoaniline, the main product being quinoline.

Palmer[870] points out that an increase in cyclization *ortho* to the halogen substituent, i.e. 5-halo-isomer formation, increases as the electronegativity of the halogen decreases. This suggests that the inductive effect of the halogen is more important than the mesomeric effect in determining the site of cyclization; a similar but more marked trend is observed in the nitration of halobenzenes. It appears that steric effects play little part in determining the isomer ratio since yields of the 5-isomer (*ortho*-cyclization) increase as the size of the halogen atom increases.

3,4-Dichloroaniline under Skraup conditions yields a mixture of 5,6- and 6,7-dichloroquinoline, the former being the major product (67%).[870] This is in direct contrast to 3,4-dimethylaniline which yields mainly 6,7-dimethylquinoline (70%). In general, Palmer finds that, in the case of the anilines (**287**) when X = halogen, there is a tendency towards formation of the 5,6-disubstituted quinoline, which increases as the electron-donating power of group R increases. For example, 3-chloro-4-nitroaniline (**287**; R = NO_2, X = Cl) yields a mixture of 7-chloro-6-nitroquinoline

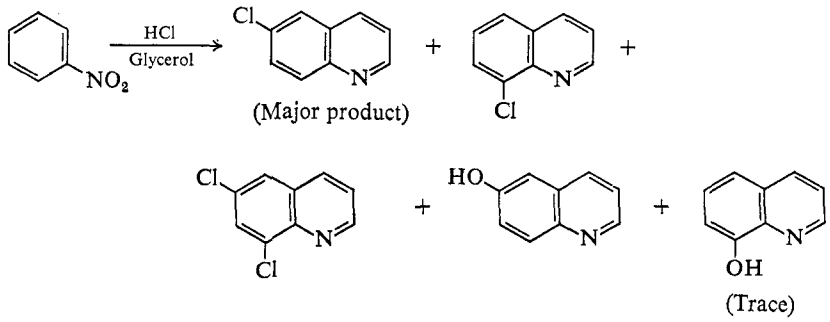


287 **288** **289**

(**288**; R = NO_2, X = Cl) (65%) and 5-chloro-6-nitroquinoline (**289**; R = NO_2, X = Cl) (37%),[873] whereas 3-chloro-4-nitrophenol with glycerol and concentrated sulphuric acid yields only 5-chloro-6-hydroxyquinoline (**289**; R = HO, X = Cl).[874] These results are in harmony with a mechanism for the Skraup and related reactions originally hinted at by Roberts and Turner,[91] and more recently proposed by Palmer,[870] and later by Badger and his co-workers.[875]

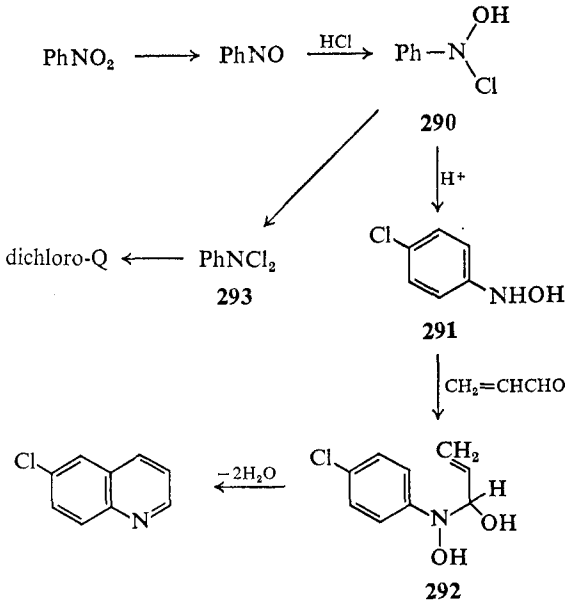
Haloquinolines have also been synthesized by the Skraup reaction using acetylated amines[232, 240, 647] and nitro-compounds[229, 874] as precursors rather than the free amine. The reaction of nitro-compounds with hydrochloric acid under modified Skraup conditions has been extensively investigated by Mazoński and his co-workers. They find[876] that nitrobenzene reacts with glycerol and concentrated hydrochloric acid to give a mixture of products as indicated in reaction Scheme 24.

p-Nitrotoluene and *p*-ethylnitrobenzene behave similarly in that a mixture of 6-alkyl- and 6-alkyl-8-chloro-quinoline are formed.[877, 878] *o*- and *p*-Chloronitrobenzene under the same conditions yield mainly 6,8-dichloroquinoline,[879] whereas with glycerol and sulphuric acid *o*-chloronitrobenzene is reported[858] to yield mainly 8-chloro-6-hydroxyquinoline. In explanation of their results Mazoński and his co-workers have put forward a mechanism, outlined in Scheme 25, in which it is



SCHEME 24

proposed that the first step in the reaction involves reduction of the nitro- to the nitroso-compound.[876, 879] The nitroso-compound then forms an *N*-chlorohydroxylamine (**290**) which undergoes acid-catalysed rearrangement to the *p*-chlorohydroxylamine (**291**). Reaction of the hydroxylamine with acrolein, formed by oxidation of

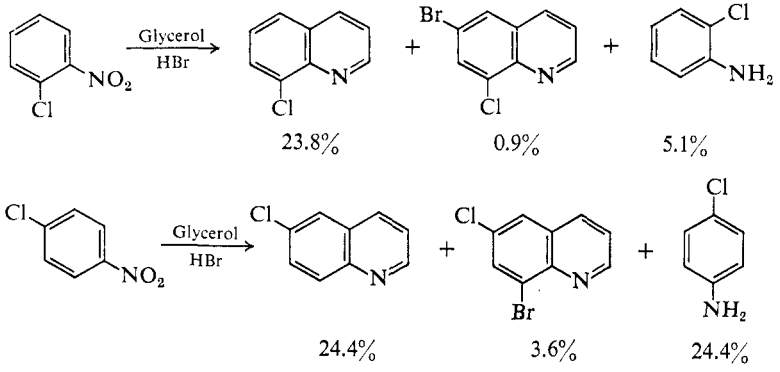


SCHEME 25

the glycerol, yields the intermediate (**292**) which cyclizes to the chloroquinoline. Dichloroquinolines are thought[876] to arise via an *N*,*N*-dichloro-intermediate (**293**), whereas hydroxyquinolines may be formed by a competing Bamberger rearrangement of the chlorohydroxylamine (**290**). Reactions of this type have been used by Lachowicz and Mazoński for the preparation of chloroisopropylquinolines.[880]

Bromonitrobenzenes with concentrated hydrochloric acid and glycerol undergo either loss of bromine or bromine–chlorine exchange.[881] *o*-Bromonitrobenzene yields

a mixture of 6-chloroquinoline (27.7%), 8-bromo-6-chloroquinoline (14.1%), and *p*-chloroaniline (8%), whereas *p*-bromonitrobenzene yields 6-bromo-8-chloroquinoline (16.6%), 6-chloroquinoline (26.1%), and *p*-chloroaniline (1.3%). If the reaction is repeated but with *o*- or *p*-chloronitrobenzene, glycerol, and hydrobromic acid, then no halogen exchange takes place. However, bromination at the 6- and 8-positions is observed (Scheme 26). In every case quinoline formation is accompanied by reduction

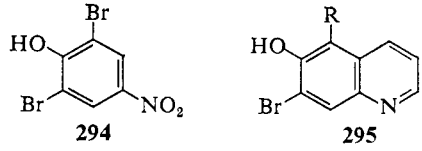


SCHEME 26

of the nitrobenzene to the corresponding amine, which can be isolated. Acetic acid, formed by oxidation of glycerol by the nitro-compound, has also been detected.[881] It appears that under the reaction conditions bromine, but not chlorine, is labile, since both *o*- and *p*-bromonitrobenzene on treatment with hydrobromic acid and glycerol yield the expected products, 8- (10.5%) and 6-bromoquinoline (7.9%), together with quinoline in 4.9% and 7.5% yield, respectively. *p*-Fluoronitrobenzene reacts with concentrated hydrochloric acid and glycerol in a sealed tube at 180 °C to yield a mixture of 8-chloro-6-fluoroquinoline, 6-fluoroquinoline, and *p*-fluoroaniline.[714]

As an outcome of these studies a thin-layer chromatographic technique for the determination of chloroquinolines in the presence of chloroanilines has been developed.[882]

Loss of bromine during a modified Skraup reaction on a bromonitro-compound has also been noted by Fujita and his co-workers.[883] They observed that the dibromonitrophenol (**294**) with glycerol and concentrated sulphuric acid in the



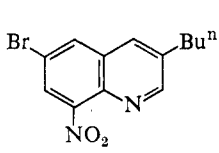
294 **295**

presence of acetic acid gives 5,7-dibromo-6-hydroxyquinoline (**295**; R = Br). In the presence of formic acid, however, a small amount of 7-bromo-6-hydroxyquinoline (**295**; R = H) is formed. In contrast, replacement of acetic acid by concentrated phosphoric acid leads to sole formation of the monobromoquinoline (**295**; R = H).

Further investigations[884] show that in the presence of strong acid, e.g. hydrobromic or phosphoric acid, the dibromohydroxyquinoline (**295**; R = Br) (prepared by a

normal Skraup reaction on 3,5-dibromo-4-hydroxyaniline) undergoes ready loss of the 5-bromo-substituent. If the reaction is carried out in the presence of phenol and 48% hydrobromic acid, then the 7-bromo-quinoline (**295**; R = H) and *o*-bromophenol are formed in 4.9% and 11.5% yield, respectively. No mechanistic explanation of these results is offered by the authors. Similar reactions have been observed by Babu and Rao.[885]

By using substituted acroleins rather than glycerol the Skraup reaction can be employed for the synthesis of quinolines substituted in both the heterocyclic and the carbocyclic ring. Crotonaldehyde, either as the free aldehyde[886] or, better, as the diacetal,[887] with *o*- and *p*-chloroaniline yields 8-chloro-2-methylquinoline and 6-chloro-2-methylquinoline (55%), respectively. Other alkylchloroquinolines have also been prepared by this method.[687] Substitution of 2-methylacrolein for crotonaldehyde leads to the formation of the corresponding 3-methylated chloroquinolines,[887] and in a similar manner *p*-bromoaniline reacts with 2-methylacrolein in the presence of *o*-nitrophenol, sulphuric acid, and ferrous sulphate, to give 6-bromo-3-methylquinoline.[888] 2-Nitro-4-bromoaniline is reported[889] to yield 6-bromo-3-(*n*-butyl)-8-nitroquinoline (**296**) (25%) on treatment with 2-(*n*-butyl)acrolein and arsenic pentoxide in 89% phosphoric acid.



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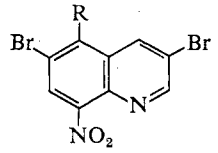

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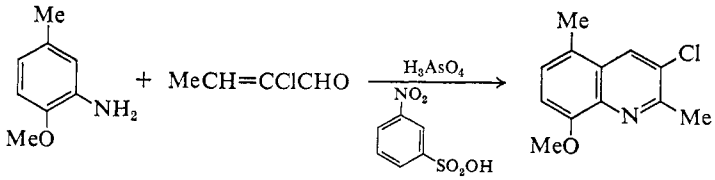
Palmer and his co-workers[890] have shown that *m*-haloanilines react with crotonaldehyde in a modified Skraup reaction to give mixtures of 5- and 7-halo-2-methylquinolines in high yield. They find that the ratio of 7- to 5-haloquinoline decreases as the electronegativity of the halogen decreases. This compares with the trend observed[870] for *m*-haloanilines under normal Skraup conditions.

The melting point (38 °C) recorded by Palmer for 7-fluoro-2-methylquinoline monohydrate is significantly different from that (56 °C) recorded by Mirek[675] for the same compound prepared by a Doebner–von Miller reaction on *m*-fluoroaniline; the latter product may have been the anhydrous compound or the hitherto unreported 5-fluoro-2-methylquinoline.

3-Haloquinolines can be prepared by the Skraup process using an α-halo-α,β-unsaturated aldehyde in place of glycerol. For example, 2-nitro-4-methoxyaniline reacts with 2-chloroacrolein to give 3-chloro-6-methoxy-8-nitroquinoline in good yield.[891] 2-Chloro- and 2-bromo-crotonaldehyde have been used[892] to prepare a series of substituted 2-methyl-3-chloro- and 2-methyl-3-bromo-quinolines as formulated below.



o-Anisidine and 2-bromoacrolein fail to yield 3-bromo-8-methoxyquinoline,[304] and attempts to prepare 3-bromo-6-methoxy-8-nitroquinoline from 2-bromoacrolein

and 4-methoxy-2-nitroaniline gave only traces of the required product.[105] However, 4-bromo-2-nitroaniline and 4,5-dibromo-2-nitroacetanilide react under Skraup conditions with 2-bromoacrolein diacetate [CH_2=$CBrCH(OAc)_2$] to give 3,6-dibromo-8-nitroquinoline (**297**; R = H) and 3,5,6-tribromo-8-nitroquinoline (**297**; R = Br) in 38.4% and 24.3% yield, respectively.[893]

Compounds prepared by the Skraup reaction are recorded in Table 22.

TABLE 22. Haloquinolines by the Skraup Reaction

Haloquinoline	Yield (%)	M.p. (°C)	References
NOT FURTHER SUBSTITUTED			
5-Fluoro-	18	Oil	870, 872
6-Fluoro-	98	Oil	714, 846
7-Fluoro-	54	Oil	870, 872
8-Fluoro-	72	Oil	871
5-Chloro-	24.5	45	269, 698, 699, 852, 866, 870, 871, 872
6-Chloro-	88	41	843, 852, 871, 876, 879, 881, 894, 895
7-Chloro-	66.5	32	269, 494, 698, 699, 852, 866, 870, 871, 872
8-Chloro-	67	Oil	844, 852, 871, 876, 896
5-Bromo-	43	47	13, 287, 448, 699, 715, 725, 841, 867, 870
6-Bromo-	45	24	13, 843, 881
7-Bromo-	66	35.5	13, 287, 448, 699, 715, 725, 841, 867, 870, 871
8-Bromo-	45	Oil	13, 287, 823, 841, 871, 881
5-Iodo-	33	103	870
6-Iodo-	5	88	147
7-Iodo-	34	103	870
5,6-Dichloro-	45	86.5	838, 870
5,7-Dichloro-	90	117	703, 860
5,8-Dichloro-	73	93	843, 844, 895, 898
6,7-Dichloro-	30	134	838, 870
6,8-Dichloro-	35	104	648, 843, 876, 879, 895
5,7-Dibromo-		110	217, 283
5,8-Dibromo-		125	655, 899
6,8-Dibromo-	67	101	217, 655, 843
5,7-Di-iodo-		132	845
8-Chloro-6-fluoro-		102.5	714
8-Bromo-6-fluoro-	65	77	900

TABLE 22 (*cont.*)

Haloquinoline	Yield (%)	M.p. (°C)	References
8-Bromo-6-chloro-	56	94	881, 900
6-Bromo-8-chloro-	16.6	120	881
5,6,8-Trifluoro-		87	271, 721
6,7,8-Trifluoro-		101.5	271, 721
5,6,7-Trichloro-		159	895
5,6,8-Trichloro-		135	895
5,6,8-Tribromo-		159	298
5,6,7-Tri-iodo-		102	845
5,6,7,8-Tetrafluoro-		93.5	271, 721
ALKYL- AND ARYL-SUBSTITUTED			
5-Fluoro-2-methyl-	17		890
7-Fluoro-2-methyl-	51	38	890
3-Chloro-2-methyl-		69	892
3-Chloro-2,5-dimethyl-		97.5	892
3-Chloro-2,7-dimethyl-			892
5-Chloro-2-methyl- (trihydrate)	34	53	870, 890
5-Chloro-6-methyl-	32	47	419, 870, 901
5-Chloro-6,8-dimethyl-		44	705
5-Chloro-2,6,8-trimethyl-		64	705
6-Chloro-2-methyl-	55	96	887, 902
6-Chloro-3-methyl-	58	82	240
6-Chloro-8-methyl-		65.5	647, 877
6-Chloro-8-ethyl-	68.8	Oil	632, 903
6-Chloro-8-isopropyl-	25	Oil	880
6-Chloro-2,5,8-trimethyl-	57	95	687
7-Chloro-2-methyl-	60	78	870, 887, 890
7-Chloro-3-methyl-	52	84.5	887
7-Chloro-6-methyl-	34	78	419, 870, 901
7-Chloro-8-methyl-	74	48	699
7-Chloro-2,6-dimethyl-		92	687
7-Chloro-6,8-dimethyl-		41	705
7-Chloro-2,5,8-trimethyl-	73	109	687
8-Chloro-2-methyl-		64	886, 902, 904
8-Chloro-5-methyl-		54	848, 905
8-Chloro-6-methyl-	58	61.5	419, 877
8-Chloro-6-ethyl-	61.7	Oil	878, 903
8-Chloro-6-isopropyl-	35	Oil	880
8-Chloro-2,7-dimethyl-	54	65	687
3-Bromo-2-methyl-		78	892
3-Bromo-2,5-dimethyl-			892
3-Bromo-2,7-dimethyl-			892
5-Bromo-2-methyl-	37		890
5-Bromo-7-methyl-		24	99
5-Bromo-8-methyl-		38	850
6-Bromo-3-methyl-		103	888
6-Bromo-8-methyl-	60	59	647, 849, 900
6-Bromo-8-ethyl-	67.7	Oil	903
6-Bromo-8-phenyl-	40	72	900
7-Bromo-2-methyl-	35	77	890
7-Bromo-5-methyl-		67	99
7-Bromo-8-methyl-		48.5	850

TABLE 22 (*cont.*)

Haloquinoline	Yield (%)	M.p. (°C)	References
8-Bromo-5-ethyl-	13.9	40	425
8-Bromo-6-methyl-	36	52	650
8-Bromo-7-methyl-		97.5	99
8-Bromo-6-ethyl-	57.5	Oil	903
8-Bromo-6-phenyl-	58	68	900
5-Iodo-2-methyl-	30		890
7-Iodo-2-methyl-	38	81	890
8-Iodo-6-methyl-		66	337
5,8-Dichloro-2,6-dimethyl-	74	84	687
5,8-Dichloro-2,7-dimethyl-	60	97	687
6,8-Dichloro-5-methyl-	57	119	906
6,8-Dibromo-5-ethyl-	57	95.5	425
5,6,7,8-Tetrafluoro-2-methyl-		52	271, 721
5,6,7,8-Tetrafluoro-4-methyl-		81.5	271, 721
ALKOXY- AND HYDROXY-SUBSTITUTED			
5-Fluoro-6-methoxy-8-nitro-	5	156	90
5-Fluoro-8-methoxy-	37	36.5	230
3-Chloro-6-methoxy-8-nitro-		160	891
3-Chloro-8-methoxy-2,5-dimethyl-			892
5-Chloro-6-hydroxy-	45	197	857, 874
5-Chloro-6-methoxy-8-nitro-	53	204	907
7-Amino-5-chloro-6,8-dimethoxy-			861
5-Chloro-8-hydroxy-	60	123	228, 229, 857, 859, 874, 908
5-Chloro-8-methoxy-	40	54	859
5-Chloro-8-hydroxy-2-methyl-	25.8	71	908
6-Chloro-8-hydroxy-		144	232, 877
6-Chloro-8-hydroxy-5-nitro-			909
7-Chloro-8-hydroxy-	80	156	910
7-Chloro-8-hydroxy-5-(*n*-pentyl)-		107.5	856
8-Chloro-6-hydroxy-		237	858
8-Chloro-6-hydroxy-5-(*n*-pentyl)-		124	856, 858
8-Chloro-6-methoxy-5-nitro-			404
3-Bromo-6-methoxy-8-nitro-	73	162	105
5-Bromo-6-hydroxy-			883
5-Bromo-6-methoxy-			722
5-Bromo-6,7-dimethoxy-			409, 860
5-Bromo-6-methoxy-8-methyl-		117	107
5-Bromo-6-methoxy-8-nitro-	85.5	206	853, 907, 911
5-Bromo-8-hydroxy-	Poor	124	133, 169
5-Bromo-8-hydroxy-2-methyl-	37	68	169
6-Bromo-8-methoxy-		51	304
7-Bromo-6-hydroxy-		262	883, 884, 885
7-Bromo-6-methoxy-		111	722
7-Bromo-6-ethoxy-		90	722
7-Bromo-6-methoxy-8-methyl-		135	107
7-Bromo-8-methoxy-5-methyl-	56	63	156
5,7-Dichloro-8-hydroxy-		179	74, 874
5,7-Dibromo-6-hydroxy-		212	883, 884
5,7,8-Trichloro-6-hydroxy-		242	858

TABLE 22 (*cont.*)

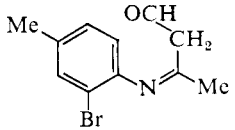
Haloquinoline	Yield (%)	M.p. (°C)	References
NITRO- AND AMINO-SUBSTITUTED			
5-Fluoro-6-methoxy-8-nitro-	5	156	90
6-Fluoro-8-nitro-	61.5	120	714, 846, 854, 912
3-Chloro-8-nitro-	5	139	240
3-Chloro-6-methoxy-8-nitro-		160	891
3-Chloro-8-nitro-6-phenyl-	5	160	240
5-Chloro-6-nitro-		153	852, 855, 873
5-Chloro-8-nitro-	68	136	547, 852, 855, 873, 913
5-Chloro-6-methoxy-8-nitro-	53	204	907
6-Chloro-5-nitro-		129	281, 852, 855
6-Chloro-8-hydroxy-5-nitro-		235	909
6-Chloro-8-methyl-5-nitro-	9.3	100	647
6-Chloro-8-ethyl-5-nitro-	87.5	57	632, 903
6-Chloro-7-nitro-		160	281, 852, 855
6-Chloro-8-nitro-	75	158	281, 840, 853, 914, 915, 916
6-Chloro-3-methyl-8-nitro-	56	204	240
7-Chloro-6-nitro-		156	852, 873
7-Chloro-8-nitro-		186	852
8-Chloro-5-nitro-	63	145	852, 855
8-Chloro-6-methyl-5-nitro-	26.7	118	646
8-Chloro-6-ethyl-5-nitro-	20.3		903
8-Chloro-6-methoxy-5-nitro-			404
8-Chloro-6-nitro-		154	895, 917
5-Bromo-6-methoxy-8-nitro-	85.5	206	853, 907, 911
6-Bromo-8-nitro-		172	854, 915, 918
6-Bromo-8-methyl-5-nitro-		118	647
6-Bromo-8-ethyl-5-nitro-		87	903
6-Bromo-3-(*n*-butyl)-8-nitro-	25	74	889
8-Bromo-6-methyl-5-nitro-		134	650
8-Bromo-6-ethyl-5-nitro-	14	90	903
8-Bromo-6-nitro-	60	164	288, 919
8-Bromo-5-ethyl-6-nitro-	37.9	139	425
6-Iodo-8-nitro-		180	854
3,6-Dichloro-8-nitro-	14	161	240
5,6-Dichloro-8-nitro-	68	178	240
5,8-Dichloro-6-nitro-	20	136	898
6,8-Dichloro-5-nitro-	78	126.5	648
3,6-Dibromo-8-nitro-	38.4	181	893
5,6-Dibromo-8-nitro-	29.4	196	893
3,5,6-Tribromo-8-nitro-	24.3	209	893
7-Amino-5-chloro-6,8-dimethoxy-			861
7-Amino-5,6,8-trichloro-	53.5	145	861
CARBOXYLIC AND SULPHONIC ACIDS			
8-Chloro-5-carboxylic acid	83	318	863
8-Bromo-5-carboxylic acid		275	862
8-Bromo-5-sulphonic acid			864
8-Bromo-6-(carboxymethyl)-		154	851
6,8-Dichloro-5-carboxylic acid	24	262	906

*K. Haloquinolines by the Doebner–von Miller Reaction**

The Doebner–von Miller reaction may be regarded as a variation of the Skraup synthesis and is another classical method for the preparation of quinolines. Basically the reaction involves heating an α,β-unsaturated aldehyde or ketone with an aromatic amine in the presence of concentrated hydrochloric acid and/or zinc chloride. Oxidizing conditions increase the yield, as does the use of mild rather than strong acid media.[920]

In many instances the α,β-unsaturated aldehyde is generated *in situ* by heating paraldehyde with hydrochloric acid, and the crotonaldehyde so formed has been treated with a variety of haloanilines to give halogenated 2-methylquinolines.[675, 859, 921–924] Crotonaldehyde has also been used directly in the reaction.[163, 925, 926] 2-Chloro-3-methylaniline with acrolein diacetate [CH_2=CH.CH$(OAc)_2$] in acetic acid in the presence of ferric chloride gives 8-chloro-7-methylquinoline (16%).[927] In a similar reaction 3-ethoxyacrolein diacetal[EtOCH=CH.CH$(OMe)_2$] and 2-chloro-5-hydroxyaniline give 8-chloro-5-hydroxyquinoline.[928]

The preformed anil (**298**) of 2-bromo-4-methylaniline cyclizes easily in warm acid solution to give 8-bromo-2,6-dimethylquinoline plus a small amount of the tetrahydroquinoline (**299**).[929] However, heating the anil at 200 °C leads to cyclization with loss of bromine, yielding 2,6-dimethylquinoline as the hydrobromide.



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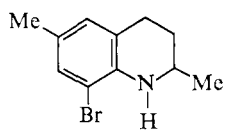
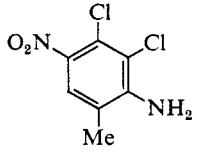


299

Greatly increased yields of chloro-2-methylquinolines are obtained by using *m*-nitrobenzenesulphonic acid in sulphuric acid as the oxidizing/cyclizing agent.[768] Using this reagent, Spivey and Curd[768] were able to prepare 5-chloro- and 7-chloro-2-methylquinoline from *m*-chloroaniline and crotonaldehyde in much greater yields than those achieved by Doebner and von Miller[930] in their pioneering studies. Optimum yields (60%) are obtained by using 60% sulphuric acid, when the isomeric composition of the mixture is found to be 5-chloro-2-methylquinoline 25% and 7-chloro-2-methylquinoline 75%. The overall yield decreases with increasing acid strength (36% with 80% sulphuric acid), whereas the percentage of 5-chloro-isomer shows a slight increase (33% with 80% sulphuric acid). The isomers were separated by fractional crystallization of their picrates from 2-ethoxyethanol. In general it appears[931] that *m*-haloanilines react under Doebner–von Miller conditions to give mainly the 7-halo-derivative.

During the reductive deamination of the dichloronitroarylamine (**300**) a 7% yield of the anomalous 7,8-dichloro-2,5-dimethylquinoline (**301**) was obtained;[932] acetaldehyde was also detected amongst the products, which suggests that the



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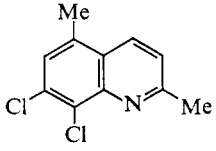

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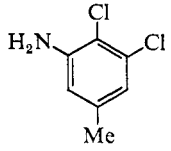
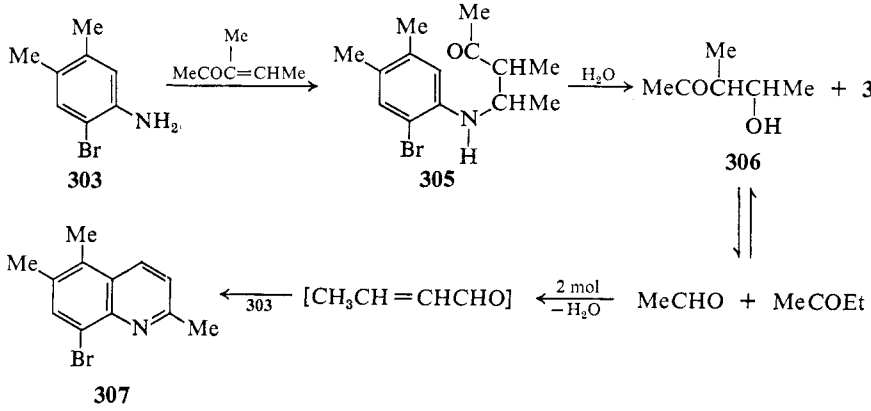


302

* See also Addenda, p. 680.

dichloroquinoline (**301**) is formed by a Doebner–von Miller reaction on the dichloro-amine (**302**) produced as a by-product in the copper–ethanol–sulphuric acid-induced deamination. Support for this idea was obtained by heating the dichloro-amine (**302**) with acetaldehyde under the reaction conditions, whereupon the dichloro-quinoline (**301**) was formed.

Another anomalous reaction is evident during the reaction of 2-bromo-4,5-dimethylaniline (**303**) with 3-methylpent-3-en-2-one (MeCOCMe=CHMe).[933] This affords the bromotrimethylquinoline (**307**) (6.7%) rather than the expected 8-bromo-2,3,4,5,6-pentamethylquinoline. In order to explain this loss of two methyl groups the authors suggest that the 6-position of the amine (**303**) is subject to steric hindrance such that ring closure of intermediate (**305**) (Scheme 27) is slow, and hydrolysis to the



SCHEME 27

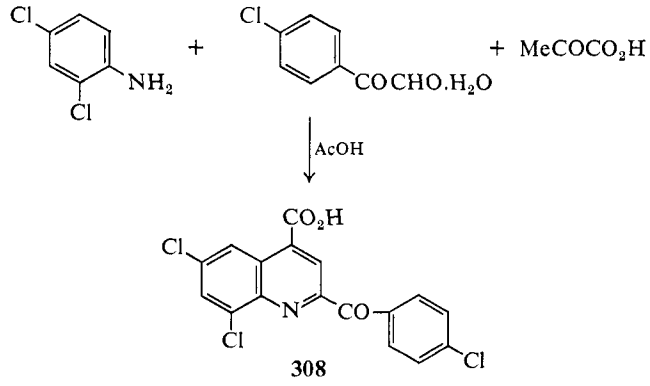
aldol (**306**) occurs. A retroaldol condensation then yields butan-2-one and acetaldehyde. The acetaldehyde can then undergo self-condensation to give crotonaldehyde which enters into a normal Doebner–von Miller reaction with the dimethylaniline (**303**) to yield the product 8-bromo-2,5,6-trimethylquinoline (**307**).

Chloroacetone and formaldehyde condense *in situ* to give 1-chlorovinyl methyl ketone which with aniline, under Doebner–von Miller conditions, yields 3-chloro-4-methylquinoline.[934] Similarly acetone and formaldehyde in the presence of ferric chloride and hydrochloric acid react with *o*-chloroaniline to give 8-chloro-4-methylquinoline.[935] Other halo-4-methylquinolines are available by condensation of haloanilines with methyl vinyl ketones.[875, 936]

Benzaldehyde and pyruvic acid under Doebner–von Miller conditions condense to give 2-oxo-4-phenylbut-3-enoic acid which reacts with haloanilines to yield the corresponding halogenated 2-phenylquinoline-4-carboxylic acids.[937–939]

In a similar reaction Saggiomo and his co-workers[940] condensed 2,4-dichloro-aniline with *p*-chlorophenylglyoxal monohydrate and pyruvic acid and obtained the 2-acylquinoline-4-carboxylic acid (**308**) in 21% yield. Several other acylhalo-quinolines have also been reported.

Occasionally the Doebner–von Miller synthesis applied to an aromatic aldehyde and pyruvic acid yields a pyrrolidinedione, e.g. (**310**), as a by-product.[931, 938, 939] For example, *p*-chloroaniline with a mixture of benzaldehyde and pyruvic acid in the presence of sulphuric acid gives 6-chloro-2-phenylquinoline-4-carboxylic acid (**309**) together with a pyrrolidinedione as the anil (**311**; R = *p*-ClC_6H_4).[931] The dione



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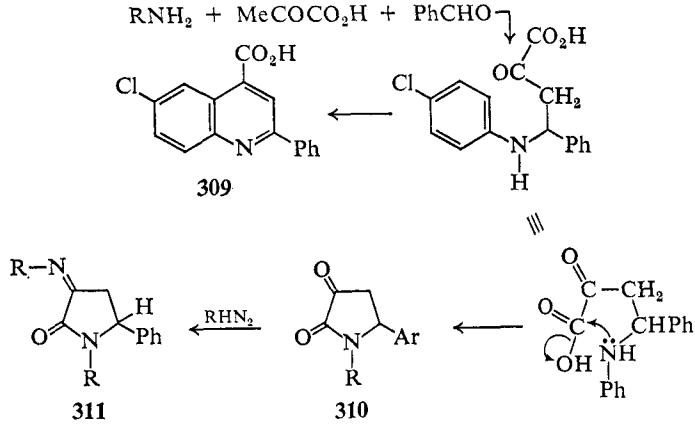
probably arises from a competing cyclization process as indicated in Scheme 28. The dione is generally isolated as the anil (**311**), although in the reaction of *p*-fluorobenzaldehyde with pyruvic acid and *m*-chloroaniline the dione (**310**; Ar = *p*-FC_6H_4, R = *m*-ClC_6H_4), itself is isolated.[931] Atkinson and Puttick[941] have shown that the pyrrolidone anil (**311**; R = 2,4-$F_2C_6H_3$) is the only isolable product from the reaction of 2,4-difluoroaniline with benzaldehyde and pyruvic acid.

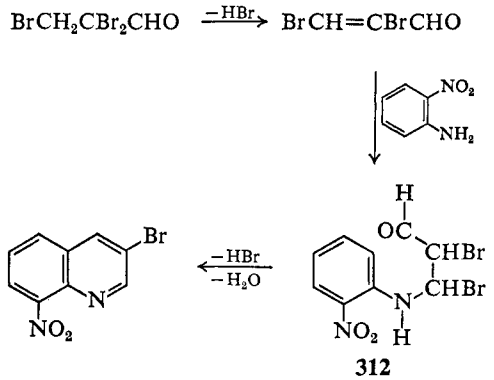


SCHEME 28

Campbell and his co-workers[942] find that 1,3,3-trimethoxybutane (readily available from vinylacetylene) is a useful substitute for methyl vinyl ketone in the Doebner–von Miller reaction, and several 4-methyl-substituted haloquinolines have been prepared by means of this reagent.[367, 920, 942, 943]

3-Bromoquinolines may be synthesized by treating 2,2,3-tribromopropanal with arylamines.[105] The reaction appears to proceed most efficiently with 2,4-disubstituted anilines, whereas with anilines unsubstituted at the *para*-position a complex mixture is obtained.[105, 944] Aniline reacts with 2,3,3-tribromopropanal to give unidentifiable products, as do the monobromoanilines.[944] *o*-Nitroaniline, however, yields a mixture of 3,6-dibromo-8-nitroquinoline (14%), 3-bromo-8-nitroquinoline (1%), and 6-bromo-8-nitroquinoline (23%).[105] The 3-bromo-compound is probably formed as

indicated in Scheme 29. The question remains whether bromination at the 6-position occurs before or after ring closure of intermediate (**312**).



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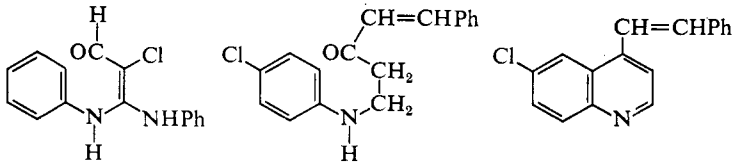
SCHEME 29

2-Bromoacrolein has also been used for the synthesis of 3-bromoquinolines,[945] and aniline is reported[946] to react with 2,3,3-trichlorobutanal to give 3-chloro-2-methylquinoline. Apparently trichloroacrolein, but not its diacetal, will react with a primary aromatic amine to give the Skraup-type intermediate (**313**) which in concentrated sulphuric acid cyclizes to give 3-chloro-2-quinolone.[364]

Alkyl styryl ketones and haloanilines react smoothly in hydrochloric acid to give halogenated 4-alkyl-2-phenylquinolines,[947, 948] while 2-chloroethyl methyl ketone and *p*-chloroaniline in a mixture of nitrobenzene and concentrated hydrochloric acid at 100 °C give 6-chloro-4-methylquinoline.[949]

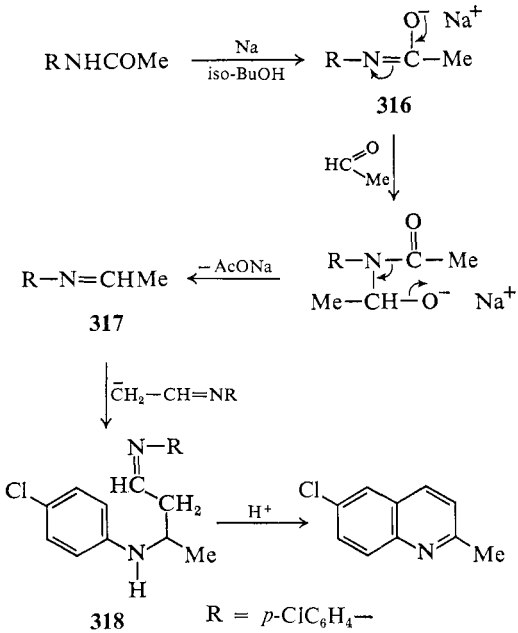


313 **314** **315**

The styryl ketone (**314**) cyclizes in the presence of a mixture of stannic chloride, zinc chloride, aniline hydrochloride, and ethanol to give 6-chloro-4-ω-styrylquinoline (**315**) in 25% yield.[950]

A new modification of the Doebner–von Miller reaction has been published by Minkin.[951] The method involves treating *p*-chloroacetanilide with sodium in isobutyl alcohol to yield the sodio-compound (**316**) which with paraldehyde yields the ethylideneaniline (**317**). This in turn undergoes an aldol condensation with another molecule of ethylideneaniline to give the extended anil (**318**), which in acid solution cyclizes to the chloroquinaldine as indicated in Scheme 30 (R = *p*-ClC_6H_4 throughout).

Minkin and his co-workers[952] have also shown that *p*-haloanilines with propionaldehyde in methanol containing a catalytic amount of acetic acid give 6-halogenated 4-(arylamino)-2-ethyl-3-methyl-quinolines (**319**; R = Cl, Br, or I) in 28%, 30%, and 65% yield, respectively.



SCHEME 30

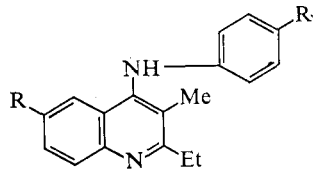


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Table 23 lists haloquinolines prepared as described in this Section.

TABLE 23. Haloquinolines by the Doebner–von Miller Reaction

Haloquinoline	Yield (%)	M.p. (°C)	References
3-HALO-			
3-Chloro-2-methyl-		72	946
3-Chloro-4-methyl-		55	934
3-Bromo-8-methoxy-5-nitro-	50	213	944
3-Bromo-6-chloro-8-nitro-		175	105
3-Bromo-6-chloro-8-carboxylic acid	72	238	944
3-Bromo-6-methoxy-8-nitro-	73	162	105
3-Bromo-6-methyl-8-nitro-	60	190	944
3-Bromo-6,8-dimethyl-	32	60	944
3-Bromo-6,8-dinitro-	40	157	944
3-Bromo-8-chloro-6-nitro-	64	204	944
3-Bromo-8-methoxy-6-nitro-	78	220	944
3-Bromo-8-methyl-6-nitro-	80	191	944

TABLE 23 (*cont.*)

Haloquinoline	Yield (%)	M.p. (°C)	References
3-Bromo-8-nitro-6-phenyl-	79	186	944
3,6-Dibromo-8-nitro-		180	105
3,8-Dibromo-6-nitro-	41	219	944
3-Bromo-8-nitro-		124	105
3-Bromo-1-methyl-6-carboxylate		241	945
3-Bromo-1-butyl-6-carboxylate		222	945
1-Benzyl-3-bromo-6-carboxylate		221	945
5-HALO-			
5,6,7,8-Tetrafluoro-4-methyl-		81.5	721
5-Chloro-2-methyl- (trihydrate)	15	53	706, 768, 870, 904
5-Chloro-2,6,8-trimethyl		64	705
5-Chloro-2,6-dimethyl-		45	710
5-Chloro-4-methyl-		106.5	943
5-Chloro-2-methyl-8-nitro-			706
5-Chloro-8-hydroxy-2-methyl-	30	68	859
5-Chloro-8-methoxy-2-methyl-	53	93	859
5-Chloro-8-(2-diethylaminoethoxy)-2-methyl-	58	61	923
6-HALO-			
6-Fluoro-2-methyl		59	675
2-(*p*-Chlorophenyl)-6-fluoro-8-(trifluoromethyl)-4-carboxylic acid	41	265	953
6-Chloro-2-methyl-	79	91	904, 921, 925, 951
6-Chloro-3,4-dimethyl-	12	130	875
6-Chloro-2-phenyl-4-carboxylic acid	9	242	939
6-Chloro-4-methyl-	30	66.5, 71	367, 949
6-Chloro-4-methyl-2-phenyl-		91.5	947
6-Chloro-4-ethyl-2-phenyl-		66	948
6-Chloro-4-(*p*-chloroanilino)-2-ethyl-3-methyl-	28	142	952
6-Chloro-4-styryl-	25	85	950
6-Chloro-2-(*p*-chlorophenyl)-8-(trifluoromethyl)-4-carboxylic acid	22		953
6,8-Dichloro-2-methyl-		122	954
6,8-Dichloro-5-methyl-2-phenyl-	14	149	906
6,8-Dichloro-2-(*p*-chlorobenzoyl)-4-carboxylic acid	21	326	940
6,8-Dichloro-4-(*p*-chlorophenyl)-2-carboxylic acid			954
6,8-Dichloro-2-[*p*-(trifluoromethyl)benzoyl]-4-carboxylic acid	23	285	940
6,8-Dichloro-2-[3,5-bis(trifluoromethyl)-benzoyl]-4-carboxylic acid	33	296	940
6-Chloro-2-(*p*-chlorobenzoyl)-8-(trifluoro-methyl)-4-carboxylic acid	24	276	940
6-Chloro-2-(3,4-dichlorobenzoyl)-8-(trifluoro-methyl)-4-carboxylic acid	38	278.5	940
6-Chloro-2-(3,5-dichlorobenzoyl)-8-(trifluoro-methyl)-4-carboxylic acid	39	286.5	940
6-Chloro-8-(trifluoromethyl)-2-[*m*-(trifluoro-methyl)benzoyl]-4-carboxylic acid	25	228	940

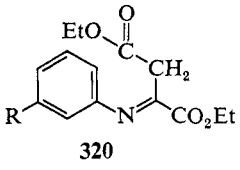
TABLE 23 (*cont.*)

Haloquinoline	Yield (%)	M.p. (°C)	References
6,8-Dichloro-2-methyl-5-carboxylic acid		245	906
6-Bromo-2-methyl-	33	97	904, 921, 924
6-Bromo-4-methyl-2-phenyl-		100	947
6-Bromo-8-chloro-2-phenyl-	20	92	900
6-Bromo-8-methyl-2-phenyl-	12.5	96	900
6-Bromo-8-nitro-		173	105
6-Bromo-4-(*p*-bromoanilino)-2-ethyl-3-methyl-	30	148	952
6-Iodo-2-methyl-		112	147, 675
6-Iodo-2-phenyl-4-carboxylic acid		250	937
6-Iodo-4-methyl-2-phenyl-		50	947
2-Ethyl-6-iodo-4-(*p*-iodoanilino)-3-methyl-	65	174	952
7-HALO-			
7-Fluoro-2-methyl-		56	675
7-Fluoro-2-(*p*-fluorophenyl)-4-carboxylic acid	50	257	941
7-Chloro-2-methyl-	30	78	706, 769, 904, 930, 942
7-Chloro-2,6-dimethyl-		92	710
7-Chloro-4-methyl-		61	943
7-Chloro-8-hydroxy-2-methyl-	25	118	163
7-Chloro-2-phenyl-4-carboxylic acid	10	246	939
7-Chloro-6-methoxy-2-phenyl-4-carboxylic acid	20	272	931
7-Chloro-2-(*p*-chlorophenyl)-4-carboxylic acid	22	279	931
7-Chloro-2-(*p*-chlorophenyl)-6-methoxy-4-carboxylic acid	22	286	931
7-Chloro-2-(*p*-chlorophenyl)-8-methyl-4-carboxylic acid	22	301	931
7-Chloro-8-methyl-2-phenyl-4-carboxylic acid	24	279	931
7-Chloro-4-(*p*-chlorophenyl)-6-methoxy-2-carboxylic acid	34	226	954
7-Chloro-2-(*p*-fluorophenyl)-4-carboxylic acid	24	285	931
7,8-Dichloro-2-methyl-		71	706
7,8-Dichloro-2,5-dimethyl-	7	124	932
8-HALO-			
8-Chloro-2-methyl-	20	64	904, 922, 951
8-Chloro-4-methyl-	23	107	920, 935, 936
8-Chloro-2-phenyl-4-carboxylic acid		246	938
8-Chloro-2-phenyl-5-carboxylic acid	Low	253	906
8-Chloro-5-hydroxy-		269	928
8-Chloro-5-hydroxy-4-methyl-		253	928
8-Chloro-4-methyl-2-phenyl-		80	947
8-Chloro-5-methyl-2-phenyl-	14	129	906
8-Chloro-6-methyl-2-phenyl-	20	95.5	900
8-Chloro-7-methyl-	16	45	927
8-Bromo-2-methyl-	37	69.5	926
8-Bromo-2,6-dimethyl-		97	929
8-Bromo-2,5,6-trimethyl-	6.7	91	933
8-Bromo-6-methyl-2-phenyl-	10	105	900

*L. Haloquinolines by the Conrad–Limpach Reaction**

In its simplest form the Conrad–Limpach reaction involves the cyclization of a 3-anilinocrotonic ester, e.g. (**322**), to a 4-quinolone, e.g. (**323**). These esters are readily prepared by condensing an aromatic amine with a β-keto-ester, e.g. ethyl acetoacetate, and there is available a wide choice of cyclizing agent. Originally paraffin oil was the medium of choice, but subsequently "Dowtherm", a mixture of biphenyl and diphenyl ether, has been introduced[439, 768] with great success. Acid-catalysed ring closures are also of synthetic utility; sulphuric acid, acetic acid, acetic anhydride, and, more recently, polyphosphoric acid have been employed, and examples of their use are discussed in this Section.

Adaptation of the crotonate ester enables a wide variety of 2- and 3-substituted 4-quinolones to be synthesized. For example, cyclization of 2-(arylimino)succinates of type (**320**) and malonic esters of type (**321**) yield 4-quinolone-2- and -3-carboxylate derivatives, respectively.



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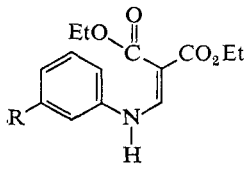

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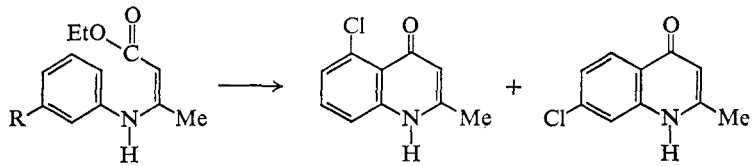
Many other variations have been documented, and in many instances the reactions involve haloanilines with the resultant formation of halo-4-quinolones. Such reactions are discussed in the present Section and a list of halo-substituted 4-quinolones so formed is given in Table 24 (p. 469). Of note is the use[390, 453, 627] of ethyl (trifluoroaceto)acete ($CF_3COCH_2CO_2Et$) for the synthesis of halo-substituted 2-(trifluoromethyl)-4-quinolones. Ethyl (trichloroaceto)acetate is now commercially available, and several instances of its use for the preparation of 2-(trichloromethyl)-4-quinolones have been reported.[955] For example, in the presence of polyphosphoric acid, ethyl (trichloroaceto)acetate and *p*-chloroaniline give 6-chloro-2-(trichloromethyl)-4-quinolone in 68% yield.

As in the Skraup and Doebner–von Miller reactions cyclization of *m*-haloanilinocrotonates (**322**; R = halogen) gives rise to mixtures of 5- and 7-halo-4-quinolones. Early workers[956, 957] report that the crotonate ester (**322**; R = Cl) on cyclization yields only 7-chloro-2-methyl-4-quinolone. Spivey and Curd,[768] however, have shown



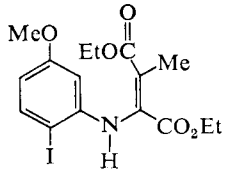
322 **323** **324**

that a mixture of the 5- (**323**) and the 7-chloro compound (**324**) is in fact formed; they were, however, able to effect only a partial separation of the mixture by fractional crystallization of the picrates. A complete separation of the isomers by fractional

* See also Addenda, p. 680.

crystallization from aqueous ethanol has since been reported.[958] Subsequent results confirm that in general *m*-haloanilines under Conrad–Limpach conditions yield a mixture of the 5- and 7-halo-4-quinolones.[321, 463, 477, 494, 959-964]

Steck and Hallock[485] report that the (*o*-iodoanilino)succinate (**325**) in hot "Dowtherm" cyclizes with loss of iodine to yield ethyl 7-methoxy-3-methyl-4-quinolone-2-carboxylate (**326**). Steck and his co-workers,[960] in an earlier report,



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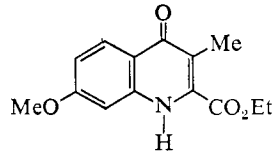

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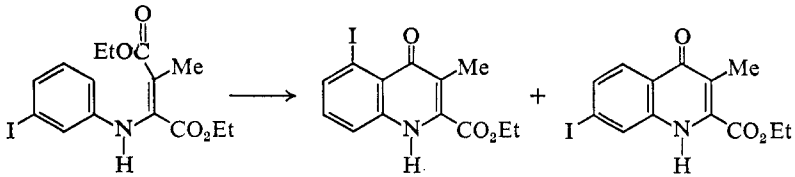
noted that the (*m*-iodoanilino)succinate (**327**) cyclizes to give a mixture of the expected 5- and 7-iodo-4-quinolones; however, during saponification the 5-iodo-isomer underwent loss of iodine to give a product of undetermined composition.



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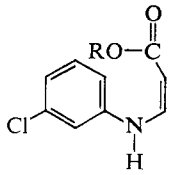
In comparison, the malonate (**321**; R = I)[753, 754, 965] and the iminosuccinate (**320**; R = I)[494] cyclize to the 7-iodo-4-quinolone-3- and -2-carboxylic esters, respectively, hydrolyses of which proceed normally.

Price and his co-workers[956] have observed the formation of ureas as by-products during the cyclization of (*m*-chloroanilino)crotonates. In fact, a concentrated solution of the ethyl ester (**328**; R = Et) in boiling diphenyl ether gives urea (**329**) as the sole



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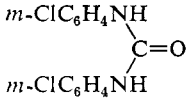

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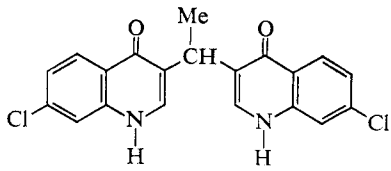
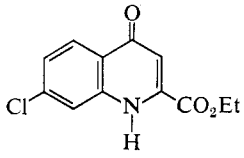


330

product. Under high-dilution conditions, however, the ester cyclizes normally to give a mixture of 5- (10%) and 7-chloro-4-quinolone (40%), together with the diquinolone (**330**) (10%). The diquinolone was shown by control experiments to arise by condensation of 7-chloro-4-quinolone with acetaldehyde, formed *in situ*. The formation of ureas as by-products during the reaction of aromatic amines with ketonic esters has been commented on by Adams and Hey.[471]

Ethyl 7-chloro-4-quinolone-2-carboxylate (**331**) is a key intermediate in the synthesis of 4,7-dichloroquinoline, which is itself the precursor of the highly successful antimalarial, "Chloroquine" (**332**).



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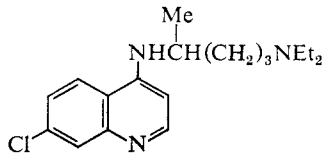

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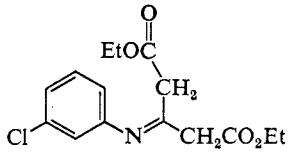
The ester (**331**) has been prepared by a variety of methods many of which employ a Conrad–Limpach-type cyclization. The commercial preparation involves cyclization of the iminosuccinate (**320**; R = Cl) and the process has been described in detail.[439] The 5- and 7-chloro-4-quinolone-2-carboxylates are obtained in about equal amounts and can be efficiently separated by fractional crystallization from a pyridine–ethanol mixture. The cyclization has been studied in some detail by Lisk and Stacy[966] who find that the use of a limited amount of "Dowtherm" as cyclizing medium results in the formation of virtually only the 5-chloro-isomer, whereas with a large excess of "Dowtherm" (ester to "Dowtherm" ratio 1 : 30) only 40% of the 5-chloro-isomer is produced. The total yield of mixed isomers, however, varies widely with the degree of dilution.

Occasionally Conrad–Limpach type cyclizations yield only one chloro-isomer. For example, the 3-iminoglutaric ester (**333**) yields only the 7-chloro-4-quinolone (**334**) (62%),[469] while the chloro-methyl compound (**335**; R = Me) in "Dowtherm"



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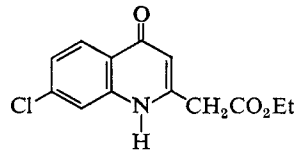

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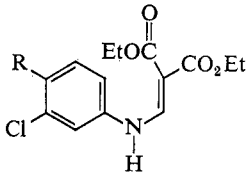

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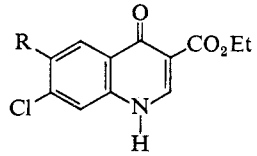


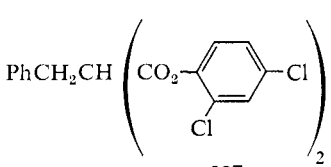
336

at 275 °C yields a single product that is thought to be the 7-chloro-6-methyl-4-quinolone (**336**; R = Me) rather than the 5-chloro-isomer.[967]

A change in cyclizing agent occasionally influences the isomeric composition of the product. For example, Price and Roberts[968] obtained ethyl 7-chloro-4-quinolone-3-carboxylate (**336**; R = H) by cyclization of the ester (**335**; R = H) in hot "Dowtherm", and only minor amounts of the isomeric 5-chloro-compound were formed. In contrast, cyclization of the ester in a mixture of acetic anhydride and sulphuric

acid is reported[969] to yield exclusively the 5-chloro-isomer.* Several other examples of 5- rather than 7-chloro-4-quinolone formation under these conditions have been reported,[474, 969] and similar results are obtained using sulphuric acid–phthalic anhydride mixtures.[970] Polyphosphoric acid has been used with great success as a cyclizing agent in the Conrad–Limpach synthesis.[511, 971, 972] A whole series of halogenated 4-quinolones have been prepared using this reagent,[511] and in the case of *m*-haloanilines mixtures of 5- and 7-halo-4-quinolones are produced.

2,4-Dibromoaniline reacts normally with bis-(2,4-dichlorophenyl) benzylmalonate (**337**) at 300 °C to give 3-benzyl-6,8-dibromo-4-hydroxy-2-quinolone (**338**) (72%).[128]



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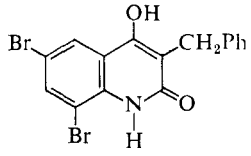

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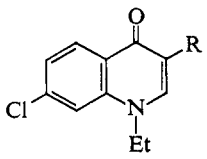
p-Bromoaniline under similar conditions, however, appears to disproportionate to give aniline and 2,4-dibromoaniline, with the result that the dibromoquinolone (**338**) is again formed, albeit in lesser yield (31%).

Occasionally during the large-scale preparation of ethyl 7-chloro-4-quinolone-3-carboxylate (**336**; R = H) from the ester (**335**; R = H), various by-products, for example, 7-chloro-1-ethyl-4-quinolone-3-carboxylic acid (**339**; R = CO_2H), 7-chloro-4-ethoxyquinoline (**340**), 7-chloro-1-ethyl-4-quinolone (**339**; R = H), and 7-chloro-4-quinolone (**341**), have been observed.[125, 211]



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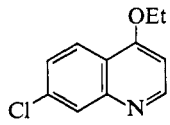

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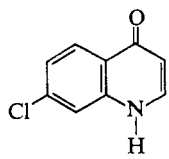


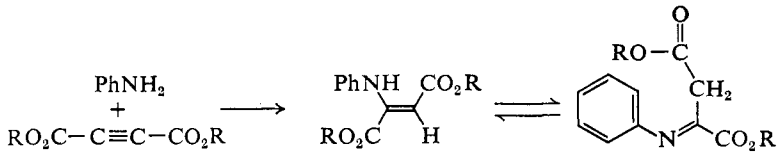
341

The *N*-ethylated products (**339**; R = CO_2H or H) and the 4-ethoxy-derivative (**340**) are considered to arise through alkyl—oxygen fission of the ethyl ester, yielding an ethyl carbonium ion, which ethylates the quinolonecarboxylic acid either at the ring-nitrogen, to give the 1-ethyl derivative (**339**; R = CO_2H), or at oxygen or nitrogen of the decarboxylated quinolone to give products (**340**) and (**339**; R = H), respectively. 7-Chloro-4-quinolone arises by simple decarboxylation of the main product (**336**; R = H).

Halogenated 1-alkyl-4-quinolones can be prepared by cyclizing esters of type (**342**), derived by condensing secondary aromatic amines with diethyl ethoxymethylenemalonate, $EtOCH{=}C(CO_2Et_2)$.[973, 974]

Huisgen and his co-workers[975] have shown that aromatic primary amines can add to acetylenedicarboxylates to give 2-iminosuccinates, as indicated in Scheme 31, and Heindel and his co-workers[54, 963] have since used this method to prepare a whole series of β-anilino-α,β-unsaturated esters. A closely related reaction had been

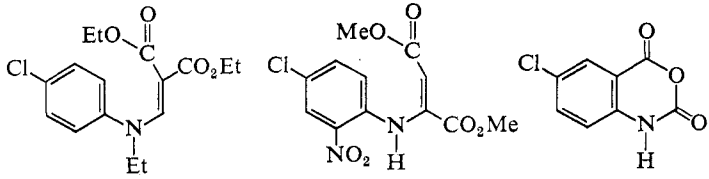
* A later study shows this result to be in error and that a mixture of isomers is always obtained regardless of the cyclizing agent.[2035]



SCHEME 31

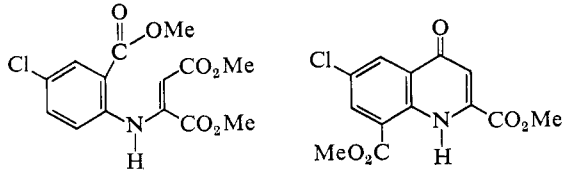
reported earlier by Mosher and his co-workers[976] who treated *m*-chloroaniline with methyl propiolate to obtain the adduct (**328**; R = Me), which on cyclization yielded 7-chloro-4-quinolone (**341**).

In the haloaniline series cyclization of these esters under normal Conrad–Limpach conditions yields the expected halo-4-quinolones. Some *o*-nitro-esters, however, proved more difficult: for example, the chloronitro-ester (**343**), formed by addition of dimethyl acetylenedicarboxylate to 4-chloro-2-nitroaniline, cyclizes only in the presence of polyphosphoric acid.[977]



342 **343** **344**

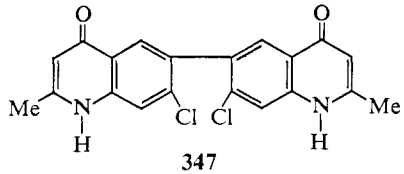
6-Chloroisatoic anhydride (**344**) reacts with dimethyl acetylenedicarboxylate in the presence of sodium methoxide to give the Michael adduct (**345**), which cyclizes above



345 **346**

its melting point to the quinolonedicarboxylic ester (**346**) in 65% yield.[978] 6-Bromo- and 6-iodo-isatoic anhydride behave similarly, whereas 5,7-dichloro- and 5,7-dibromo-isatoic anhydride fail to react.

Dichloro-4,4′-biquinolones (e.g. **347**) have been prepared by cyclization of dicrotonate esters, derived from 2,2′- and 3,3′-dichlorobenzidine, in boiling diphenyl ether.[442, 979]



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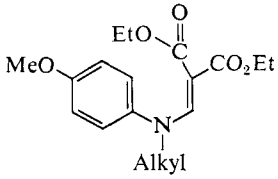
On several occasions cyclization of crotonate esters has been brought about by phosphorus oxychloride and, as expected, in such cases 4-chloroquinolines are obtained by chlorodehydroxylation of the initially formed 4-quinolones.[451, 512, 513, 526, 528, 532, 561, 581, 589, 777]

A series of 1-alkyl-4-chloroquinolinium-3-carboxylates (e.g. **349**) has been synthesized[974] by cyclizing diethyl (*N*-alkylanilinomethylene)malonates, e.g. (**348**), with hot phosphorus oxychloride. The products are initially formed as chlorides or



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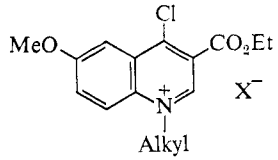
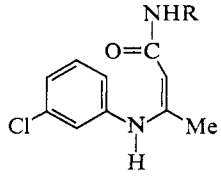


349

dichlorophosphates (**349**; X = Cl or PO_2Cl_2), but are more conveniently isolated and characterized as the iodides (**349**; X = I).

Cyclization of 3-(haloanilino)crotonanilides, e.g. (**350**; R = *p*-$MeOC_6H_4$), with concentrated sulphuric acid,[972, 980] polyphosphoric acid,[972, 980, 981] phosphorus pentoxide in xylene,[982] or phosphorus oxychloride[983] yields the corresponding halo-4-



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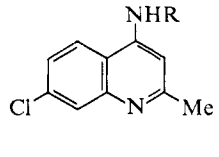
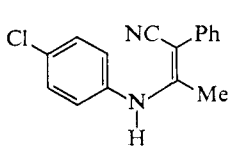


351

anilinoquinolines, e.g. (**351**; R = *p*-$MeOC_6H_4$). Comparative studies[972, 980] indicate that polyphosphoric acid is a better cyclizing agent than concentrated sulphuric acid, and that the yield of quinoline (**351**) is greatest (50%) when using polyphosphoric acid and least (22%) with phosphorus pentoxide in xylene. Phosphorus oxychloride also appears to be superior to phosphorus pentoxide as a cyclizing agent.[982]

A list of 4-aminoquinolines so prepared is given in Table 24a (p. 475).

The α,β-unsaturated nitrile (**352**) cyclizes in the presence of aluminium chloride at 255 °C to give the aminochloroquinoline (**353**).[984]



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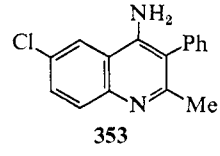

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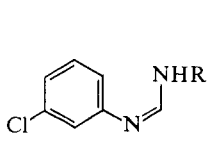
Price and Roberts[985] have shown that the reaction between *N,N'*-diarylformamidines, e.g. (**354**; R = *m*-ClC_6H_4), and diethyl malonate can be controlled so that condensation occurs to give the substituted malonate (**355**) rather than the anilide

(**356**). These malonates (**355**) are of interest in that they serve as a useful route to the synthesis of 4-quinolones, and Price and Roberts[964] have synthesized several chloro-4-quinolones by this method.



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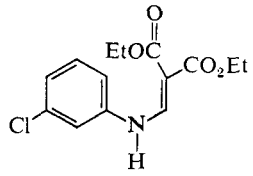

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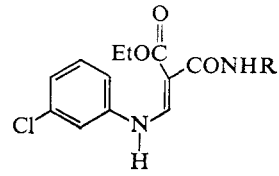

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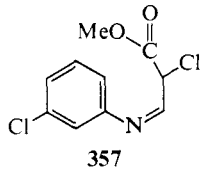
m-Chloroaniline can react with the sodium salt, $NaOCH{=}CClCO_2Me$, from methyl α-formyl-α-chloroacetate, yielding the chloro-anil (**357**), which in "Dowtherm" at 245 °C (30 min) cyclizes to 3,7-dichloro-4-quinolone (**358**).[604, 986]



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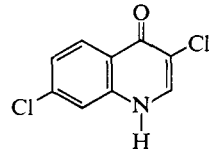

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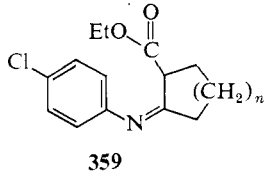
Reaction of *p*-chloroaniline with ethyl 2-oxocyclohexane- or 2-oxocycloheptane-carboxylate in boiling benzene containing a few drops of concentrated hydrochloric acid yields the anils (**359**; $n = 2$ or 3, respectively), which in mineral oil at 280 °C



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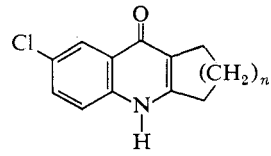

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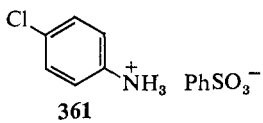
cyclize to, respectively, the chlorotetrahydroacridone (**360**; $n = 2$) or chlorotetrahydroheptaquinolone (**360**; $n = 3$).[987]

Hardman and Partridge[988] have treated *p*-chloroanilinium benzenesulphonate (**361**) with ethyl cyanoacetate at 210 °C for 1 hour to obtain 2-amino-6-chloro-4-quinolone (**362**) (21%). *o*-Chloroaniline behaves in a similar manner, but *m*-chloroaniline gives a mixture of 2-amino-5- (4%) and -7-chloroquinolone, (22%).[120]



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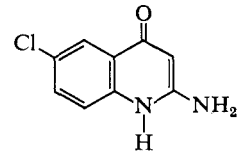

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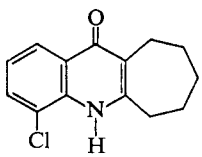
Very numerous Conrad–Limpach syntheses of halo-4-quinolones are recorded in Tables 24 and 24a.

TABLE 24. Halo-4-quinolones by the Conrad–Limpach Reaction

Halo-4-quinolone*	M.p. (°C)	Yield (%)	References
ALKYL- AND ARYL-SUBSTITUTED			
2-Chloro-3-ethyl-	248		579
2-Chloro-3-ethyl-8-methyl-	225.5		579, 580
3,7-Dichloro-	315		604, 986
3,8-Dichloro-2-methyl-	295	44	511
5-Chloro-	268	10	956
5-Chloro-2-methyl-	261	40	474, 958, 970, 971
5-Chloro-2-phenyl-	280	80	480, 989
5-Chloro-2,3-dimethyl-	370		990
5-Chloro-2,8-dimethyl-	291		991
5-Chloro-3-cyclopentyl-2-methyl-	278		992
5-Chloro-3-ethyl-2-methyl-	350 d	39	511
5-Chloro-3-methyl-	269.5		956
5-Chloro-3-phenyl-			993
5,8-Dichloro-2-methyl-	267	62	511
5,8-Dichloro-2,3-dimethyl-	240	98	511
5,8-Dichloro-3-ethyl-2-methyl-	207	92	511
6-Fluoro-2-methyl-	266		994
6-Fluoro-2-(trifluoromethyl)-	260	74	995
6-Chloro-2-methyl-	322	68	452, 474, 476, 839, 971, 996
6-Chloro-2-phenyl-	352	75	479, 544, 972, 997
6-Chloro-2-(trichloromethyl)-	225	69	955
6-Chloro-2-(trifluoromethyl)-	275	70	627
6-Chloro-2,3-dimethyl-	344 d	82	511
6-Chloro-3-ethyl-2-methyl-	348 d	77	511
6-Chloro-2,8-dimethyl-	311		991
6-Chloro-3-(*p*-methoxybenzyl)-2-methyl-	286	86	998
6-Chloro-3-(*p*-ethoxybenzyl)-2-methyl-	291	83	998
6-Chloro-3-phenyl-	349.5		471
6,8-Difluoro-2-(trifluoromethyl)-	165	63	995
6,8-Dichloro-2-methyl-	290	54	511, 999
6,8-Dichloro-2,3-dimethyl-	305 d	85	511
6,8-Dichloro-3-ethyl-2-methyl-	269	69	511
6,8-Dichloro-2-(trifluoromethyl)-	181	58	627
6,7,8-Trichloro-			484
6-Bromo-2-methyl-	338		452, 999
6-Bromo-2-phenyl-	333, 360	69	213, 972
6-Bromo-2-(trichloromethyl)-	230	63	955
6-Bromo-2-(trifluoromethyl)-	260	84	453
6-Bromo-2,3-dimethyl-	342 d	98	511
6-Bromo-3-ethyl-2-methyl-	352 d	90	511
6-Bromo-3-(*p*-methoxybenzyl)-2-methyl-	300	94	998
6-Bromo-3-(*p*-ethoxybenzyl)-2-methyl-	297	88	998

* This column contains also some 2-quinolones; these are named there as 2-hydroxy-compounds and are marked with an asterisk.

TABLE 24 (*cont.*)

Halo-4-quinolone*	M.p. (°C)	Yield (%)	References
6-Bromo-2-methyl-3-[*p*-(*n*-propoxy)benzyl]-	264	82	998
6-Bromo-3-phenyl-	365		471
6-Iodo-2-phenyl-	306	67	972
7-Fluoro-2-methyl-	258		994
7-Chloro-	250, 277.5	40	956, 976
7-Chloro-2-methyl-	315, 328	72	474, 768, 956, 958, 971
7-Chloro-2-phenyl-	358	19	454, 480
7-Chloro-2-(*p*-chlorophenyl)-		58	1000
7-Chloro-2,3-dimethyl-	345		990
7-Chloro-3-ethyl-2-methyl-	348	27	511
7-Chloro-3-cyclopentyl-2-methyl-	365	39	992
7-Chloro-3-(*n*-heptyl)-2-methyl-	262	9	992
7-Chloro-2,8-dimethyl-	306		991
7-Chloro-3-methyl-	337	65	956
7-Chloro-3-phenyl-	361.5	36.5	471, 993, 1001
7-Bromo-2-methyl-	>300		999
7,7′-Dichloro-6,6′-biquinoline-4,4′-dione	305		442
7,7′-Dichloro-2,2′-dimethyl-6,6′-biquinoline-4,4′-dione	>360		442
8-Fluoro-2-methyl-	433 ?		994
8-Fluoro-2-(trifluoromethyl)-	145	69	995
8-Chloro-2-methyl-	216, 230	29	839, 971, 999, 1002
8-Chloro-2-(trichloromethyl)-	194	43	955
8-Chloro-2-(trifluoromethyl)-	135	55	627
8-Chloro-2,3-dimethyl-	257	79	511
8-Chloro-3-ethyl-2-methyl-	248	77	511
8-Chloro-2,3,5-trimethyl-	188.5	82	511
8-Chloro-3-ethyl-2,3-dimethyl-	168	62	511
8-Chloro-2,5-dimethyl-	233.5	48	511
8-Chloro-3-phenyl-	251		471
8,8′-Dichloro-6,6′-biquinoline-4,4′-dione	>360		442
8-Bromo-2-methyl-	210	82	511
8-Bromo-2-(trichloromethyl)-	195	59	955
8-Bromo-2,3-dimethyl-	235	98	511
8-Bromo-3-ethyl-2-methyl-	234	90	511
8-Bromo-3-(*p*-methoxybenzyl)-2-methyl-	222	87	998
8-Bromo-3-(*p*-ethoxybenzyl)-2-methyl-	200	90	998
	265		987

* This column contains also some 2-quinolones; these are named there as 2-hydroxy-compounds and are marked with an asterisk.

TABLE 24 (*cont.*)

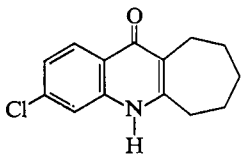
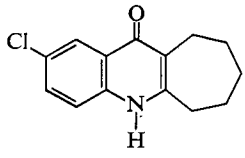
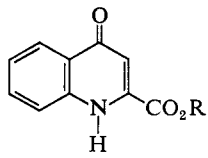
Halo-4-quinolone*	M.p. (°C)	Yield (%)	References
	360		987
	360		987
HYDROXY- AND ALKOXY-SUBSTITUTED			
5-Chloro-8-hydroxy-2-methyl-	235	40	859
5-Chloro-8-methoxy-			484
5,6- and 6,7-Dichloro-2-hydroxy-*		78	593
5,8-Dichloro-2-hydroxy-*	360	60	582, 593
6-Fluoro-2-hydroxy-*	345	73	593
6-Chloro-2-hydroxy-*	350	78	582, 585, 593
6-Chloro-3-ethyl-2-hydroxy-*	264		411
6-Chloro-2-hydroxy-3-(*p*-methoxybenzyl)-*	210	66	596
6-Chloro-8-methoxy-2-methyl-	250	60	511
6-Chloro-8-methoxy-2,3-dimethyl-	215	83	511
6-Chloro-3-ethyl-8-methoxy-2-methyl-	220	63	511
6,8-Dichloro-2-hydroxy-*	360	10	593
6,7,8-Trichloro-2-hydroxy-*	350	92	593
6-Chloro-3-(3-chlorobut-2-enyl)-2-hydroxy-*	217	68.5	596
6-Bromo-2-hydroxy-3-(*p*-methoxybenzyl)-*	246	74	596
6-Bromo-3-(3-chlorobut-2-enyl)-2-hydroxy-*	236	57.2	596
3-Benzyl-6,8-dibromo-2-hydroxy-*	284	72	128
7-Chloro-2-hydroxy-*	360	92	399, 581, 582, 585, 595
7-Chloro-2-hydroxy-3-methyl-*	280		990
7-Chloro-2-hydroxy-8-methyl-*	325	82	593
7-Chloro-3-methoxy-	202	17	321
8-Chloro-2-hydroxy-*	292	83	593
8-Chloro-5-hydroxy-2-methyl-	226		1003
8-Chloro-5-methoxy-2-methyl-	194	63	511
8-Chloro-5-methoxy-2,3-dimethyl-	169	67	511
8-Chloro-5-ethoxy-2,3-dimethyl-	169	79	511
8-Chloro-3-ethyl-5-methoxy-2-methyl-	187	62	511
8-Chloro-6-methoxy-2-methyl-	301		475
CARBONYL-SUBSTITUTED			
3-Acetyl-5-chloro-	248		969
3-Acetyl-5- or 7-chloro-2-phenyl-	300	44	454, 1004
3-Acetyl-6-chloro-	> 300	52	969, 1005

TABLE 24 (*cont.*)

Halo-4-quinolone	M.p. (°C)	Yield (%)	References
3-Acetyl-6-bromo-	> 300		1006
3-Acetyl-6-chloro-2-phenyl-	300	12.5	1004
3-Acetyl-7-chloro-	315	90	969
3-Acetyl-8-chloro-	294	60	969, 1005
3-Acetyl-8-chloro-2-phenyl-	286	12	1004
3,3′-Diacetyl-8,8′-dichloro-6,6′-biquinoline-4,4′-dione	275 d	96	979
AMINO-SUBSTITUTED			
2-Amino-5-chloro-	353	4	120
2-Amino-6-chloro-	361 d	21	988
2-Amino-7-chloro-	349	22	120
7-Chloro-3-(*m*-chlorobenzoamido)-	322	50	1001
2-Amino-8-chloro-	323 d	8	988

4-QUINOLONE-2-CARBOXYLIC ESTERS

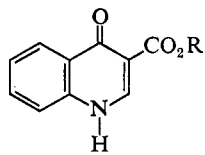


Halo-4-quinolone	R	M.p. (°C)	Yield (%)	References
5-Fluoro-3-methyl-	Et	199	45	961
5-Fluoro-6-methoxy-	Me			963
5-Chloro-	Et	200		439, 494, 959, 1007
5-Chloro-	Me	257	15	963
5-Chloro-3-methyl-	Et	220.5	47	463, 959, 1008
5-Chloro-3-(*n*-propyl)-	Et	171	45	961
5- or 7-Chloro-3-(*m*-chloroanilino)-	Me	226.5	97	962
5-Chloro-6-methoxy-	Me	248	25	963
5-Chloro-3,6-dimethyl-	Me			321
5-Bromo-3-methyl-	Et	220	45	463
5-Bromo-6-methoxy-	Et	222		505
5-Iodo-3-methyl-	Et	237.5	32	960
5,6- or 6,7-Dichloro-	Et	253	90	1009
5,7-Dichloro-	Et	254	55	691
5,7-Dichloro-	Me	287	90	963
5,8-Dichloro-	Et	154	50	691, 1009
5,7-Dibromo-	Et	257	70	691
6-Fluoro-	Et	240	55	244
6-Fluoro-	Me	254	73	963
6-Fluoro-3-methyl-	Et	234	89	961
6-Fluoro-3-(*p*-fluoroanilino)-	Me	226	79	962
6-Chloro-	Et	243	84	1010, 1011
6-Chloro-	Me	267	89	975

TABLE 24 (*cont.*)

Halo-4-quinolone	R	M.p. (°C)	Yield (%)	References
6-Chloro-8-nitro-	Me	199	36	977
6-Chloro-3-methyl-	Et	243, 251	95	321, 464, 532
6-Chloro-3-(*p*-chloroanilino)-	Me	248.5	89	244, 962
(6-Chloro-2-quinolyl) acetate	Et	230		1012
6-Bromo-3-methyl-	Et	251	77	464
6-Bromo-3-(*p*-bromoanilino)-	Me	262	92	244
(6-Bromo-2-quinolyl) acetate	Et	228		1012
6-Iodo-3-methyl-	Et	234	82	960
6,8-Dichloro-	Et	148.5		691, 1009, 1013, 1014
6,7-Dichloro-3-(3,4-dichloroanilino)-	Me	253	90	244, 962
7-Fluoro-3-methyl-	Et	225	53	961
7-Fluoro-6-methoxy-	Me			963
7-Chloro-	Et	251, 276	89	439, 494, 959, 1007
7-Chloro-	Me	293	48	963
7-Chloro-3-methyl-	Et	230	58	463, 959, 1008
7-Chloro-3,6-dimethyl-	Et			321
7-Chloro-6-methoxy-	Me	299	60	963
7-Chloro-8-methyl-	Et	208	63	966
7-Chloro-3-(*n*-propyl)-	Et	218.5	50	961
7-Chloro-3-(*m*-chloroanilino)-	Me	226	97	244, 962
(7-Chloro-2-quinolyl) acetate	Et	238	62	469, 1012
7-Bromo-	Et	252		494
7-Bromo-3-methyl-	Et	228.5	53	463
7-Bromo-6-methoxy-	Et	278		505
(7-Bromo-2-quinolyl) acetate	Et	230		1012
7-Iodo-	Et	250		494
7-Iodo-3-methyl-	Et	231.5	60	960
8-Fluoro-3-methyl-	Et	135	80	961
8-Chloro-	Me	149	81	963
8-Chloro-3-methyl-	Et	88, 146	68	321, 482
8-Chloro-5-(trifluoromethyl)-	Me	127	68	963
8-Chloro-3,5-dimethyl-	Me	121	62	321
(8-Chloro-2-quinolyl) acetate	Et	203		1012
8-Bromo-3-methyl-	Et	112	59	482
(8-Bromo-2-quinolyl) acetate	Et	216		1012
8-Iodo-3-methyl-	Et	180	89	960

4-QUINOLONE-3-CARBOXYLIC ACIDS AND ESTERS



5-Chloro-	Et	271	18	969, 1015, 2035
5-Chloro-2-methyl-	Et			1016
5-Chloro-2-phenyl-	H	245		1017

TABLE 24 (*cont.*)

Halo-4-quinolone	R	M.p. (°C)	Yield (%)	References
5-Chloro-6,8-dimethoxy-	Et	297		529
5,8-Dichloro-	Et	205	26	1011
6-Fluoro-	Et	289, 314		495, 529
6-Fluoro-7-methyl-	Et	329		529
6-Fluoro-7-(trifluoromethyl)-	Et	341		529
6-Chloro-	H	277	35	964
6-Chloro-	Et	293, 305 d	60	481, 1015, 1018, 1019
6-Chloro-2-phenyl-	Et	252	30	1020, 1021
6-Chloro-1-methyl-	Et	176		973
6-Bromo-	Et	287	99	212
6,7-Dichloro-	Et	337		529, 1015
6,8-Dichloro-	Et	278 d	50	1011
7-Fluoro-	Et	310		495, 529, 1015
7-Chloro-	Et	297	90	441, 496, 968, 969, 1015, 1018, 1022, 2035, 2067, 2086
7-Chloro-	H	247 d	36	964
7-Chloro-5-methoxy-	Et			495
7-Chloro-6-methoxy-	Et	299 d		495
6-(Benzylthio)-7-chloro-	Et	266		481
7-Chloro-2-(methylthio)-	Et	138	55	451
7-Chloro-6-methyl-	Et	> 280	92	967
7-Chloro-8-methoxy-	Et	240		487
7-Chloro-2-phenyl-	Et	237	30	477, 1020
7-Chloro-1-methyl-	Et	170		973
7-Chloro-2-phenyl-	H	352	27.5	1017
7-Bromo-	Et	309	44	965, 1015
7-Iodo-	Et	304	94	753, 754, 965
7,8-Dichloro-	Et			1015
8-Chloro-	H	258 d	7	964
8-Chloro-	Et	254	96	964, 969, 1015, 1019
8-Chloro-2-phenyl-	Et	156	32	1020
8-Chloro-2-phenyl-	H	186		1020
8-Chloro-5-phenyl-	Et	303	42	1024
5-Benzyl-8-chloro-	Et	226	32	1024
8-Chloro-5-phenethyl-	Et	177	15	1024
8-Chloro-5-styryl-	Et	247	55	1024
8-Chloro-5-(4-phenylbutyl)-	Et	—	90	1024
8-Chloro-5-(6-phenylhexyl)-	Et	124	51	1024
8-Chloro-5-(3-phenoxypropoxy)-	Et	144	62	1024
8-Chloro-5-(4-phenoxybutoxy)-	Et	184	65	1024
8-Chloro-5-methyl-	Et	198	51	1011
8-Chloro-5-(4-methylphenethyl)-	Et	198	40	1025
5-[2-(*o*-Biphenylyl)ethyl]-8-chloro-	Et	180	25	1025
5-[2-(*m*-Biphenylyl)ethyl]-8-chloro-	Et	167	23	1025
5-[2-(*p*-Biphenylyl)ethyl]-8-chloro-	Et	205	56	1025
8-Chloro-5-[β-(1-naphthyl)styryl]-	Et	279	56	1025

TABLE 24 (*cont.*)

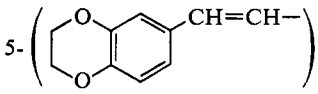
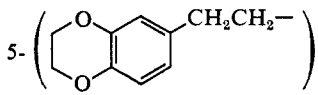
Halo-4-quinolone	R	M.p. (°C)	Yield (%)	References
8-Chloro-5-[2-(2-naphthyl)ethyl]-	Et	209	50	1025
8-Chloro-5- 	Et	271	50	1025
8-Chloro-5- 	Et	199	76	1025
8-Chloro-5-(*m*-fluorophenethyl)-	Et	156	44	1025
8-Chloro-5-(*m*-chlorophenethyl)-	Et	163	9	1025
8-Chloro-5-(*p*-chlorophenethyl)-	Et	197	38	1025
8-Chloro-5-[β-(2,6-dichlorophenyl)styryl]-	Et	234	64	1025
8-Chloro-5-(2,6-dichlorophenethyl)-	Et	203	50	1025
8-Chloro-5-(2,5-dichlorophenethyl)-	Et	199	48	1025
8-Chloro-5-(2,4-dichlorophenethyl)-	Et	216	69	1025
8-Chloro-5-(3,4-dichlorophenethyl)-	Et	192	32	1025
8-Chloro-7-methyl-	Et	266	73	321
8-Bromo-	Et	251	27	1011
MISCELLANEOUS				
7-Chloro-3-carboxylic acid *m*-chloroanilide		322	58	660, 964, 985, 1022, 1023
7-Chloro-3-cyano-		370	90	660, 1001
Me_2 6-chloro-2,8-dicarboxylate		195	70	978
Me_2 6-bromo-2,8-dicarboxylate		209	71	978
Me_2 6-iodo-2,8-dicarboxylate		222	70	978
2-Et 8-Me 6-chloro-2,8-dicarboxylate		162	65	978

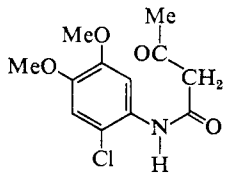
TABLE 24a. Halogenated 4-Aminoquinolines by Reactions of Conrad–Limpach Type

Halogenated 4-aminoquinoline	M.p. (°C)	Yield (%)	References
4-(*n*-Butylamino)-7-chloro-3-cyano-	147	65	982
7-Chloro-3-cyano-4-(*n*-hexylamino)-	134	50	982
7-Chloro-3-cyano-4-(5-cyanopentylamino)-	161	12	982
7-Chloro-4-(*m*-chloroanilino)-3-cyano-	295	25	982
Et 7-chloro-4-(*m*-chloroanilino)-3-carboxylate	123	57	982
7-Chloro-4-(*p*-hydroxyanilino)-2-methyl-	270	50	980
7-Chloro-4-(*p*-methoxyanilino)-	212	80	981
7-Chloro-4-(*p*-methoxyanilino)-2-methyl-	189	22	980
7-Chloro-4-(*p*-methoxyanilino)-3-carboxamide	190	40	981
Et 7-chloro-4-(*p*-chloroanilino)-3-carboxylate	144	65	982
Et 7-chloro-4-(*p*-methoxyanilino)-3-carboxylate	134		983
4-Amino-6-chloro-2-methyl-3-phenyl-	242	42	984

*M. Haloquinolines by the Knorr Synthesis**

Condensation of β-keto-esters and aromatic amines at high temperature leads to the formation of acetoacetanilides which, in the presence of acid, cyclize to yield 2-quinolones. This reaction constitutes the well-known Knorr synthesis of quinolones and has been successfully applied to the preparation of a number of halo-2-quinolones,[409, 419, 420, 839, 859, 1026–1028] which are listed in Table 25 (p. 480).

Most of these cyclizations appear to proceed smoothly in concentrated sulphuric acid although occasionally some difficulties are encountered. For example, cyclization of the chlorodimethoxyacetoacetanilide (**363**) in cold concentrated sulphuric acid results in the formation of a mixture of 8-chloro-5,6-dimethoxy-4-methyl-2-quinolone (**364**; R = Me) and its 5,6-dihydroxy-analogue (**364**; R = H).[274] Also, various authors[419, 420] report that other *o*-chloroacetoacetanilides cyclize to 8-chloro-4-methyl-2-quinolones with difficulty and in poor yield. Hamada and his co-workers,[839]



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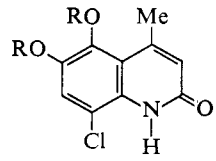

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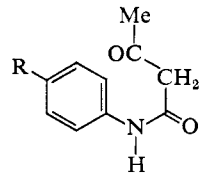
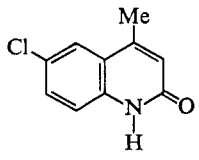


365

in fact, record that they were unable to cyclise *o*-chloro- and *o*-bromo-acetoacetanilide, whereas the *p*-chloro-isomer (**365**; R = Cl) readily cyclized to give the 6-chloro-2-quinolone (**366**).

More recently, Egyptian workers[1029] have failed to cyclize the *o*-chloroacetoacetanilide (**367**), formed by reaction of *o*-chloroacetanilide with ω-nitrostyrene in



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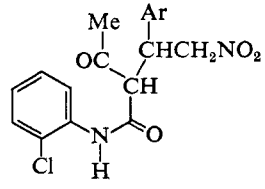

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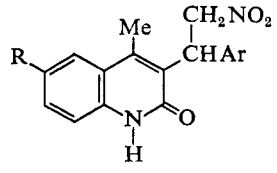


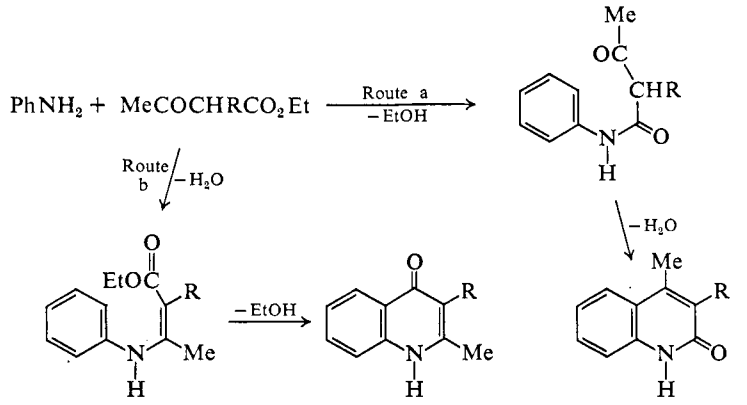
368

the presence of base, whereas the *p*-chloro- and *p*-bromo-derivatives in a mixture of concentrated sulphuric and polyphosphoric acid yield the desired 2-quinolones (**368**; R = Cl and Br, respectively).

Aromatic amines and β-keto-esters have been reacted directly, without prior formation of the acetoacetanilide, in hot polyphosphoric acid.[511] Generally, under high-temperature conditions, acetoacetanilide formation is favoured (Scheme 32; route a) but in hot acid the main products were found to be 4-quinolones, indicating that crotonic ester formation (route b) is preferred.

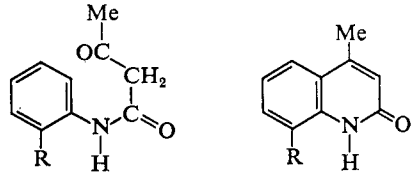
This reaction is, however, complex since the formation of 2- or 4-quinolone depends on a number of factors including the position and nature of the substituents present in the acetoacetanilide, and the amount of polyphosphoric acid used. For

* See also Addenda, p. 680.



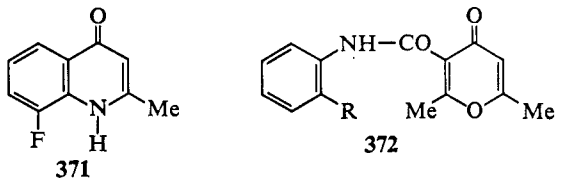
SCHEME 32

instance, anilides (**365**; R = Me or MeO) yield only the expected 4-methyl-2-quinolones under all the reaction conditions studied. However, anilides bearing halogen substituents (e.g. **365**; R = Cl or Br), with a large excess of polyphosphoric acid, yield 6-halo-4-methyl-2-quinolones, whereas with a small amount of acid 6-halo-2-methyl-4-quinolones and arylamines are obtained. The arylamines are formed by hydrolysis of the acetoacetanilides, a process that appears to be of negligible importance in the presence of a large excess of acid. If, however, the anilides bear an *o*-halo-substituent, e.g. (**369**; R = Cl or Br), then formation of the 6-halo-2-methyl-4-quinolone is observed regardless of the amount of polyphosphoric acid used.



369 **370**

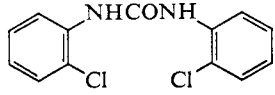
Various authors[511, 1030] have noted the formation of 4-pyrones during the polyphosphoric acid-induced cyclization of acetoacetanilides. For example, Garner and Suschitzky[1030] found that *o*-fluoroacetoacetanilide (**369**; R = F) yields 8-fluoro-4-methyl-2-quinolone (**370**; R = F) exclusively in concentrated sulphuric acid, whereas in polyphosphoric acid a mixture of the 2-quinolone (**370**; R = F), 8-fluoro-2-methyl-4-quinolone (**371**), and the 4-pyrone (**372**; R = F) is formed. *o*-Chloroacetoacetanilide yields the pyrone (**372**; R = Cl) as the major product.



371 **372**

The 4-pyrones are thought to arise from attack on the acetoacetanilide side chain by an acetoacetylium ion ($CH_3COCH_2CO^+$), formed by hydrolysis of the anilide.

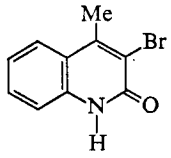
Hydrolysis of the anilide, followed by recombination to give a crotonic ester, which then cyclizes to yield 2-methyl-4-quinolone in a typical Conrad–Limpach manner, has led to some confusion in the early literature. For instance, Kermack and Muir[697] cyclized the *o*-chloroacetoacetanilide (**369**; R = Cl) in concentrated sulphuric acid and obtained what they thought was the 8-chloro-4-methyl-2-quinolone, m.p. 230 °C. A similar product resulted on thermal cyclization of the anilide in mineral oil at 240 °C. Johnson and Hamilton[420] carried out the same cyclization and obtained a product of m.p. 212 °C, which they also claimed to be 8-chloro-4-methyl-2-quinolone. The following year, however, Krahler and Burger[1002] during their investigations on the nitration of 2-chlorolepidine showed that the product of m.p. 230 °C, as obtained by Kermack and Muir, is in fact the isomeric 8-chloro-2-methyl-4-quinolone. A later investigation by Marais and Backeberg[419] further demonstrated that the product obtained by thermal cyclization of *o*-chloroacetoacetanilide is not the chloro-2-quinolone as stated,[697] but the symmetrical di-(*o*-chlorophenyl)urea (**373**).



373

Effenberger and Hartmann[1031] have prepared chloroacetoacetanilides by treating chloroanilines with 3-ethoxyacryloyl chloride, EtOCH=CHCOCl. The resulting anilides, including the *o*-chloro-isomer cyclize in strong acid to give the corresponding chloro-2-quinolones in quantitative yield.

Knorr[111] in one of his original papers on the cyclization of acetoacetanilides states that bromination of acetoacetanilide and cyclization of the resulting monobromo-derivative in concentrated sulphuric acid yields 3-bromo-4-methyl-2-quinolone (**374**), so demonstrating that bromination of the acetoacetanilide had occurred at the α-carbon centre.



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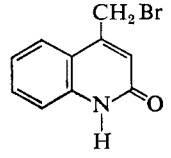


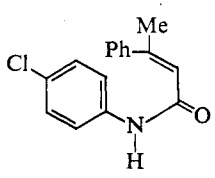
375

Chick and Wilsmore,[112] however, later showed that the Knorr product is in fact the 4-(bromomethyl) compound (**375**), and this structure has since been confirmed by several workers.[114, 115, 355] It, therefore, appears that the bromoacetoacetanilide is in fact the ω-bromo-derivative ($PhNHCOCH_2COCH_2Br$) rather than the α-bromo-isomer, as assumed by Knorr.

α-Bromoacetoacetanilide, PhNHCOCHBrCOMe, has been prepared by brominating acetoacetanilide in aqueous methanol under alkaline conditions.[1032] Cyclization of the anilide in concentrated sulphuric acid yields 3-bromo-4-methyl-2-quinolone (**374**). Several 3-bromo-2-quinolones have since been prepared in a similar manner.[1033]

A report[113] apparently supporting structure (**374**) for the Knorr product has recently been refuted.[114]

Cyclization of the cinnamanilide (**376**) in concentrated sulphuric acid yields 6-chloro-1,2,3,4-tetrahydro-4-methyl-4-phenyl-2-oxoquinoline (**377**).[1034, 1035]



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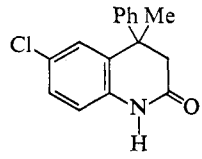

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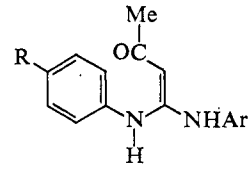
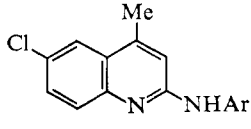


378

2,2-Dianilinovinyl ketones of type (**378**), prepared by condensing 1,1-dichlorobut-1-en-3-one ($CH_3COCH{=}CCl_2$) with an excess of arylamine, readily cyclize in the presence of polyphosphoric acid to give 4-alkyl-2-anilinoquinolines.[1036] 6-Chloro-2-(*p*-chloroanilino)-4-methylquinoline (**379**; Ar = *p*-ClC_6H_4) has been so prepared from the diaminovinyl ketone (**378**; R = Cl; Ar = *p*-ClC_6H_4).



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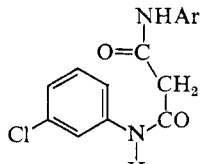

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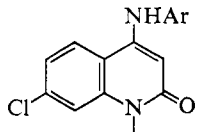
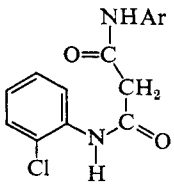


381

Malondianilides of type (**380**; Ar = *m*-ClC_6H_4) cyclize when heated in the presence of aluminium chloride to yield the corresponding 4-anilino-2-quinolones (**381**; Ar = *m*-ClC_6H_4).[1037, 1038] However, the *o*-chlorophenyl derivative (**382**; Ar = *o*-ClC_6H_4) in the presence of aluminium chloride and sodium chloride at 250 °C cyclizes with loss of an *o*-chloroanilino-residue to give 8-chloro-4-hydroxy-2-quinolone (**383**) in high yield (83%).[593]



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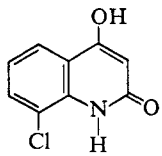

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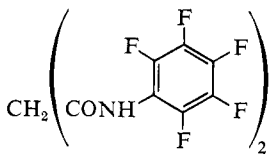


384

Tanabe and Ishikawa[1039] have cyclized the highly fluorinated malondianilide (**384**) under similar conditions to those quoted above. However, the structure of the resulting 2-quinolone is unresolved since fluorine–chlorine exchange takes place during the reaction.

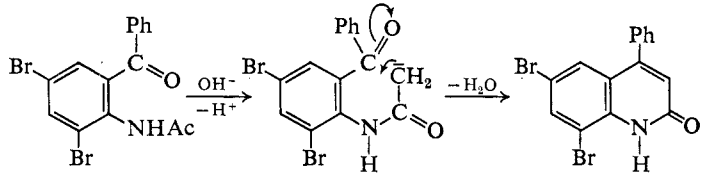
TABLE 25. Halo-2-quinolones by the Knorr Synthesis

Halo-2-quinolone	M.p. (°C)	Yield (%)	References
3-Bromo-4,6-dimethyl-			1033
3-Bromo-6-ethoxy-4-methyl-			1033
3-Bromo-4-methyl-			1032, 1033
5-Bromo-6,7-dimethoxy-4-methyl-	276	60	409
6-Bromo-4-(bromomethyl)-	278		114
6-Bromo-4-methyl-	292	29	511, 1026
6-Bromo-4-methyl-3-[α-(nitromethyl)benzyl]-	193	50	1029
7-Bromo-4-methyl-	288		1026
3-Chloro-4-methyl-	276	78	593, 1040
5-Chloro-		22	1031
5-Chloro-8-methoxy-4-methyl-	213		859
6-Chloro-	275	100	1031
6-Chloro-2-(*p*-chloroanilino)-4-methyl-	145	93	1036
6-Chloro-4-hydroxy-	370	78	585, 593, 2066
6-Chloro-7-hydroxy-4-methyl-	328		1028
6-Chloro-8-methoxy-4-methyl-	216	9	511
6-Chloro-4-methyl-3-[*p*-methoxy-α-(nitromethyl) benzyl]-	215	40	1029
6-Chloro-4-methyl-3-[α-(nitromethyl)benzyl]-	202	43	1029
6-Chloro-1,2,3,4-tetrahydro-4-methyl-4-phenyl-	210		1034, 1035
6-Chloro-4-methyl-	294		511, 614, 839, 1026
6-Chloro-4-phenyl-	254	62	1027
6-Fluoro-4-hydroxy-	345	73	593
6-Fluoro-4-methyl-	287		994
7-Chloro-		78	1031
4-(Bromomethyl)-7-chloro-	262		114
7-Chloro-4-(*m*-chloroanilino)-	341	75	1037, 1038
7-Chloro-4,6-dimethyl-	327		419
7-Chloro-4-hydroxy-	360	92	585, 593
7-Chloro-4-hydroxy-8-methyl-	325	82	593
7-Chloro-4-methyl-			614
8-Chloro-	210	100	1031
4-(Bromomethyl)-8-chloro-		32	511
8-Chloro-5,6-dihydroxy-4-methyl-	> 380	45	274
8-Chloro-5,6-dimethoxy-4-methyl-	168	36	274
8-Chloro-3,4-dimethyl-	209	80	1041
8-Chloro-4,6-dimethyl-	235		419
8-Chloro-4-hydroxy-	292	83	593, 2066
8-Chloro-4-methyl-	214.5	26	419, 420, 614, 697, 1030
8-Fluoro-4-methyl-	235	10	1030
5,6- and 6,7-Dichloro-4-hydroxy-		78	593
5,8-Dichloro-4-(2,5-dichloroanilino)-	256	83	1037, 1038
5,8-Dichloro-4-hydroxy-	360	60	593
6,8-Dichloro-	257	75	1031
6,8-Dichloro-4-hydroxy-	360	10	593
6,8-Dichloro-4-methyl-	243	16	511
6,7,8-Trichloro-4-hydroxy-	350	92	593

*N. Haloquinolines from o-Aminocarbonyl Compounds**

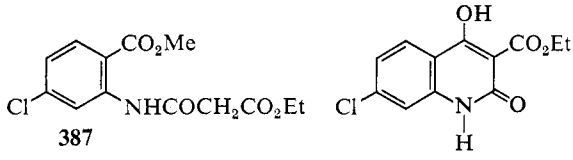
The Friedländer synthesis of quinolines involves condensation of an *o*-aminoaryl ketone or aldehyde with a carbonyl compound containing an active methylene or methyl group. The reaction is, however, somewhat limited in its application since the required *o*-aminocarbonyl compounds are not readily available. Related is the Camps synthesis which involves base-catalysed cyclization of *o*-acylaminoaryl ketones. The former reaction has been largely superseded by the Pfitzinger reaction (see following Section) but nevertheless both the above reactions have been employed for the synthesis of haloquinolines as outlined in this Section, and Table 26 (p. 486).

Treatment of 2-acetamido-3,5-dibromobenzophenone (**385**) with ethanolic potassium hydroxide brings about cyclization to the dibromo-2-quinolone (**386**) as illustrated.[1042]

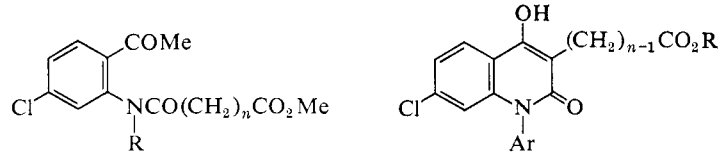


385 386

Various chloro-substituted *o*-acylamido-benzo-[1043] and -aceto-phenones[990, 1044] have also been cyclized in this manner. The monoanilide (**387**) of malonic ester undergoes cyclization to the 7-chloro-4-hydroxy-2-quinolone (**388**) on treatment with sodium ethoxide;[594] apparently only one isomer is formed.



387 388

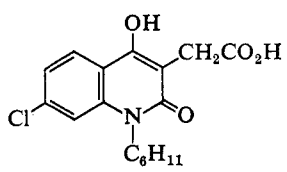


389 390

A series of *N*-substituted *o*-aminoacetophenones, e.g. (**389**; R = Ar), have been cyclized to yield 4-hydroxy-2-quinolone-3-carboxylic esters of type (**390**; R = Me),[1045] and the acid (**390**; R = H, Ar = Ph, $n = 2$) has been shown to possess marked aldosterone-antagonistic activity in rats.

The amide (**389**; R = C_6H_{11}, $n = 2$), on cyclization followed by hydrolysis, yields the expected carboxylic acid (**391**) together with the 4-oxobutyric acid (**392**),[1046] the presence of which suggests the intermediary formation of an azepinedione. In fact, careful hydrolysis of the reaction mixture allows isolation of 8-chloro-1-cyclohexyt 2,3,4,5-tetrahydro-2,5-dioxo-1*H*-benzazepine (**393**).

* See also Addenda, p. 682.



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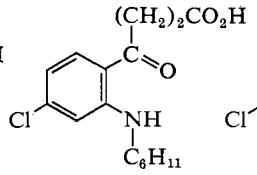

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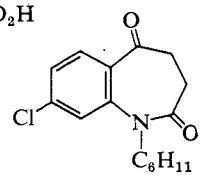
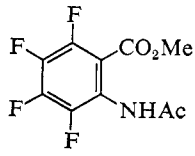


393

Tanabe and Ishikawa[1039] have shown that methyl 2-acetamido-3,4,5,6-tetrafluorobenzoate (**394**) with sodium in boiling toluene undergoes cyclization to give the tetrafluoro-2-quinolone (**395**) in 30% yield.



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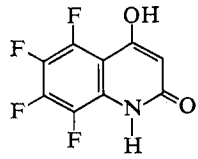
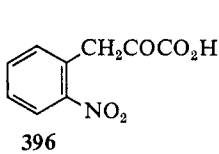


395

Numerous 2- and 3-substituted 6-chloro-4-phenylquinolines have been prepared by condensing 2-amino-4-chlorobenzophenone with a variety of methyl ketones in the presence of base.[1047, 1048] 2-Amino-5-bromoacetophenone condenses with (*o*-nitrophenyl)pyruvic acid (**396**) in the presence of zinc chloride at 140 °C to give the 6-bromoquinoline (**397**).[1049]



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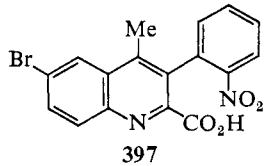
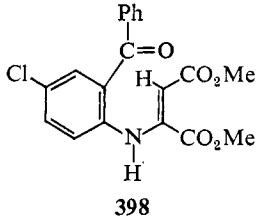


397

The adduct (**398**) formed of 2-amino-5-chlorobenzophenone and dimethyl acetylenedicarboxylate cyclizes in boiling methanol to the quinolinedicarboxylate (**399**) in high yield (78%).[1050]



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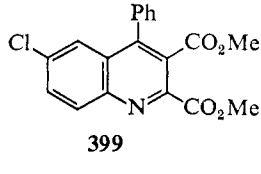
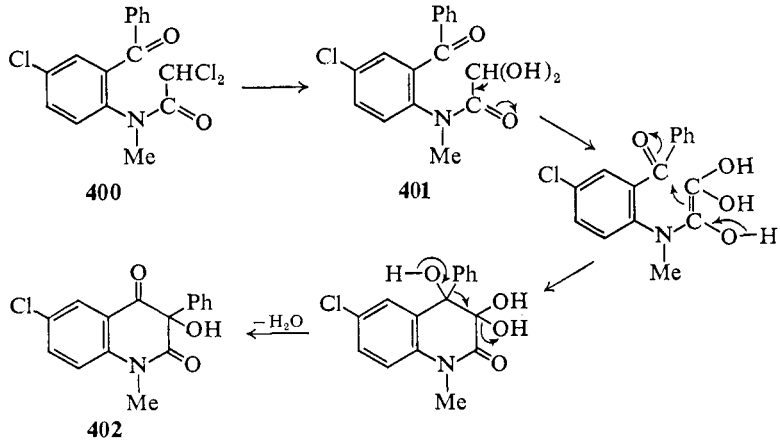


399

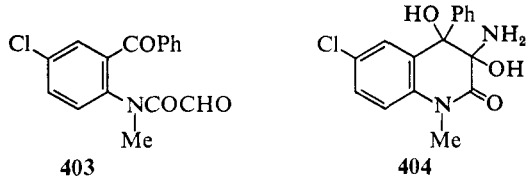
Podesva, Solomon, and Vagi[1051] investigated the hydrolysis of the dichloroacetanilide (**400**) in the hope of preparing the glyoxalamido derivative (**403**). However, in the presence of base, cyclization to give 6-chloro-1,2,3,4-tetrahydro-3-hydroxy-1-methyl-2,4-dioxo-3-phenylquinoline (**402**) is observed. A rather complicated reaction

mechanism involving initial formation of the *gem*-dihydroxy-compound (**401**), which cyclizes with loss of water and simultaneous phenyl migration (Scheme 33), is

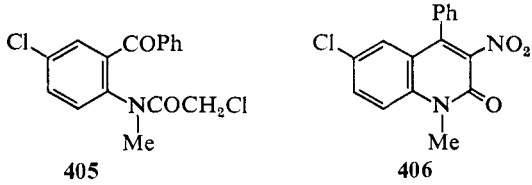


SCHEME 33

put forward by the authors to explain the formation of dioxo-compound (**402**). If allowed to stand overnight at room temperature in a mixture of concentrated ammonia solution and dimethylformamide, the dichloro-compound (**400**) forms the aminodihydroxy-compound (**404**) in 65.9% yield.[1052]

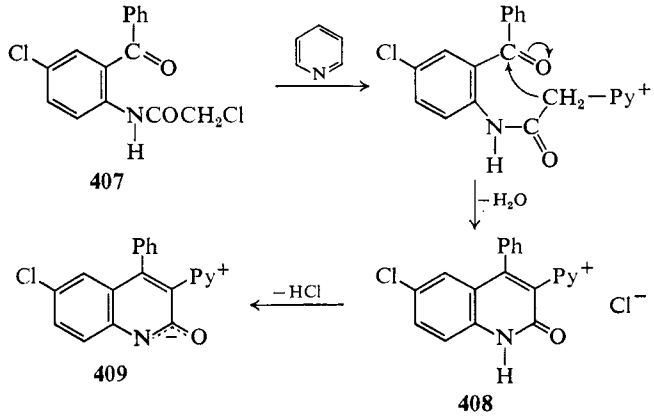


The monochloroacetanilide (**405**) on treatment with sodium nitrite in aqueous ethanol cyclizes to give the 3-nitro-2-quinolone (**406**) in 47.7% yield.[1052]



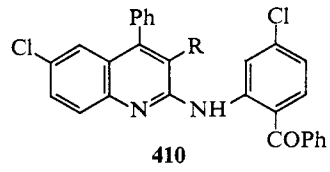
In a similar manner the chloroacetanilide (**407**) cyclizes in hot pyridine to the chloro-3-pyridinio-2-quinolone (**408**) (Scheme 34) which is isolated in 92% yield as the betaine (**409**).[1053]

Ishiwaka and his co-workers,[1054] following earlier work of Drukker and Judd,[1043] have shown that *o*-aminobenzophenones react with aliphatic acids in the presence of polyphosphoric acid to give 2-(*o*-benzoylanilino)-4-phenylquinolines



SCHEME 34

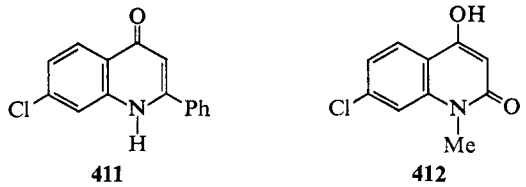
(**410**). For example, 2-amino-4-chlorobenzophenone in a mixture of acetic acid and polyphosphoric acid at 145 °C yields the chloro-2-anilinoquinoline (**410**; R = H) (89%); in the presence of propanoic acid or butanoic acid the 3-methyl and the 3-ethyl derivative (**410**; R = Me or Et, respectively) are produced. An interesting



410

variation involves the use of bromoacetic acid in which case the 3-bromo-derivative (**410**; R = Br) is obtained in 82% yield. The authors discuss the mechanism of the reaction in some detail and suggest that, as a first step, the amine undergoes acylation by the carboxylic acid, whereafter reaction with the 2-aminobenzophenone yields the product (**410**).

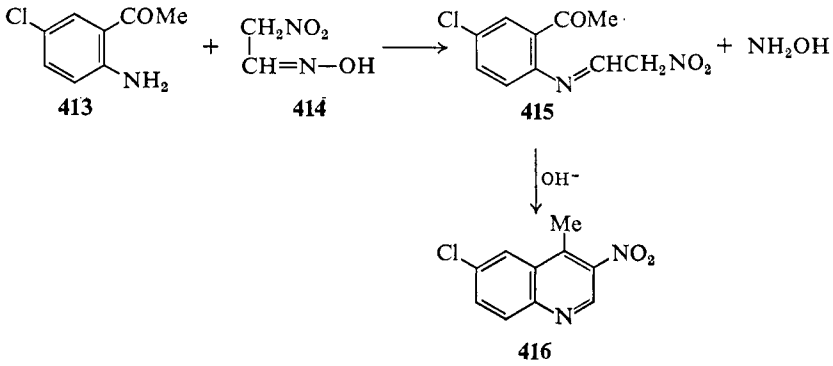
Fuson and Burness[1055] have shown that anthranilic acid or, better, its ethyl ester with acetophenone diethyl acetal in hot diphenyl ether yields 2-phenyl-4-quinolone. Applications of the reaction to ethyl 2-amino-4-chlorobenzoate leads to the formation of 7-chloro-2-phenyl-4-quinolone (**411**) (74%). Replacement of the ester by the acid leads to a drop in yield (to 48%), but in neither case is any 5-chloro-isomer



411 **412**

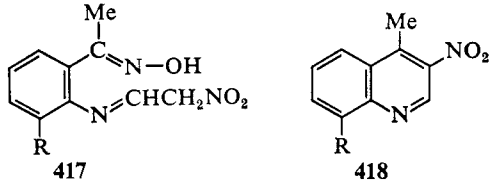
formed. The reaction fails with 2-amino-3,5-dibromobenzoic acid. 4-Chloro-2-(methylamino)benzoic acid cyclizes in boiling acetic anhydride to 7-chloro-4-hydroxy-1-methyl-2-quinolone (**412**).[565]

Of particular interest is the use of the Friedländer synthesis for the preparation of 3-nitroquinolines of which several bearing a halogen substituent have been reported.[1056-1058] Condensation of a 2-aminoacetophenone, e.g. (**413**), with methazonic acid (**414**) yields the 2-(2-nitroethylideneamino)acetophenone (**415**), which in



413 **414** **415** **416**

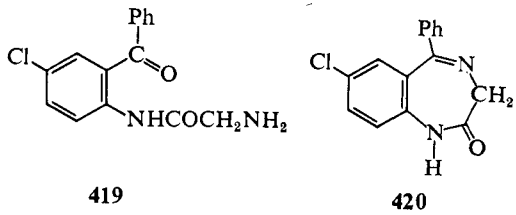
dilute alkali cyclizes to 6-chloro-4-methyl-3-nitroquinoline (**416**) in 86% yield.[1057] Schofield and Theobald,[1057] however, have found that 2-amino-3-chloro-, -3-bromo-, and -3-iodo-acetophenone react with methazonic acid to give, not the nitroquinoline, but products for which structures (**417**; R = Cl, Br, and I, respectively) have been



417 **418**

suggested. These oximes resolidify above their melting points to yield products identical with those obtained by base-catalysed cyclization of anils of type (**415**), i.e. the 8-halo-3-nitroquinolines (**418**; R = Cl, Br, or I).

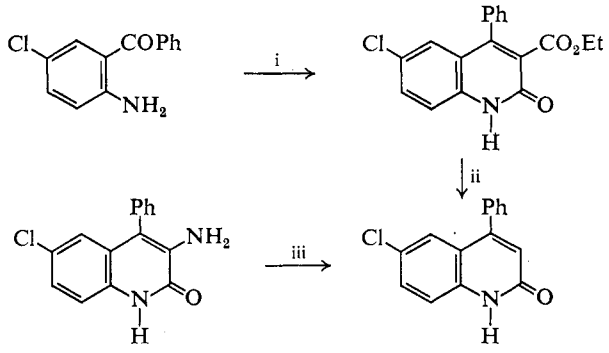
2-Amino-5-chlorobenzophenone condenses with glycine acid chloride hydrochloride ($NH_2CH_2COCl.HCl$) to give the aminoacylamide (**419**), which on being



419 **420**

heated cyclizes to yield mainly the diazepinone (**420**) together with 3-amino-6-chloro-4-phenyl-2-quinolone (**421**) (15%).[1059] The structure of the 2-quinolone was confirmed by unambiguous synthesis of the deaminated product (**422**) as outlined in Scheme 35.

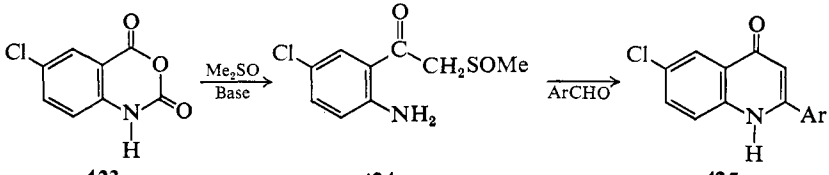
In the presence of base, dimethyl sulphoxide reacts with either 2-amino-5-chloroacetophenone or 6-chloroisatoic anhydride (**423**), to give the methyl phenacyl



421 422

i, $CH_2(CO_2Et)_2$, 160 °C, 1h. ii, NaOEt–EtOH, then Ph_2–Ph_2O. iii, $NaNO_2$–H_2SO_4–EtOH.

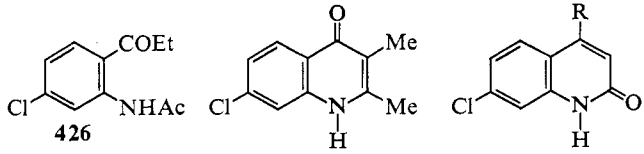
SCHEME 35



423 424 425

sulphoxide (**424**), which with aldehydes undergoes ring closure to the 2-aryl-4-quinolones (**425**).[1060]

A Camps reaction on 2-acetamido-4-chloropropiophenone (**426**) yields a mixture of 7-chloro-2,3-dimethyl-4-quinolone (**427**), 7-chloro-4-ethyl-2-quinolone (**428**; R = Et), and 2-acetamido-4-chlorobenzoic acid.[990] 2-Acetamido-4-chloroacetophenone yields a mixture of 7-chloro-2-methyl-4-quinolone, the acetylated chloroanthranilic acid, and 7-chloro-4-methyl-2-quinolone (**428**; R = Me). In each case the 2-quinolone is the major product.



426 427 428

TABLE 26. Haloquinolines by Cyclization of *o*-Aminocarbonyl Compounds

Haloquinoline*	M.p. (°C)	Yield (%)	References
BROMO-			
2-(*o*-Benzoylanilino)-3-bromo-4-phenyl-	211	71	1054
2-(2-Benzoyl-5-chloroanilino)-3-bromo-6-chloro-4-phenyl-	228	82	1054
2-(2-Benzoyl-5-methylanilino)-3-bromo-6-methyl-4-phenyl-	217	72	1054

* See footnote to Table 1, p. 340.

TABLE 26 (*cont.*)

Haloquinoline*	M.p. (°C)	Yield (%)	References
6-Bromo-4-methyl-3-(*o*-nitrophenyl)-2-carboxylic acid	197 d		1049
6-Bromo-4-hydroxy-2-quinolone	>340	94	2066
6-Bromo-3-nitro-4-quinolone	>300		1056
8-Bromo-4-hydroxy-2-quinolone	271	100	2066
8-Bromo-4-methyl-3-nitro-	201		1057
6-CHLORO-			
3-Acetyl-6-chloro-2-methyl-4-phenyl-	155		1048
3-Amino-6-chloro-1,2,3,4-tetrahydro-3,4-dihydroxy-1-methyl-2-oxo-4-phenyl-	174	66	1052
3-Amino-6-chloro-4-phenyl-2-quinolone	241	15	1059
2-(*p*-Aminophenyl)-6-chloro-4-phenyl-	185		1047
2-(2-Benzoyl-5-chloroanilino)-6-chloro-3-ethyl-4-phenyl-	230	92	1054
2-(2-Benzoyl-5-chloroanilino)-6-chloro-3-methyl-4-phenyl-	224	94	1043, 1054
2-(2-Benzoyl-5-chloroanilino)-6-chloro-4-phenyl-	190	89	1043, 1054
3-Benzyl-6-chloro-2-methyl-4-phenyl-	131		1048
2-(*p*-Bromophenyl)-6-chloro-4-phenyl-	175		1047
3-(*n*-Butyl)-6-chloro-2-methyl-4-phenyl-	79		1048
6-Chloro-2-(*p*-chlorophenyl)-4-phenyl-	160		1047
6-Chloro-2-(3,4-dimethoxyphenyl)-4-phenyl-	159		1047
6-Chloro-2,3-dimethyl-4-phenyl-	118		1048
6-Chloro-1,2,3,4-tetrahydro-3-hydroxy-1-methyl-2,4-dioxo-3-phenyl-	172	41.5	1051
6-Chloro-1,2,3,4-tetrahydro-3-hydroxy-2,4-dioxo-3-phenyl-	245	26	1051
6-Chloro-2,4-diphenyl-	131		1047
6-Chloro-2-methyl-3,4-diphenyl-	197		1048
6-Chloro-2-ethyl-4-phenyl-	71		1048
6-Chloro-3-ethyl-2-methyl-4-phenyl-	140		1048
6-Chloro-2-(3-hydroxy-4-methoxyphenyl)-4-quinolone	345	49	1060
6-Chloro-3-(isobutyl)-2-methyl-4-phenyl-	112		1048
6-Chloro-4-hydroxy-1-methyl-2-quinolone	318	37	2066
6-Chloro-1-ethyl-4-hydroxy-2-quinolone	308	39	2066
6-Chloro-2-isobutyl-4-phenyl-	66		1048
6-Chloro-2-isopentyl-4-phenyl-	Liq.		1048
6-Chloro-2-(*p*-methoxybenzyl)-4-phenyl-	97		1048
6-Chloro-2-(*o*-methoxyphenyl)-4-phenyl-	157		1047
6-Chloro-3-(*p*-methoxyphenyl)-2-methyl-4-phenyl-	177		1048
6-Chloro-2-(*p*-methoxyphenyl)-4-phenyl-	136		1047
6-Chloro-1-methyl-3-nitro-4-phenyl-2-quinolone	210	48	1052
6-Chloro-2-methyl-4-phenyl-	90		1048
Et 6-chloro-2-methyl-4-phenyl-3-carboxylate	102		1048
6-Chloro-4-methyl-3-nitro-	150	86	1057
6-Chloro-4-methyl-2-quinolone			1044
6-Chloro-2-(*p*-tolyl)-4-phenyl-	133		1047
6-Chloro-2-(2-methyl-5-pyridyl)-4-phenyl-	171		1047
6-Chloro-2-(1-naphthyl)-4-phenyl-	124		1047

TABLE 26 (*cont.*)

Haloquinoline*	M.p. (°C)	Yield (%)	References
6-Chloro-2-(2-naphthyl)-4-phenyl-	155		1047
6-Chloro-3-nitro-4-phenyl-	163		1058
6-Chloro-2-(*n*-pentyl)-4-phenyl-	Liq.		1048
Et_2 6-chloro-4-phenyl-2,3-dicarboxylate	163	78	1050
Et 6-chloro-4-phenyl-2-quinolone-3-carboxylate	235	58	1059
6-Chloro-2-phenethyl-4-phenyl-	72		1048
6-Chloro-4-phenyl-3-pyridinio-2-quinolone chloride	375	90	1053
6-Chloro-4-phenyl-2-(2-pyridyl)-	180		1047
6-Chloro-4-phenyl-2-(3-pyridyl)-	195		1047
6-Chloro-4-phenyl-2-(4-pyridyl)-	187		1047
6-Chloro-4-phenyl-2-quinolone	261		1043, 1054
6-Chloro-4-phenyl-2-(*n*-propyl)-	98		1048
6-Chloro-2-(3,4,5-trimethoxyphenyl)-4-phenyl-	193		1047
6-Chloro-2-(4-pyridyl)-4-quinolone	345	47	1060
7-CHLORO-			
7-Chloro-4-quinolone	274		990
7-Chloro-2,3-dimethyl-4-quinolone	340		594
7-Chloro-4-ethyl-2-quinolone	262		594
7-Chloro-4-hydroxy-2-quinolone		31	594
7-Chloro-4-hydroxy-1-methyl-2-quinolone	309	37	2066
Et 7-chloro-4-hydroxy-2-quinolone-3-carboxylate			594
7-Chloro-4-hydroxy-1-methyl-2-quinolone	286	43.5	565
7-Chloro-2-methyl-4-quinolone	316		594
7-Chloro-3-methyl-4-quinolone	325		594
7-Chloro-4-methyl-2-quinolone	280		594
7-Chloro-4-methyl-3-nitro-	138	60	1057
7-Chloro-2-phenyl-4-quinolone	362	74	1055
8-CHLORO-			
8-Chloro-4-hydroxy-2-quinolone	305	100	2066
8-Chloro-4-methyl-3-nitro-	219		1057
POLYHALO-			
6,8-Dibromo-4-phenyl-2-quinolone	211	37	1042
5,8-Dichloro-2-methyl-	46		1061
5,6,7,8-Tetrafluoro-4-hydroxy-2-quinolone		30	1039

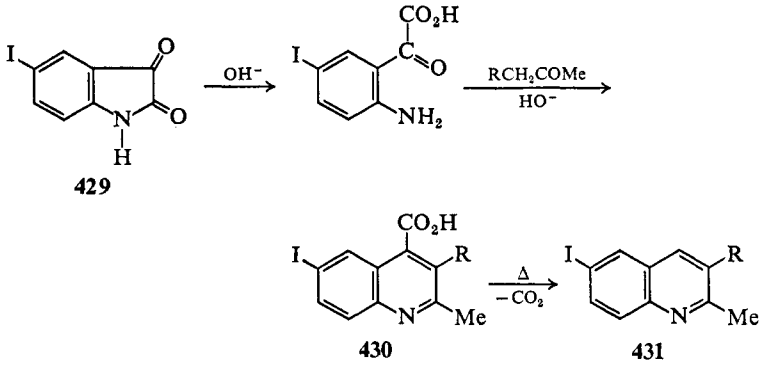
O. Haloquinolines by the Pfitzinger Reaction †

The lack of readily available *o*-aminoaryl aldehydes and ketones led to the development of the Pfitzinger variation of the Friedländer quinoline synthesis. Isatins in the presence of base readily undergo ring opening to give *o*-amino-α-keto-acids which, in the presence of a compound containing a reactive methylene group, undergo a Friedländer-type condensation and cyclization to yield quinoline-4-carboxylic acids as outlined in Scheme 36.

* See footnote to Table 1, p. 340.

† See also Addenda, p. 682.

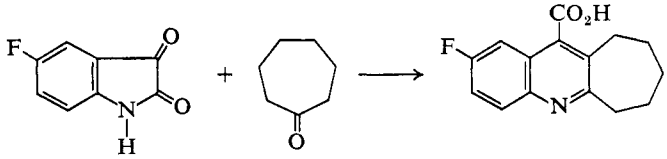
Halogenated isatins are readily available from the halo-arylamine by the Staudinger reaction (arylamine, chloral hydrate, and hydroxylamine) and many haloquinoline-4-carboxylic acids have been reported. The reaction is particularly useful since quinoline-4-carboxylic acids undergo decarboxylation at or above their melting points, and hence haloquinolines are accessible by this route.



SCHEME 36

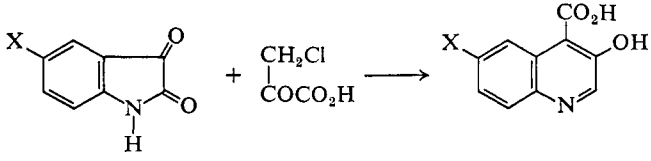
As an example, 5-iodoisatin (**429**) reacts with acetone in ethanolic potassium hydroxide solution to yield 6-iodo-2-methylquinoline-4-carboxylic acid (**430**; R = H), which at 300 °C is decarboxylated to 6-iodo-2-methylquinoline (**431**; R = H).[379] Many examples of this type are known (see Table 27, p. 491). 5-Bromoisatin has been used, especially by Buu-Hoï and his co-workers,[1062-1065] for the synthesis of a multitude of 2- and 3-substituted 6-bromoquinoline-4-carboxylic acids, and they have discussed[1066, 1067] in some detail the application of the Pfitzinger reaction to the synthesis of quinoline-4-carboxylic acids.

Alicyclic ketones react to give quinolines which have a 2,3-bridging polymethylene chain, as illustrated for cycloheptanone, in Scheme 37, and several similar examples have been reported[1068, 1070] (see Table 27, p. 491).

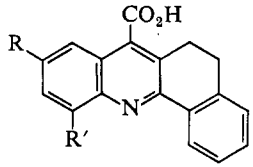


SCHEME 37

Attempts to prepare 3,6-dihaloquinolines by treating 5-haloisatins with 3-chloro- or 3-bromo-pyruvic acid failed.[1071] 6-Halo-3-hydroxyquinoline-4-carboxylic acids, rather than the expected 3,6-dihalo-derivatives, are obtained, indicating that hydrolysis of the halopyruvic acid is occurring at some stage in the reaction.



A similar replacement of halogen by hydroxide has been documented by Al-tai and his co-workers[1072] who found that 5-bromoisatin with α-tetralone in the presence of 33% ethanolic potassium hydroxide gives not the expected 6-bromoquinoline-4-carboxylic acid derivate (**432**; R = Br, R′ = H), but the 6-hydroxy-compound (**432**; R = OH, R′ = H); at 110 °C with the same reagents 5,7-dibromoisatin yields the 6,8-dihydroxy-compound (**432**; R = R′ = OH).



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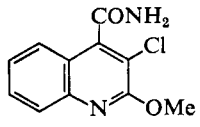
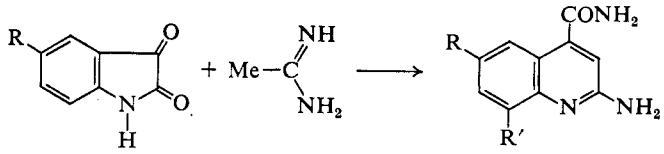


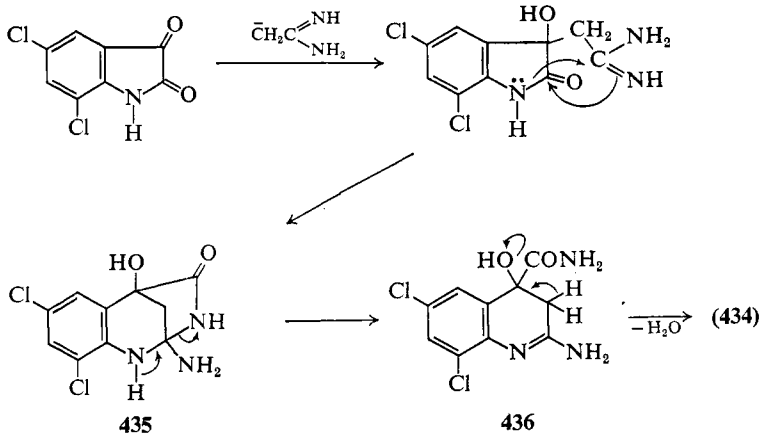
433

Of interest is a variation on the Pfitzinger reaction by which 2-methoxy- and 2-amino-quinoline-4-carboxyamides may be synthesized.[1073] For example, the methyl α-chloro-acetimidic ester $ClCH_2C(OMe)=NH$ reacts with isatin to yield 3-chloro-2-methoxyquinoline-4-carboxamide (**433**). If a substituted amidine is employed in the reaction, then a 2-aminoquinoline-4-carboxamide, e.g. (**434**; R = Cl, R′ = H), is formed.



434

The mechanism of these reactions is discussed by the authors (Ried and Kohlhaas) and is somewhat different from that accepted for the Pfitzinger reaction. It is proposed that initial attack by the carbanion $\bar{C}H_2C(NH_2)=NH$ (derived from the amidine) at the ketonic-carbonyl centre of the isatin is followed by formation of the



435 **436**

SCHEME 38

tricyclic system (**435**) (as indicated in Scheme 38) which, under the reaction conditions, undergoes ring cleavage (**435** → **436**) with loss of water to yield product (**434**; R = R′ = Cl).

The haloquinoline-4-carboxamides that have been prepared by this method are listed in Table 27a (p. 500). A comprehensive list of haloquinoline-4-carboxylic acids prepared by Pfitzinger reaction is given in Table 27, and where the information is available the melting points of the decarboxylation products, i.e. the haloquinolines, are also tabulated.

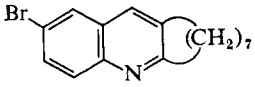
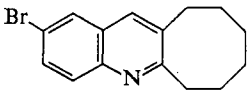
TABLE 27. Haloquinoline-4-carboxylic Acids by Pfitzinger Reaction, and their Decarboxylation Products

Haloquinoline-4-carboxylic acid	M.p. (°C)	Decarboxyln. product; m.p. (°C)	References
6-BROMO-			
2-(5-Acenaphthyl)-6-bromo-3-methyl-	>310		1067
2-(2-Benzo[*b*]furanyl)-6-bromo-3-methyl-	140	140	1109
2-(4-Biphenylyl)-6-bromo-	306	222	1067
2-(4-Biphenylyl)-6-bromo-3-ethyl-	292	172	1067
2-(4-Biphenylyl)-6-bromo-3-methyl-	317	196	1067
6-Bromo-2-(*p*-bromophenyl)-	259	188	1067
6-Bromo-2-(*p*-bromophenyl)-3-carboxymethyl-	>307		1067
6-Bromo-2-(*p*-bromophenyl)-3-ethyl-	>310	110	1067
6-Bromo-2-(*p*-bromophenyl)-3-methyl-	325	190	1067
6-Bromo-2-(*p*-bromophenyl)-3-phenyl-	>310	172	1067
6-Bromo-2-(2-bromo-4-chlorophenyl)-	260	178	1104
6-Bromo-2-(2-bromo-5-chlorophenyl)-	239	163	1104
6-Bromo-2-(5-bromo-6-methoxy-2-naphthyl)-	296		1077
6-Bromo-2-(5-bromo-2-thienyl)-	248	176	1067
6-Bromo-2-(5-bromo-2-thienyl)-3-ethyl-	261		1067
6-Bromo-2-(5-bromo-2-thienyl)-3-methyl-	285	148	1067
6-Bromo-2-(5-bromo-2-thienyl)-3-phenyl-	275		1067
6-Bromo-2-[*p*-(*n*-butoxyphenyl)]-3-methyl-	300	133	1110
6-Bromo-2-[*p*-(*tert*-butyl)phenyl]-3-methyl-	>311	132	1067
6-Bromo-5-chloro-2-styryl-	279		1076
6-Bromo-2-(*p*-chlorophenyl)-	271	177	1067
6-Bromo-2-(*p*-chlorophenyl)-3-methyl-	307	160	1067
6-Bromo-2-(*p*-chlorophenyl)-3-phenyl-	>328	161	1067
6-Bromo-2-(3-chloro-4-ethoxyphenyl)-	235		1095
6-Bromo-2-(3-chloro-4-methoxyphenyl)-	287	169	1095
6-Bromo-2-(3-chloro-4-methoxyphenyl)-3-methyl-	>320		1106
6-Bromo-2-(2-chloro-4-methylphenyl)-3-phenyl-	312		1087
6-Bromo-2-[3-chloro-4-(methylthio)phenyl]-	254	145	1085
6-Bromo-2-[3-chloro-4-(methylthio)phenyl]-3-methyl-	>320	182	1085
6-Bromo-2-(5-chloro-2-thienyl)-	271		1067
6-Bromo-2-(5-chloro-2-thienyl)-3-ethyl-	282		1067
6-Bromo-2-(5-chloro-2-thienyl)-3-methyl-	279		1067
6-Bromo-2-cyclopropyl-	270		1067
6-Bromo-2-(3,4-dichlorophenyl)-	252		1067
6-Bromo-2-(2,4-dimethoxyphenyl-3-phenyl-	298	89	1067
6-Bromo-2-(3,4-dimethoxyphenyl)-3-ethyl-	240		1067

TABLE 27 (*cont.*)

Haloquinoline-4-carboxylic acid	M.p. (°C)	Decarboxyln. product; m.p. (°C)	References
6-Bromo-2,3-di-(*p*-methoxyphenyl)-	317		1106
6-Bromo-2,3-dimethyl-	291	82	1066
6-Bromo-2-(2,4-dimethylphenyl)-	235	98	1067
6-Bromo-2-(2,4-dimethylphenyl)-3-methyl	> 321	122	1067
6-Bromo-2-(2,5-dimethylphenyl)-	239	124	1067
6-Bromo-2-(2,5-dimethylphenyl)-3-methyl	345	109	1067
6-Bromo-2-(3,4-dimethylphenyl)-	227	135	1067
6-Bromo-2-(2,5-dimethyl-3-thienyl)-	235		1067
6-Bromo-2-[β-(*p*-dimethylaminostyryl)]-	265		1076
6-Bromo-2-(4-ethoxy-3-methylphenyl)-	263	175	1062
6-Bromo-3-ethyl-2-(*p*-fluorophenyl)-	> 300	121	1063
6-Bromo-3-ethyl-2-(3-fluoro-4-methoxyphenyl)-	296	125	1064
6-Bromo-3-ethyl-2-(*n*-hexyl)-	163		1067
6-Bromo-3-ethyl-2-(*p*-isopropylphenyl)-	276	93	1067
6-Bromo-3-ethyl-2-(6-methoxy-2-naphthyl)-	302	185	1065
6-Bromo-3-ethyl-2-(3-pyrenyl)-	> 310		1067
6-Bromo-3-ethyl-2-(2-tetralyl)-	310	97	1067
6-Bromo-3-ethyl-2-[*m*-(trifluoromethyl)-phenyl]-	280	56	1105
6-Bromo-2-(*p*-ethylphenyl)-3-methyl-	301	115	1067
6-Bromo-2-(5-ethyl-2-thienyl)-	238	107	1098
6-Bromo-2-(5-ethyl-2-thienyl)-3-methyl-	239	80	1098
6-Bromo-2-(*p*-fluorophenyl)-	265	152	1063
6-Bromo-2-(*p*-fluorophenyl)-3-methyl-	> 315	105	1063
6-Bromo-2-(*p*-fluorophenyl)-3-phenyl-	> 310		1063
6-Bromo-2-(3-fluoro-4-hydroxyphenyl)-3-phenyl-	> 330		1106
6-Bromo-2-(5-fluoro-2-hydroxyphenyl)-3-phenyl-			1106
6-Bromo-2-(3-fluoro-4-methoxyphenyl)-	> 355	186	1064
6-Bromo-2-(3-fluoro-4-methoxyphenyl)-3-methyl-	315	136	1064
6-Bromo-2-(2-fluoro-5-methylphenyl)-	246	72	1084
6-Bromo-2-(2-fluoro-5-methylphenyl)-3-methyl-	279	132	1084
6-Bromo-2-(2-fluoro-5-methylphenyl)-3-phenyl-	> 320	154	1084
6-Bromo-2-(4-fluoro-2-methylphenyl)-	240	118	1084
6-Bromo-2-(4-fluoro-2-methylphenyl)-3-methyl-	310	130	1084
6-Bromo-2-(4-fluoro-2-methylphenyl)-3-phenyl-	318	136	1084
6-Bromo-2-(4-fluoro-1-naphthyl)-	> 310		1086
6-Bromo-2-(4-fluoro-1-naphthyl)-3-methyl-	293		1086
6-Bromo-2-[(*o*-fluorophenylthio)methyl]-	288	85	1096
6-Bromo-2-[(*m*-fluorophenylthio)methyl]-	280	79	1096
6-Bromo-2-[(*p*-fluorophenylthio)methyl]-	300	99	1096
6-Bromo-2-[2-fluoro-4(methylthio)phenyl]-	240		1096
6-Bromo-2-[3-fluoro-4-(methylthio)phenyl]-	250		1096
6-Bromo-2-[5-fluoro-2-(methylthio)phenyl]-	181		1096

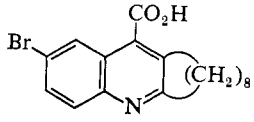
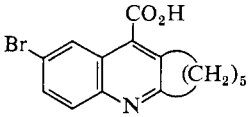
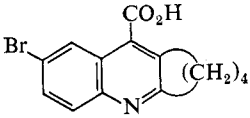
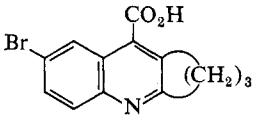
TABLE 27 (*cont.*)

Haloquinoline-4-carboxylic acid	M.p. (°C)	Decarboxyln. product; m.p. (°C)	References
	289		1070
6-Bromo-2-(*n*-heptyl)-	155	(150)[a]	1070
6-Bromo-2-[*p*-(*n*-hexadecyloxy)phenyl]-3-methyl-	237	50	1065
	318		1097
6-Bromo-2-(*n*-hexyl)-	153	(154)[a]	1066
6-Bromo-3-hydroxy-	234	238	1071
6-Bromo-2-(*m*-hydroxyphenyl)-	325		1106
6-Bromo-2-(*p*-hydroxyphenyl)-	320		1106
6-Bromo-2-(*p*-hydroxyphenyl)-3-methyl-		225	1089
6-Bromo-2-(*p*-hydroxyphenyl)-3-phenyl-		237	1089
6-Bromo-2-(3-carboxy-4-hydroxyphenyl)-	273 d		1101
6-Bromo-2-(*p*-iodophenyl)-	288		1102
6-Bromo-2-(4-iodo-2-methylphenyl)-	266		1103
6-Bromo-2-isobutyl-	189	46	1066[b]
6-Bromo-2-(*p*-isopropylphenyl)-	218	143	1067
6-Bromo-2-(*p*-isopropylphenyl)-3-methyl-	299	130	1067
6-Bromo-2-(*p*-methoxyphenyl)-3-methyl-	308	139	1065
6-Bromo-2-(4-methoxy-2-methylphenyl)-	225	126	1062
6-Bromo-2-(4-methoxy-2-methylphenyl)-3-methyl-	> 322	115	1062
6-Bromo-2-(4-methoxy-2-methylphenyl)-3-phenyl-	> 322		1062
6-Bromo-2-(4-methoxy-3-methylphenyl)-	254	171	1062
6-Bromo-2-(4-methoxy-3-methylphenyl)-3-methyl-	308	172	1062
6-Bromo-2-(4-methoxy-3-methylphenyl)-3-phenyl-	294	135	1062
6-Bromo-2-(6-methoxy-2-naphthyl)-	315	163	1065
6-Bromo-2-(6-methoxy-2-naphthyl)-3-methyl-	313	169	1065
6-Bromo-2-(6-methoxy-2-naphthyl-3-phenyl-	265	160	1065
6-Bromo-2-methyl-	273	100	380, 1066 1097
6-Bromo-3-methyl-2-(4-methyl-1-naphthyl)-	> 307	181	1067
6-Bromo-3-methyl-2-(*n*-pentadecyl)-	189	55	1067
6-Bromo-3-methyl-2-phenyl-	328	129	1067
6-Bromo-3-methyl-2-(3-pyrenyl)-	> 310		1067
6-Bromo-3-methyl-2-styryl-	250		1108
6-Bromo-3-methyl-2-[*p*-(*n*-tetradecyloxy)-phenyl]-	240	(124)[a]	1065
6-Bromo-3-methyl-2-(6-tetralyl)-	316	123	1067

[a] As picrate.

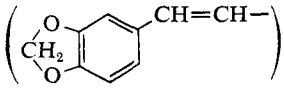
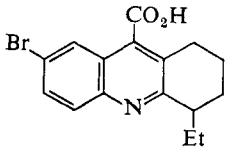
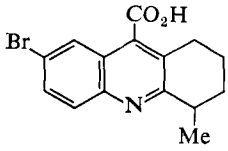
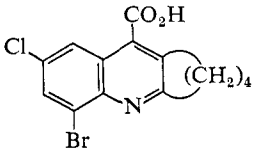
[b] Loss of carbon monoxide to give the halo-4-quinolone is also observed during the decarboxylation of these quinoline-4-carboxylic acids (see Section II.1.P).

TABLE 27 (*cont.*)

Haloquinoline-4-carboxylic acid	M.p. (°C)	Decarboxyln. product; m.p. (°C)	References
6-Bromo-3-methyl-2-(2-thienyl)-	291	90	1067
6-Bromo-3-methyl-2-(*m*-trifluoromethyl)-phenyl-	295	73	1105
6-Bromo-2-(*n*-nonyl)-	150		1066[b]
	320		1070
6-Bromo-2-(*n*-pentyl)-	180		1067
	309	128	1067, 1097
6-Bromo-2-phenyl-	239.5		825
6-Bromo-3-phenyl-2-(*m*-trifluoromethyl)-phenyl-	318	102	1105
6-Bromo-2-(*n*-propyl)-	212		1066[b]
6-Bromo-3-(*n*-propyl)-2-(*m*-trifluoromethyl)-phenyl-	246	42	1105
6-Bromo-2-(3-pyrenyl)-	>310	205	1067
6-Bromo-2-(2-pyridyl)-	258, 326		1097, 1099
6-Bromo-2-(3-pyridyl)-	309		1097, 1099
6-Bromo-2-(4-pyridyl)-	298, 310		1097, 1099
6-Bromo-2-styryl-	287		1076
6-Bromo-2-(6-tetralyl)-	235	133	1067
6-Bromo-2-(2-thienyl)-	250, 272	124	1067, 1078
6-Bromo-2-[(*m*-trifluoromethyl)phenyl]-	230	82	1105
6-Bromo-3-[(*o*-trifluoromethylphenylthio)-methyl]-	274 d	122	1107
	292		1097
	288		1097
6-Bromo-2-(*n*-undecyl)-	152	(137)[a]	1070
6-Bromo-2-carboxylic acid	314 d		380

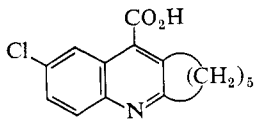
[a,b] See footnotes on p. 493.

TABLE 27 (*cont.*)

Haloquinoline-4-carboxylic acid	M.p. (°C)	Decarboxyln. product; m.p. (°C)	References
6-Bromo-3-(*p*-methoxyphenyl)-2-carboxylic acid	157 d	292[c]	1111
6-Bromo-3-(*p*-tolyl)-2-carboxylic acid	177 d	304[d]	1111
6-Bromo-3-phenyl-2-carboxylic acid	170 d	290[e]	1111
6-Bromo-2-quinolone	220		378
6-Bromo-3-phenyl-2-quinolone			198
6-Bromo-2-[$(CH_2)_2CO_2H$]-3-CH_2CO_2H	196		1112
6-Bromo-2-(PhCH=CH—CH=CH)-	256		1100
6-Bromo-2- 	305		1076
	299	92	1067
	273	(197)[a]	1067
7-BROMO-			
7-Bromo-2-carboxylic acid		250 d[f]	995
8-BROMO-			
8-Bromo-6-chloro-2,3-dimethyl-			1118
8-Bromo-6-chloro-2-methyl-			1118
8-Bromo-6-chloro-2-(β-naphthyl)-			1118
8-Bromo-6-chloro-2-phenyl-			1118
8-Bromo-6-chloro-2-(*n*-propyl)-			1118
			1118
8-Bromo-6-chloro-2-(2-thienyl)-			1118

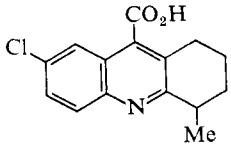
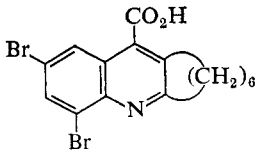
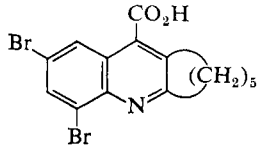
[a] See footnote on p. 493.
[c] 6-Bromo-3-(*p*-methoxyphenyl)quinoline-4-carboxylic acid.
[d] 6-Bromo-3-(*p*-tolyl)quinoline-4-carboxylic acid.
[e] 6-Bromo-3-phenylquinoline-4-carboxylic acid.
[f] 7-Bromoquinoline-4-carboxylic acid.

TABLE 27 (*cont.*)

Haloquinoline-4-carboxylic acid	M.p. (°C)	Decarboxyln. product; m.p. (°C)	References
5-CHLORO-			
5-Chloro-2-(*p*-chlorophenyl)-	260 d		931
5-Chloro-2-(4-chloro-2-methylphenyl)-	243		931
5-Chloro-2-phenyl-	235 d		931, 1074
5-Chloro-2-carboxylic acid	219	255[g]	1075
5-Chloro-3-phenyl-2-carboxylic acid	190		359
6-CHLORO-			
3-Acetyl-6-chloro-	229.5		1079
6-Chloro-2-(*p*-chlorophenyl)-	275		931
6-Chloro-2-(2-chloro-4-methylphenyl)-3-phenyl-	306 d	149	1087
6-Chloro-2-[3-chloro-4-(methylthio)phenyl]-	215	124	1085
6-Chloro-2-[3-chloro-4-(methylthio)phenyl]-3-methyl-	> 320	135	1085
6-Chloro-2-cyclopropyl-	230, 237	Liq.	1067, 1068
6-Chloro-2-(2,4-dimethylphenyl)-3-phenyl-	325 d		1087
6-Chloro-2-(3-fluoro-4-methoxyphenyl)-3-methyl-	328		1064
6-Chloro-2-(2-fluoro-5-methylphenyl)-	238	73	1084
6-Chloro-2-(2-fluoro-5-methylphenyl)-3-methyl-	300	128	1084
6-Chloro-2-(2-fluoro-5-methylphenyl)-3-phenyl-	312		1084
6-Chloro-2-(4-fluoro-1-naphthyl)-	294	132	1086
6-Chloro-2-(4-fluoro-1-naphthyl)-3-methyl-	295		1086
6-Chloro-2-(2-furyl)-	287		1080
6-Chloro-2-(*n*-hexyl)-	143		1067
6-Chloro-3-hydroxy-	226	255	1071
6-Chloro-2-(*p*-hydroxyphenyl)-3-methyl-		202	1089
6-Chloro-2-methyl-	171.5		380, 1079
6-Chloro-2-(*p*-tolyl)-	271		931, 1067
6-Chloro-2-(*p*-tolyl)-3-phenyl-	313	125	1087
	251	109	1067
6-Chloro-2-phenyl-	246, 282	111	1067, 1083
6-Chloro-2-styryl-	243		1076
6-Chloro-2-(2-thienyl)-	261		1078
6-Chloro-2-carboxylic acid	250 d, 265 d	302[h]	380, 1081, 1082
6-Chloro-8-methoxy-2-carboxylic acid		[i]	1090

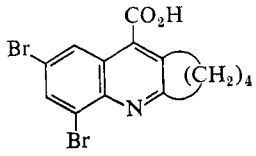
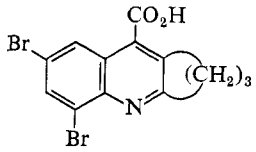
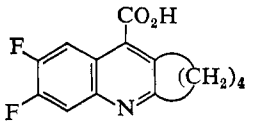
[g] 5-Chloroquinoline-4-carboxylic acid.
[h] 6-Chloroquinoline-4-carboxylic acid.
[i] 6-Chloro-8-methoxyquinoline-4-carboxylic acid.

TABLE 27 (*cont.*)

Haloquinoline-4-carboxylic acid	M.p. (°C)	Decarboxyln. product; m.p. (°C)	References
6-Chloro-3-hydroxy-2-phenyl-8-carboxylic acid	338	345[j]	1088
6-Chloro-2-quinolone	> 315		380
6-Chloro-2-[(5,6,7,8-tetrahydro-2-naphthyl)]-3-phenyl-	292		1087
	225		1067
7-CHLORO-			
3-Acetyl-7-chloro-	235		1079
7-Chloro-2-(4,5,-dichloro-2-methylphenyl)-	294		931
7-Chloro-2-(*p*-fluorophenyl)-	285		931
7-Chloro-2-(*p*-methoxyphenyl)-	225		931
7-Chloro-2-carboxylic acid	290	291[k]	1075, 1082
7-Chloro-3-phenyl-2-carboxylic acid			359
8-CHLORO-			
8-Chloro-2-(*p*-chlorophenyl)-	267		931
8-Chloro-2-phenyl-			1083
8-Chloro-2-carboxylic acid		[l]	380
DIBROMO-			
6,8-Dibromo-2-(2-bromo-1-naphthyl)-	285		1115
6,8-Dibromo-2,3-diphenyl-	250		1116
	267		1097
6,8-Dibromo-2-(*p*-iodophenyl)-	283		1115
6,8-Dibromo-2-methyl-	267 d	100	1097, 1114
	268		1097
6,8-Dibromo-2-(2-pyridyl)-	316		1097

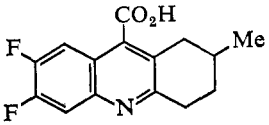
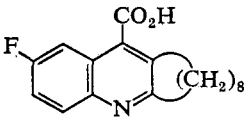
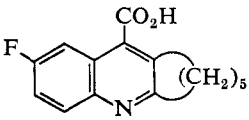
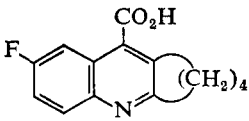
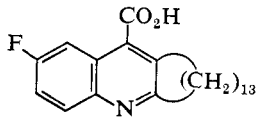
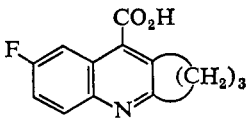
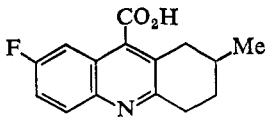
[j] 6-Chloro-3-hydroxy-2-phenylquinoline-8-carboxylic acid.
[k] 7-Chloroquinoline-4-carboxylic acid.
[l] 8-Chloroquinoline-4-carboxylic acid.

TABLE 27 (*cont.*)

Haloquinoline-4-carboxylic acid	M.p. (°C)	Decarboxyln. product; m.p. (°C)	References
6,8-Dibromo-2-(3-pyridyl)-	332		1097
6,8-Dibromo-2-(4-pyridyl)-	326		1097
6,8-Dibromo-2-styryl-	240		1076
	312		1097
	316		1097
6,8-Dibromo-2-carboxylic acid	260		1113
6,8-Dibromo-2-methyl-3-carboxylic acid	207		1113
6,8-Dibromo-2-quinolone	275		338, 378
DICHLORO-			
5,7-Dichloro-2-(5-bromo-6-methoxy-2-naphthyl)-	314		1077
5,8-Dichloro-2-phenyl-	216		931
6,7-Dichloro-2-phenyl-	278		1074
6,8-Dichloro-2-(*p*-chlorophenyl)-	270.5, 279 d		931, 1083
6,8-Dichloro-2-(3-chloro-4-ethoxyphenyl)-	219	152	1095
6,8-Dichloro-2-(3-chloro-4-methoxyphenyl)-	249		1095
6,8-Dichloro-2-(3,4-dichlorophenyl)-	296 d		931
6,8-Dichloro-2,3-dimethyl-	> 305		1066
6,8-Dichloro-2-(*p*-fluorophenyl)-	276		953
6,8-Dichloro-2-(*n*-hexyl)-	145	(141)[a]	1066[b]
6,8-Dichloro-3-hydroxy-	240	283.5	1071
6,8-Dichloro-3-hydroxy-2-methyl-	232 d		1092, 1093
6,8-Dichloro-2-isobutyl-	186		1966[b]
6,8-Dichloro-2-phenyl-	252, 267		931, 1083
6,8-Dichloro-2-(2-pyridyl)-	337		1094
6,8-Dichloro-2-[*m*-(trifluoromethyl)phenyl]-	244		953
6,8-Dichloro-2-carboxylic acid	280.5		380
6,8-Dichloro-2-quinolone	256		87
6,8-Dichloro-3-(phenylthio)-2-quinolone	292 d		1091
FLUORO-			
	336	70	1069

[a,b] See footnotes on p. 493.

TABLE 27 (*cont.*)

Haloquinoline-4-carboxylic acid	M.p. (°C)	Decarboxyln. product; m.p. (°C)	References
	341	80	1069
6-Fluoro-2-(*p*-chlorophenyl)-	248		953
6-Fluoro-2-cyclopropyl-	195		1068
6-Fluoro-2-(*p*-fluorophenyl)-	251	128	1069
6-Fluoro-2-methyl-	246		1069
	> 330	(201)[a]	1068
	300	97	1068
6-Fluoro-2-phenyl-	223	86	1069
	326	71	1069
6-Fluoro-2-(2-thienyl)-	250		1078
	317		1068
	306	88	1069
6-Fluoro-2-quinolone	> 360		1069
	319	88	1069
7-Fuoro-2-(*p*-chlorophenyl)-	228		953
7-Fluoro-2-(*p*-fluorophenyl)-	257		941
7-Fluoro-2-carboxylic acid	242 d	290 d[m]	995

[a] See footnote on p. 493.
[m] 7-Fluoroquinoline-4-carboxylic acid.

TABLE 27 (*cont.*)

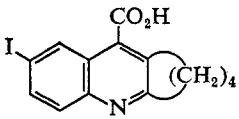
Haloquinoline-4-carboxylic acid	M.p. (°C)	Decarboxyln. product; m.p. (°C)	References
IODO-			
6-Iodo-2-(4-bromonaphthyl)-	278		1102
6-Iodo-2-(*p*-bromophenyl)-	276		1102
6-Iodo-2-cyclohexyl-	227		1117
6-Iodo-3-hydroxy-	241	255	1071
6-Iodo-2-(*p*-iodophenyl)-	> 280		1102
6-Iodo-2-(4-iodo-2-methylphenyl)-	262		1103
6-Iodo-2-methyl-	290	108	379
6-Iodo-2-phenyl-	250, 263	144	379, 937, 1103
6-Iodo-2-styryl-	296		1076
	318		1103
6-Iodo-2-methyl-3-carboxylic acid	237		1113
6-Iodo-2-quinolone	> 300		198, 379
6-Iodo-3-phenyl-2-quinolone	> 300		198
6-Iodo-2-[$(CH_2)_2CO_2$]-3-CH_2CO_2H	204		1112

TABLE 27a. Haloquinoline-4-carboxamides by Reactions of Pfitzinger Type

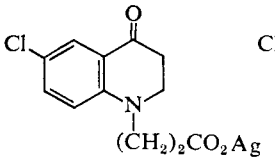
Haloquinoline-4-carboxamide	M.p. (°C)	Yield (%)	References
3-Chloro-4-methoxy-	174	26	1073
2-Amino-7-chloro-3,8-dimethyl-	272	76	1073
2-Amino-7-chloro-8-methyl-3-phenyl-	272	94	1073
7-Chloro-3,8-dimethyl-2-phenyl-	231	81	1073
2-Amino-6,8-dibromo-3-methyl-	330	75	1073
2-Amino-6,8-dibromo-3-phenyl-	292	52	1073
2-Amino-6,8-dichloro-	318 d	57	1073
2-Amino-6,8-dichloro-3-methyl-	318	68	1073
2-Amino-6,8-dichloro-3-phenyl-	289	50	1073
6,8-Dichloro-3-methyl-2-phenyl-	287	65	1073

P. Haloquinolines by Decarboxylation of Haloquinolinecarboxylic Acids

As pointed out in two previous Sections, haloquinolinecarboxylic acids are readily available by both the Conrad–Limpach and the Pfitzinger reaction. When heated, these acids readily undergo decarboxylation and particularly if the carboxylic acid function is at the 2- or the 4-position. Normally the decarboxylation is carried out by heating the acid above its melting point alone or, as is more usual, in an inert solvent. Many solvents have been employed, the common ones being "Dowtherm",[966, 1082] diphenyl ether,[969] nitrobenzene,[359, 1071, 1075, 1081] 1-chloronaphthalene,[959] and paraffin oil.[464, 494, 691, 967, 1018] Originally mineral oil was the

decarboxylation medium of choice,[464] but this has now been discarded in both laboratory and industrial processes on account of its tendency to carbonise at high temperature.[439] For example, in the preparation of the "Chloroquine" precursor, 4,7-dichloroquinoline, decarboxylation of 7-chloro-4-quinolone-2-carboxylic acid is carried out in "Dowtherm" rather than mineral oil. "Dowtherm" is reported[960] to give both superior yields and cleaner decarboxylated material.

Some quinoline-3-carboxylic acids, particularly those having a nitro-group at the 8-position, have proved to be highly resistant towards decarboxylation,[537] and recourse to decomposition of their silver salts has had to be made.[481, 539] In one instance, silver 3-(*N*-quinolyl)propanoate (**437**), thermolysis at 225 °C under reduced pressure results in loss of the alkyl side chain and formation of 6-chloro-4-quinolone (**438**; R = H).[1119]



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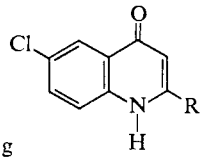

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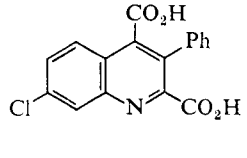

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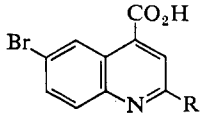
Quinoline-2,4-dicarboxylic acids, if heated, undergo preferential loss of the 2-carboxylic acid group,[380, 1075, 1082, 1111] and several haloquinoline-4-carboxylic acids have been prepared by this selective decarboxylation procedure (see Table 27). Loss of both carboxylic acid groups occurs when 7-chloro-3-phenylquinoline-2,4-dicarboxylic acid (**439**) is heated in paraffin oil at 280 °C, in the presence of copper powder, for 4 hours.[359] 2-Quinolylacetic acids, e.g. (**438**; R = CH_2CO_2H), also undergo thermal decarboxylation and several halo-2-methyl-4-quinolones, e.g. (**438**; R = Me),[1012] have been prepared by this method.

In general, decarboxylation of quinolinecarboxylic acids proceeds with few, if any, unwanted side reactions. Buu-Hoï and Royer,[1066] however, have found that some 2-alkylquinoline-4-carboxylic acids undergo decarbonylation to the 4-quinolone in addition to decarboxylation. For example, 6-bromo-2-isobutylquinoline-4-carboxylic acid (**440**; R = Me_2CHCH_2) on dry distillation yields 6-bromo-2-isobutylquinoline (**442**; R = Me_2CHCH_2) and 6-bromo-2-isobutyl-4-quinolone (**441**; R = Me_2CHCH_2). The 6-bromo-2-(*n*-propyl) compound (**440**; R = $CH_3CH_2CH_2$), however, yields only the 4-quinolone (**441**; R = $CH_3CH_2CH_2$). The reaction is



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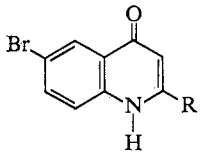

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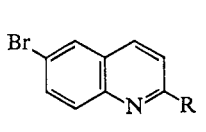

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somewhat unpredictable in that heating 6-bromo-2-(*n*-hexyl)quinoline-4-carboxylic acid [**440**; R = $CH_3(CH_2)_4CH_2$] gives only the quinoline [**442**; R = $CH_3(CH_2)_4CH_2$]. Other examples have also been noted.

Loss of iodine has been recorded during the decarboxylation of 5- and 6-iodo-3-methyl-4-quinolone-3-carboxylic acid.[485, 960]

Instances of the thermal decarboxylation of haloquinoline-3-carboxylic acids,[211, 594, 1017, 1021, 1120] -6-carboxylic acids,[878] and -7-carboxylic acids[164] have also been reported.

A list of haloquinolines prepared by decarboxylation and not included in Table 27 is given in Table 28.

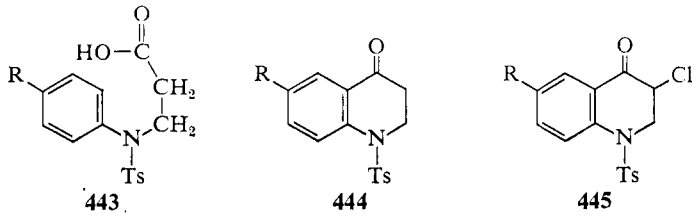
TABLE 28. Haloquinolines by Decarboxylation of Quinolinecarboxylic Acids

Haloquinoline*	M.p. (°C)	Position from which CO_2H is lost	References
3-Bromo-4-quinolone	282	2	121, 122, 1122
3-Bromo-5-chloro-4-quinolone	359	2	122
3-Bromo-7-chloro-4-quinolone	354	2	122
4-Bromo-8-methoxy-	87	2	304
5-Bromo-8-hydroxy-	124	7	164
5-Bromo-8-methoxy-	88	2	169
6-Bromo-4-methyl-2-(*o*-nitrophenyl)-	151	2	1049
6-Bromo-2-methyl-4-quinolone	336	2-CH_2CO_2H	1012
7-Bromo-2-methyl-4-quinolone	309	2-CH_2CO_2H	1012
8-Bromo-2-methyl-4-quinolone	206	2 CH_2CO_2H	1012
3-Chloro-	Liq.	4	1121
3-Chloro-4-quinolone	268	2	122
5-Chloro-3-phenyl-	113	2 and 4	359
5-Chloro-3-iodo-4-quinolone	316	2	122
6-Chloro-4-phenyl-2-quinolone	262	3	1059
6-Chloro-4-quinolone	262	1-$(CH)_2CO_2Ag$	1119
6-Chloro-2-methyl-4-quinolone	320	2-CH_2CO_2H	1012
6-Chloro-2-phenyl-4-quinolone	351	3	1021
7-Chloro-	30	2	942
7-Chloro-3-phenyl-4-carboxylic acid	288.5	2	359
7-Chloro-4-hydroxy-2-quinolone	433	3	595
7-Chloro-4-quinolone	351	3	1120
7-Chloro-3-iodo-4-quinolone	358	2	122
7-Chloro-2-methyl-4-quinolone	315	2-CH_2CO_2H	1012
8-Chloro-		6	878
8-Chloro-2-methyl-4-quinolone	230	2-CH_2CO_2H	1012
8-Chloro-2-phenyl-, hydrochloride	242	4	938
3,5-Dichloro-4-quinolone	380	2	122
3,7-Dichloro-4-quinolone	386	2	122
4,7-Dichloro-	85	2	1123
3-Iodo-4-quinolone	302	2	122

* See footnote to Table 1, p. 340.

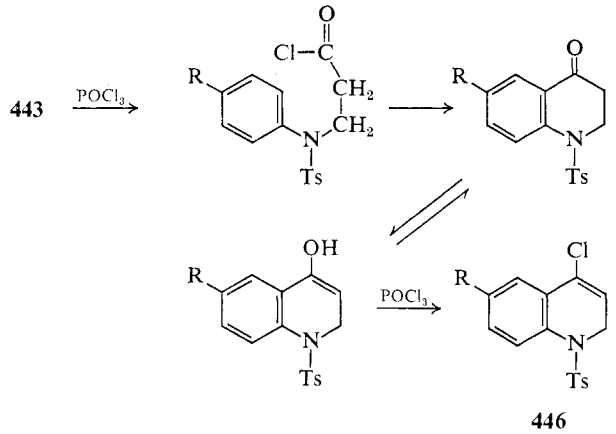
Q. Haloquinolines by Cyclization of 3-Anilinopropanoic Acids, and Related Cyclizations

The original work on the ring closure of 3-anilinopropanoic acids to 1,2,3,4-tetrahydro-4-oxoquinolines was carried out by Clemo and Perkin. They reported[1124] that the 1-tosyl derivative (**443**; R = H) with phosphorus pentoxide in boiling xylene cyclized to give the 4-quinolone (**444**; R = H), whereas with phosphorus oxychloride a chloro-derivative was obtained which they thought to be the 3-chloro-4-quinolone (**445**; R = H).



443 444 445

Further investigations showed[1125] that the *p*-toluidine compound (**443**; R = Me) behaved similarly, whereas the *p*-methoxy- and *p*-ethoxy-derivatives (**443**; R = MeO and EtO, respectively) with phosphorus oxychloride yielded a mixture of the respective 4-quinolones (**444**) and their 3-chloro-derivatives (**445**; R = MeO and EtO). The former appeared to be the major products. Clemo and Perkin found difficulty in explaining satisfactorily the formation of the 3-chloro-compounds, and some eight years later Backeberg[1126] proposed that the products were in fact 1-tosyl derivatives of 4-chloro-1,2-dihydroquinoline, i.e. (**446**; R = H, Me, MeO, or EtO). This structure is not only to be expected on the basis of the reactions outlined in Scheme 39, but also explains the anomalous reactions of the supposed 3-chloro-4-quinolones, as reported by Clemo and Perkin; for example, the conversion of the



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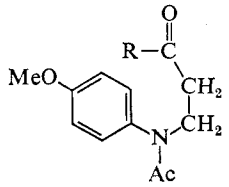
SCHEME 39

chloro-compound (**445**; R = H) into 4-methoxyquinoline on treatment with sodium methoxide.

From the cyclization of the 3-anilinopropanoic acid (**443**; R = H) Backeberg was able to isolate a small quantity of 4-chloroquinoline.[1126]

More recently, Elderfield and his co-workers[1127] have reinvestigated the problem. They find that 3-anilinopropanoic acids fail to cyclize in phosphorus oxychloride unless the secondary amino-group is protected by a tosyl group. They confirmed the formation of the 4-chloro-6-methoxy-compound (**446**; R = MeO) from the (methoxyanilino)propanoic acid (**443**; R = MeO) and showed that the (*N*-acetylanilino)-propanoic acid (**447**; R = OH) cyclizes on successive treatment with phosphorus pentachloride and stannic chloride, probably via the acid chloride (**447**; R = Cl), to an unidentified 1-acetyl-trichloro-1,2-dihydro-6-methoxyquinoline.

In a later paper Elderfield and his co-workers[489] describe the preparation of 1,2,3,4-tetrahydro-2-methyl-4-oxoquinolines by cyclization of 3-(anilino)butanoic acids. Their work-up procedure (vigorous acid hydrolysis to remove the 1-tosyl group) minimizes the chance of isolating any 4-chloro-compound. However, from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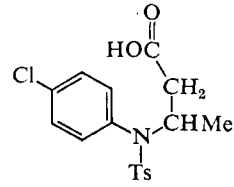
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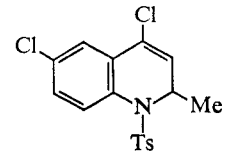
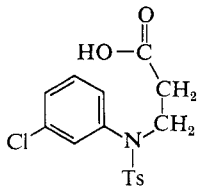

449

one acid (**448**) they report the formation of a small amount of the 4-chloro-derivative (**449**).

Improved yields of 1,2,3,4-tetrahydro-4-oxoquinolines have been obtained by Johnson and his co-workers[1128] who cyclized the acid (**443**; R = MeO) in 95% yield, using stannic chloride in benzene. This method proved unsatisfactory for the cyclization of the *m*-chloroanilinopropanoic acid (**450**). In contrast, in the presence of aluminium chloride, the 7-chloro-tetrahydro-4-oxoquinoline (**451**; R = Ts) is obtained in good yield (63%). No 5-chloro-isomer appears to be formed in this reaction, but the 7-chloro-compound is contaminated with phenyl *p*-tolyl sulphone, which presumably arises by acylation of solvent (benzene) by the *p*-toluenesulphonyl cation formed during the reaction.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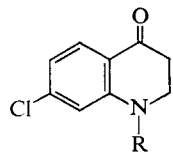
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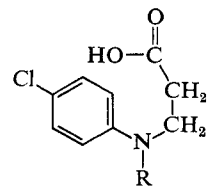
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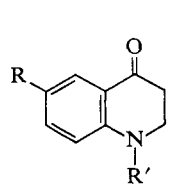
Several other halo-1,2,3,4-tetrahydro-4-oxoquinolines have since been prepared[1129] by similar methods, and polyphosphoric acid has been successfully employed[1130] to bring about the cyclization of 3-(halo-*N*-tosylanilino)propanoic acids to the corresponding halogen-substituted 1,2,3,4-tetrahydro-4-oxo-1-tosylquinolines.

As mentioned above, cyclization of 3-anilinopropanoic acids with phosphorus oxychloride is only successful with the *N*-acylated derivatives. However, various reports have appeared[472, 1131, 1132] indicating that unsubstituted 3-anilinopropanoic acids, e.g. (**452**; R = H) cyclize in polyphosphoric acid to give 4-quinolones. Clark and his co-workers[1133] find that some control of the reaction temperature is necessary in these cyclizations if formation of tarry by-products is to be avoided. The 3-(*p*-fluoroanilino)propanoic acid, as the *N*-tosyl derivative (**443**; R = F), cyclizes with loss of the tosyl group to give 6-fluoro-1,2,3,4-tetrahydro-4-oxoquinoline (**453**; R = F, R′ = H), while all attempts to cyclize 3-(*o*-iodoanilino)propanoic acid (**454**) in either polyphosphoric acid or poly(ethyl phosphate) result in partial loss of iodine and formation of a mixture of 1,2,3,4-tetrahydro-4-oxoquinoline (**453**; R = R′ = H) and its 6-iodo-derivative (**453**; R = I, R′ = H); the authors suggest that the iodoquinolone arises by iodination of the quinolone (**453**; R = R′ = H) by free iodine produced in the reaction.

3-(*p*-Chloro-*N*-phenylanilino)propanoic acid (**452**; R = Ph) is reported[1134] to yield 6-chloro-1,2,3,4-tetrahydro-4-oxo-1-phenylquinoline (**453**; R = Cl, R′ = Ph) when treated with a hot mixture of zinc chloride and acetic anhydride. In a related reaction



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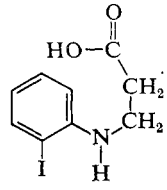

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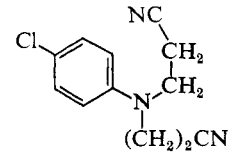
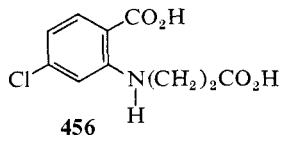


455

the *N*,*N*-di-(2-cyanoethyl) derivative (**455**) of aniline, in a mixture of chlorobenzene, aluminium chloride, and concentrated hydrochloric acid, cyclizes at 155 °C to give 6-chloro-1-(2-cyanoethyl)-1,2,3,4-tetrahydro-4-oxoquinoline (**453**; R = Cl, R′ = CH_2CH_2CN) in 40% yield;[1135] this yield was subsequently raised to 74% by carrying out the cyclization in a large excess (6 mol) of aluminium chloride at 170 °C.[1119]

The chloro-dicarboxylic acid (**456**) in boiling acetic anhydride undergoes cyclization with loss of a carboxyl group to give 1-acetyl-7-chloro-1,2,3,4-tetrahydro-4-oxoquinoline (**451**; R = Ac).[1136]



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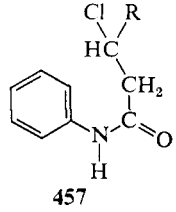

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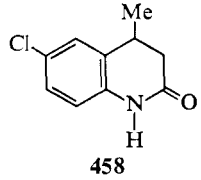

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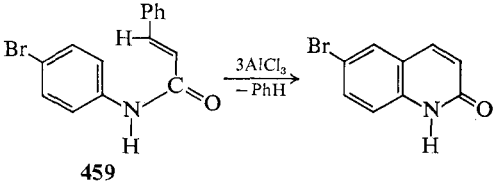
Halotetrahydro-2-oxoquinolines, e.g. (**458**), have been synthesized by cyclizing 3-chloropropanoic and 3-chlorobutanoic acid anilides (**457**; R = H and Me, respectively) in molten aluminium chloride,[249] and also by treating halogen-substituted cinnamanilides, e.g. (**459**), with hot polyphosphoric acid.[1137] Johnston[1138, 1139] has investigated the mechanism of the latter reactions and has shown that cyclization to the 2-quinolone is retarded by substituents *ortho* to the amide function.

Johnston and his co-workers[1140] have also investigated the aluminium chloride-catalysed ring closure of the halogen-substituted cinnamanilides, (**459**). In these



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reactions the aryl group is generally lost so that a 2-quinolone is obtained. The authors discuss the mechanism of the reaction in some detail, particularly the need for an excess of aluminium chloride, and relate it to the aluminium chloride–sodium chloride-induced cyclization of malondianilides[593] discussed in Section II.1.M above.

Quinoline derivatives prepared by the reactions discussed in this Section are listed in Table 29.

TABLE 29. Halo-1,2-dihydro- and -1,2,3,4-tetrahydro-quinolines by Cyclization of 3-Anilinopropanoic Acids and Related Reactions

Halo-hydroquinoline*	M.p. (°C)	Yield (%)	References
BROMO-			
6-Bromo-2-quinolone	269	55	1140
6-Bromo-1,2,3,4-tetrahydro-2-oxo-4-phenyl-	190	83	1137
8-Bromo-1,2,3,4-tetrahydro-2-oxo-4-phenyl-	128	13	1139
8-Bromo-1,2,3,4-tetrahydro-4-oxo-	56	100	1133
CHLORO-			
4-Chloro-1,2-dihydro-1-(*p*-tosyl)-	124		1124, 1126
4-Chloro-6-ethoxy-1,2-dihydro-1-(*p*-tosyl)-			1125, 1126
4-Chloro-1,2-dihydro-6-methoxy-1-(*p*-tosyl)-	244	10	1125, 1126, 1127
4-Chloro-1,2-dihydro-5-methyl-1-(*p*-tosyl)-	100		1125, 1126
4-Chloro-1,2-dihydro-6-methyl-1-(*p*-tosyl)-	177		1125, 1126
4-Chloro-1,2-dihydro-7-methyl-1-(*p*-tosyl)-	138		1125, 1126
5- and 7-Chloro-2-quinolone		90	1140
5-Chloro-1,2,3,4-tetrahydro-4-oxo-	132		472
5-Chloro-1,2,3,4-tetrahydro-6-methyl-4-oxo-	131		1130
6-Chloro-2-quinolone	266	82	1140
6-Chloro-1,2,3,4-tetrahydro-2-oxo-	168	90	249
6-Chloro-1,2,3,4-tetrahydro-2-methyl-4-oxo-	134	40	489, 1131
6-Chloro-1,2,3,4-tetrahydro-4-methyl-2-oxo-	172	92	249
6-Chloro-1,2,3,4-tetrahydro-2-oxo-4-phenyl-	186	80	1138
6-Chloro-1,2,3,4-tetrahydro-4-oxo-	112, 126	66	489, 1131, 1133
6-Chloro-1-(2-cyanoethyl)-1,2,3,4-tetrahydro-4-oxo-	137	74	1119, 1135
6-Chloro-1,2,3,4-tetrahydro-2-methyl-4-oxo-		60	1131
6-Chloro-1,2,3,4-tetrahydro-4-oxo-1-phenyl-	As oxime, m.p. 139 °C		1134
6-Chloro-1,2,3,4-tetrahydro-4-oxo-1-(*p*-tosyl)-			1129
7-Chloro-1,2,3,4-tetrahydro-4-oxo-	135	76	472, 1128
1-Acetyl-7-chloro-1,2,3,4-tetrahydro-4-oxo-	142.5	51	1136
7-Chloro-1,2,3,4-tetrahydro-6-methyl-4-oxo-	154	35	1130
7-Chloro-1,2,3,4-tetrahydro-2-oxo-4-phenyl-	210	83	1138
7-Chloro-1,2,3,4-tetrahydro-4-oxo-1-(*p*-tosyl)-	125	87	1128
8-Chloro-2-quinolone	208	56	1140

* See footnote to Table 1, p. 340.

TABLE 29 (*cont.*)

Halo-hydroquinoline*	M.p. (°C)	Yield (%)	References
8-Chloro-1,2,3,4-tetrahydro-2-oxo-	106	90	249
8-Chloro-1,2,3,4-tetrahydro-4-methyl-2-oxo-	103	79	249
8-Chloro-1,2,3,4-tetrahydro-6-methyl-2-oxo-4-phenyl-	163	60	1138
8-Chloro-1,2,3,4-tetrahydro-2-oxo-4-phenyl-	128	20	1138
8-Chloro-1,2,3,4-tetrahydro-4-oxo-	75		472, 1133
DICHLORO-			
5,6-Dichloro-1,2,3,4-tetrahydro-4-oxo-			1132
6,7-Dichloro-1,2,3,4-tetrahydro-4-oxo-			1132
6,8-Dichloro-2-quinolone	255	63	1140
6,8-Dichloro-1,2,3,4-tetrahydro-4-methyl-2-oxo-	161	84	249
6,8-Dichloro-1,2,3,4-tetrahydro-2-oxo-4-phenyl-	160	60	1139
6,8-Dichloro-1,2,3,4-tetrahydro-2-oxo-	148	100	249
7,8-Dichloro-1,2,3,4-tetrahydro-4-oxo-	277		2069
FLUORO-			
6-Fluoro-1,2,3,4-tetrahydro-2-oxo-4-phenyl-	170	82	1138
6-Fluoro-1,2,3,4-tetrahydro-4-oxo-	73	31	1133
8-Fluoro-1,2,3,4-tetrahydro-2-oxo-4-phenyl-	178	40	1139
8-Fluoro-1,2,3,4-tetrahydro-4-oxo-	129	100	1133
IODO-			
6-Iodo-1,2,3,4-tetrahydro-4-oxo-	153		1133
TRICHLORO-			
5,6,8-Trichloro-2-quinolone	266	56	1140
5,6,8-Trichloro-1,2,3,4-tetrahydro-2-oxo-4-phenyl-	171	30	1139

R. Haloquinolines by the Action of Dihalocarbenes on Indoles

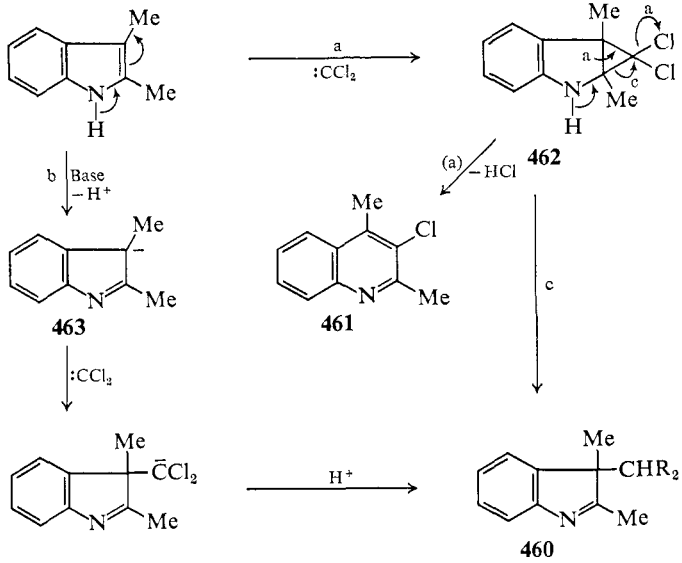
Early work by Magnanini[1141, 1142] indicates that 3-methylindole with chloroform and sodium methoxide gives 3-chloro-4-methylquinoline. Bromoform reacts similarly to give 3-bromo-4-methylquinoline, while with 2-methylindole the corresponding 3-halo-2-methylquinolines are obtained. Ellinger[1121] confirmed these results and also showed[1143] that indole, under Reimer–Tiemann conditions (chloroform and sodium hydroxide), yields the expected indole-2-carbaldehyde together with appreciable amounts of 3-chloroquinoline.

Subsequently, several reports of haloquinoline formation during the synthesis of indolecarbaldehydes have appeared. Perkin and his co-workers[1144, 1145] obtained

3-chloro-methoxyquinolines as by-products in the synthesis of methoxyindole-3-carbaldehydes, while Robson and his co-workers[1146-1148] have isolated 3-chloroquinolines during the preparation of various indole-3-carbaldehydes. Blume and Lindwall[1149] prepared 2-phenylindole-3-carbaldehyde by a Reimer–Tiemann reaction on 2-phenylindole and isolated a by-product, m.p. 93 °C, which they assumed to be 3-chloro-2-phenylquinoline.

Little work appeared on the mechanism of this interesting ring expansion until, in 1962, Robinson[1150] published some results on the reaction of 2,3-dimethylindole with chloroform in the presence of sodium ethoxide. This reaction had been investigated earlier by Plancher and Carrasco[1151] who isolated originally only one product, for which they proposed the dichloromethyl structure (**460**; R = Cl). Subsequently, however, they isolated[1152] a mixture of the dichloromethyl compound and 3-chloro-2,4-dimethylquinoline (**461**) and reported that the indolenine is converted into the quinoline on treatment with sodium ethoxide in a sealed tube at 100 °C for 5 hours.

The (dichloromethyl)indolenine structure (**460**; R = Cl) was challenged by Wynberg[1153] who, on the basis of some similar reactions carried out by Parham and his co-workers[1154] on indene, suggested the alternative dichlorocyclopropane structure (**462**). Robinson,[1150] however, confirmed the results of Plancher and Carrasco and obtained the chlorodimethylquinoline (**461**) in 7% yield together with a basic material (12%), m.p. 75 °C, which on the basis of infrared spectral measurements [i.e. no NH stretch, but ν(C=N)] was shown to be the dichloromethyl compound (**460**; R = Cl) rather than the cyclopropane (**462**). Robinson, however, was unable to convert the dichloromethyl compound into the chlorodimethylquinoline and proposed that these products are formed by different pathways, (a) and (b), as indicated in Scheme 40, rather than from a common cyclopropane intermediate (path c) as proposed previously by Nakazaki.[1155]



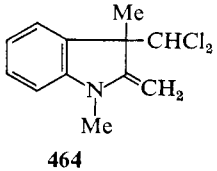
SCHEME 40

The dichlorocarbene, formed by the reaction of chloroform with strong base, can either add to the 2,3-double bond of indole (path a) or attack electrophilically at the

3-position of the indolyl anion (**463**) (path b). In the former reaction ring expansion and loss of hydrogen chloride as indicated yield the chlorodimethylquinoline.

Shortly after the appearance of this work Rees and Smithen[1156, 1157] published the results of a more extensive study on the reaction of indoles with dihalocarbenes. They confirmed Robinson's results and showed[1158] that dibromomethylene ($:CBr_2$), generated either by reaction of bromoform with sodium ethoxide or, better, by thermal decomposition of sodium tribromoacetate in hot 1,2-dimethoxyethane, yields 3-bromo-2,4-dimethylquinoline plus the (dibromomethyl)indolenine (**460**; R = Br). They found,[1157, 1158] in agreement with the proposed mechanism (Scheme 40), that the ratio of quinoline to indolenine increases as the basic strength of the reaction medium decreases. Thus with potassium *tert*-butoxide and chloroform the ratio is 0.4 : 1, while under neutral conditions (sodium trichloro- or tribromoacetate in dimethoxyethane) the ratios for the chloro- and bromo-compounds are 2.6 : 1 and 6.4 : 1, respectively. The reaction of 2,3-dimethylindole and difluorocarbene (generated by base-catalysed decomposition of ethyl chlorodifluoroacetate) yields a single product, which on the basis of proton magnetic resonance spectral measurements was shown to be 3-(difluoromethyl)indolenine (**460**; R = F).[1158]

Rees and Smithen[1158] have also shown that 3-methylindole reacts with ethyl trichloroacetate and potassium *tert*-butoxide to give 3-chloro-4-methylquinoline, while 1,3-dimethylindole yields, as the major product, a halogen-free polymer. Under Reimer–Tiemann conditions 1,2,3-trimethylindole is found to give only the 3-(dichloromethyl)indolenine (**464**), a product previously reported by Plancher and



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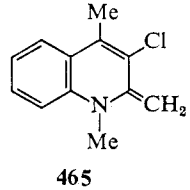

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Carrasco,[1159] whereas with sodium trichloroacetate in boiling dimethoxyethane (i.e. neutral conditions) a mixture of the indolenine (**464**) and 3-chloro-1,2-dihydro-1,4-dimethyl-2-methylenequinoline (**465**) is produced. Robinson[1150] and Rees and Smithen[1157, 1158] are, therefore, agreed that chloroquinoline formation proceeds by addition of dichlorocarbene to the 2,3-double bond of indole, whereas the indolenine arises by an electrophilic attack of the carbene at the electron-rich 3-position, as outlined in Scheme 40 and not, as suggested by Nakazaki, by ring opening of the intermediate (**462**) (Scheme 40; route c). However, radiotracer studies,[1160] involving carbon-14, on the reaction of dichlorocarbene with 2,3-dimethylindole suggest that a cyclopropane-type intermediate as proposed by Nakazaki could be involved, and the author (Dobbs) suggests that the mechanism of these reactions is still open to debate.

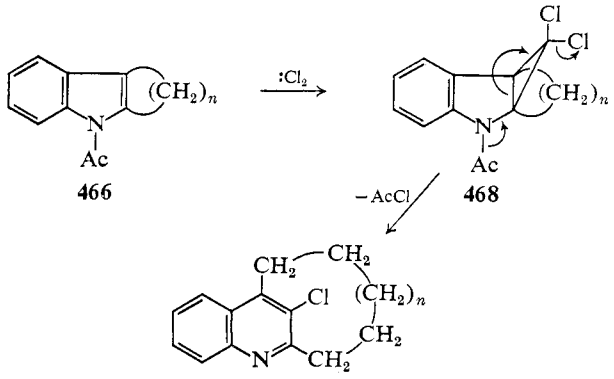
The reaction of carbenes with heterocyclic systems has been reviewed by Rees and Smithen.[1161]

Patterson and his co-workers[1162] have investigated the reaction of a series of indoles with dichlorocarbene, generated at high temperatures (550 °C) by pyrolysis of chloroform. Indole yields 3-chloroquinoline (35.6%),* and 2-methylindole and 3-methylindole yield 3-chloro-2-methylquinoline (39.5%) and 3-chloro-4-methylquinoline (42.4%), respectively, while 2,3-dimethylindole gives a 26.2% yield of

* Yields refer to the amount isolated. Gas-chromatographic analysis indicates that actual yields are some 3–13% higher.

3-chloro-2,4-dimethylquinoline. This method gives superior yields* of chloroquinolines than the reactions involving chlorocarbene at lower temperatures, and the authors claim that fewer side reactions are in evidence. Replacement of chloroform, as the carbene source, by carbon tetrachloride, ethyl trichloroacetate, or sodium trichloroacetate results in lower yields (1–20%) of chloroquinolines.

An interesting extension of these ring expansions has been exploited by Parham and his co-workers. [1163, 1164] They treated the 1-acetylindoles (**466**; $n = 6$, 8, and 10) with dichlorocarbene, generated by the thermolysis of phenyl (trichloromethyl)-mercury ($PhHgCCl_3$), and obtained the 3-chloro-2,4-quinolinophanes (**467**; n = 2, 4, and 6), as indicated in Scheme 41, in yields of 48–76%. The reaction is thought to



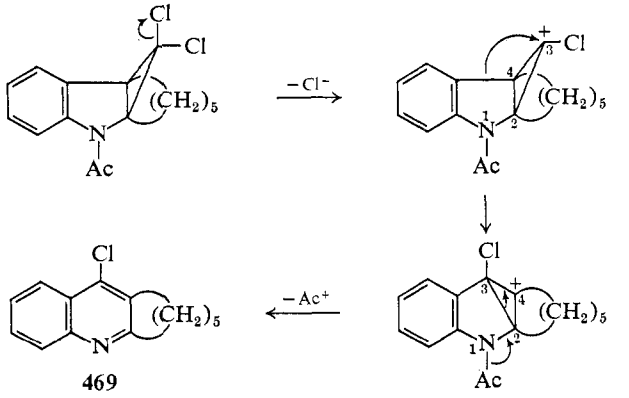
SCHEME 41

proceed via a dichlorocyclopropane intermediate (**468**; n = 6, 8, or 10) which undergoes ring expansion and loss of acetyl chloride as indicated. The 2,3-cycloheptenoindole (**466**; n = 5) fails to yield the 3-chloro-2,4-[5]quinolinophane (**467**; n = 1), presumably on account of the ring strain involved. Interestingly, however, a low yield (11%) of the isomeric 4-chloro-2,3-cycloheptanoquinoline (**469**) was isolated from the tarry products; formation of this chloroquinoline is thought to involve migration of a phenyl group (Scheme 42) as observed previously[1165] by the authors in the corresponding indene-to-chloronaphthalene ring expansion.

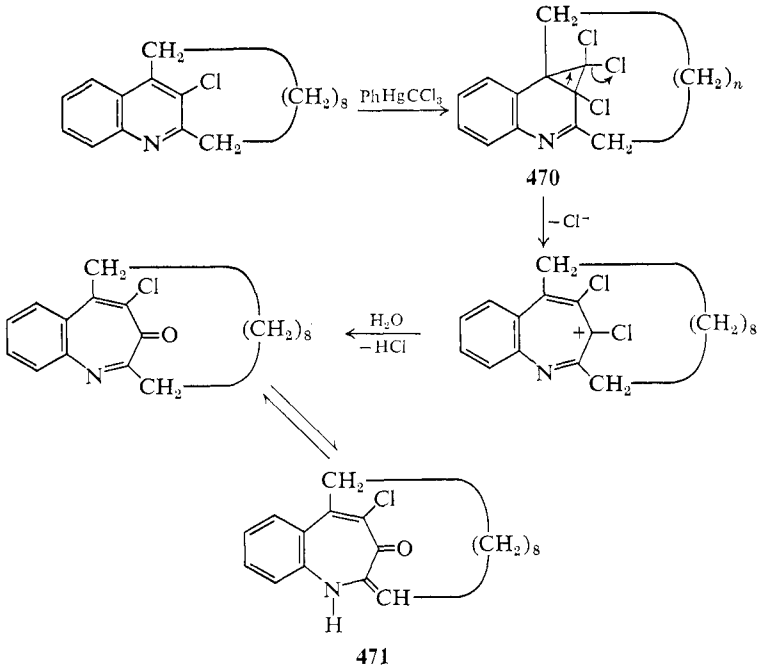
A minor product, isolated from the reaction of the cyclo-octenoindole (**466**; n = 6) with phenyl (trichloromethyl)mercury proved to be the cyclopropane derivative (**470**; n = 4);[1164] this compound is also accessible (46%) by reaction of the 2,4-[6]-quinolinophane (**467**; n = 2) with phenyl(trichloromethyl)mercury. However, the 2,4-[10]quinolinophane (**467**; n = 6) under similar conditions yields a product (8%) for which the benzazepinone structure (**471**) is proposed (Scheme 43).

The difference in reactivity of the two systems (**467**; n = 2 and n = 6) is accounted for on the basis of ring strain in the bridging polymethylene chain. In the latter case expansion of the cyclopropane ring and subsequent azepinone formation is sterically feasible, whereas in the former compound steric restraint prevents further reaction.

* Further improvement in the yield of alkylhaloquinoline is possible by using sodium hydroxide and chloroform in the presence of the phase-transfer catalyst triethylbenzylammonium chloride, which proved superior to the use of crown ether dibenzo-18-crown-6.[2100]

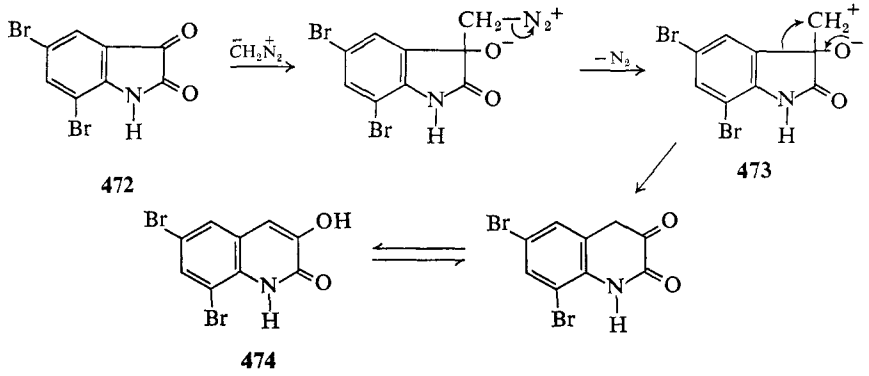


SCHEME 42



SCHEME 43

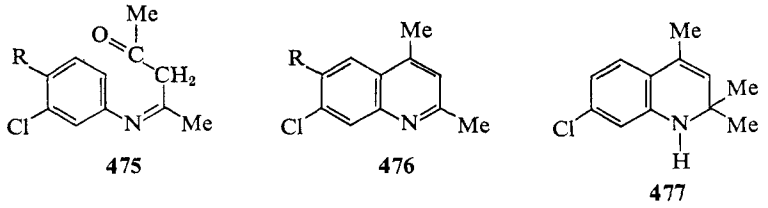
Of interest is an early unconfirmed report that 5,7-dibromoisatin (**472**) will react with diazomethane in diethyl ether solution to yield 6,8-dibromo-3-hydroxy-2-quinolone (**474**).[1166] Other haloisatins behave similarly. No mechanism has been published for these reactions but they could well proceed by attack at the 3-position of the isatin molecule, by either carbene or diazomethane, followed by a ring expansion of the resulting carbonium ion (**473**) (Scheme 44), in a Demjanow-type reaction.



SCHEME 44

*S. Miscellaneous Methods of Preparing Haloquinolines**

a. COMBES' SYNTHESIS AND RELATED REACTIONS. The acid-catalysed cyclization of the monoanil of acetylacetone constitutes the Combes quinoline synthesis.[1167] This method, although useful for the synthesis of 2,4-dimethylquinolines, has been shown by Roberts and Turner[91] to have only limited use for the synthesis of halodimethylquinolines, for they found that, whereas *o*-, *m*-, and *p*-chloroaniline, together with 2,4-, 2,5-, and 3,5-dichloroaniline, react readily with acetylacetone to give the respective monoanils, only in the case of the *m*-chloroaniline anil (**475**; R = H) is cyclization successful. The product, 7-chloro-2,4-dimethylquinoline



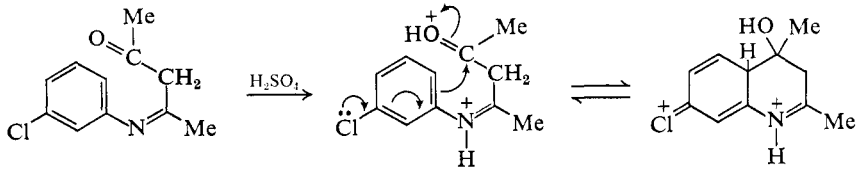
(**476**; R = H) was shown, by comparing its melting point with those of the known chlorodimethylquinolines, to be the 7- rather than the 5-chloro-isomer. On one occasion the dichlorodimethylquinoline (**476**; R = Cl) was obtained by cyclization of the anil (**475**; R = Cl), but attempts to repeat this synthesis failed.

Related reactions are observed between acetone and arylamines in the presence of iodine. The products from these reactions are the so-called "acetone anils",[201] which subsequently were shown to be 1,2-dihydro-2,2-dimethylquinolines.[202] *m*-Chloroaniline and acetone react during 30 hours to yield 7-chloro-1,2-dihydro-2,2,4-trimethylquinoline (**477**); no 5-chloro isomer is reported from the reaction and the structure of the 7-chloro-compound has been confirmed[1168] by proton magnetic resonance studies. *o*-Chloro- and *p*-chloro-aniline react similarly to yield the respective 8-chloro- and 6-chloro-1,2-dihydrotrimethylquinolines, the former in low yield.[202] The synthesis of 8-chloro-1,2-dihydro-2,2,4-trimethylquinoline from *o*-chloroaniline and 4-hydroxy-4-methylpentan-2-one, $Me_2C(OH)CH_2COMe$ (an aldol condensation

* See also Addenda, p. 684.

product of acetone), has recently been described;[1169] and ω-(*p*-chloroanilino)-propiophenone reportedly undergoes cyclization to 6-chloro-4-phenylquinoline in the presence of acid.[1170]

The kinetics of the cyclodehydration of 4-anilinopent-3-en-2-ones (i.e. acetylacetone monoanils) has been studied by Bonner and his co-workers.[1171, 1172] They found that a halogen substituent *para* to the point at which cyclization occurs (i.e. *meta* to the anil function) causes an increase in the rate (relative to the unsubstituted anil) of acid-catalysed ring closure, despite the general deactivating influence of halogen towards electrophilic substitution in the benzene nucleus. The order of activation of the halogens, which is found to be F > I > Cl > Br > H, is explained on the basis of mesomeric stabilization of the intermediate (**478**) which is thought to resemble most closely the transition state for the cyclization.



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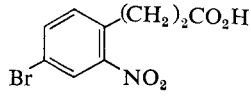
b. SYNTHESIS FROM *o*-AMINOPHENYL-ALKANOIC, -ALKENOIC, AND -ALKYNOIC ACIDS. Gabriel and Zimmermann[1173] found that 3-(4-bromo-2-nitrophenyl)propanoic acid (**479**), on reduction with tin and hydrochloric acid, gives 7-bromo-1,2,3,4-tetrahydro-2-oxoquinoline (**480**).



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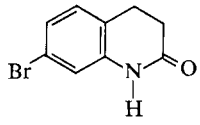

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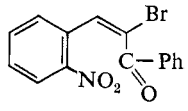

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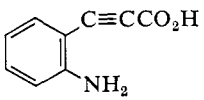
Another example of reduction accompanied by cyclization was observed[1174] on warming the bromo-nitrochalcone (**481**) with hydrobromic acid and stannous chloride: 3-bromo-2-phenylquinoline was isolated in good yield.

In a similar series of reactions Baeyer and Bloem[365] found that (*o*-aminophenyl)-acetylenecarboxylic acid (**482**), on heating under reflux with hydrochloric, hydrobromic, or hydriodic acid, undergoes addition of halogen acid followed by cyclization to give 4-chloro-, 4-bromo-, and 4-iodo-2-quinolone, respectively.

Camps[1175] has also cyclized the acetylenecarboxylic acid (**482**) with hydrochloric acid, obtaining 4-chloro-2-quinolone along with its hydrolysis product, 4-hydroxy-2-quinolone.



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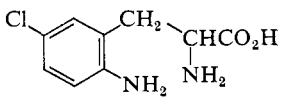

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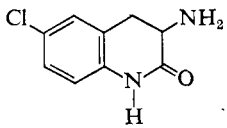

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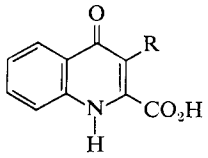
McCord and his co-workers[1176] cyclized the 2-amino-3-(*o*-aminophenyl)propanoic acid (**483**) in a mixture of concentrated hydrochloric acid and 50% aqueous methanol and obtained 3-amino-6-chloro-1,2,3,4-tetrahydro-2-oxoquinoline (**484**).

c. HOFMANN DEGRADATION OF AMIDES. Quinoline-4-carboxamide, on treatment with bromine and potassium hydroxide, is reported[171, 700] to yield 4-aminoquinoline, together with 4-amino-3-bromoquinoline.

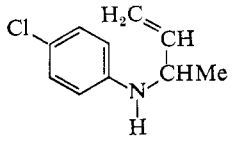
Somewhat more unusual is the report by von Niementowski and Sucharda[1122] that Hofmann degradation of the amide (**485**; R = $CONH_2$) results in formation of the amine (**485**; R = NH_2), plus 3-bromo-4-quinolone-2-carboxylic acid (**485**;



485

R = Br). The structure of the bromo-acid was established by decarboxylation to the known 3-bromo-4-quinolone.

d. SYNTHESIS FROM HALOANILINES AND ALKYNES. Early French[1177] and German patents[1178, 1179] describe the synthesis of 8-chloro-2-methylquinoline by reaction of *o*-chloroaniline with acetylene in the presence of zinc chloride and pumice at 300–320 °C. More recently Russian workers[1180] have carried out a similar reaction on *p*-chloroaniline which, in ethanol in the presence of mercuric chloride, reacts with acetylene over a period of 30 hours to give 6-chloro-2-methylquinoline in 30.5% yield. 6-Bromo-2-methylquinoline (21.4%) is also prepared, and a mechanism for the reaction involving initial formation of butadiene, followed by 1,2-addition of the amine and cyclization of the resulting *N*-(alkenyl)aniline (**486**), is suggested.



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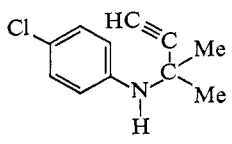
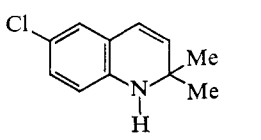


487

p-Chloroaniline has also been treated with 3-chloro-3-methylbut-1-yne, $Me_2C(Cl)C{\equiv}CH$, in the presence of copper bronze;[1181] the resulting *N*-(alkynyl)aniline (**487**), on treatment with cuprous chloride and copper bronze in the presence of the amine hydrochloride, cyclizes to give the chloro-1,2-dihydroquinoline (**488**).

An unusual reaction between hydrazobenzene and dimethyl acetylenedicarboxylate has been reported by Diels and Reese;[1182] they find that initially a 1 : 1 adduct is obtained which, heated in solution, gives a range of diverse products depending on the solvent used; in acetic acid the pyrazolone (**489**) is obtained, while in hot xylene the indole-2,3-dicarboxylate (**490**; R = H) is the sole product; alternatively, heating the adduct under reflux in pyridine yields the 2-quinolone-4-carboxylic ester (**491**; R = H, Ar = Ph). This reaction has recently been reinvestigated by Huntress and his co-workers[1183] who have shown that *p,p'*-dichlorohydrazobenzene with dimethyl



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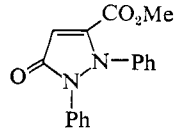

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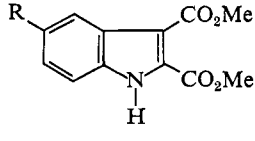

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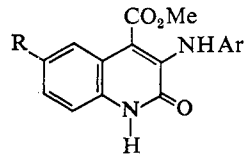
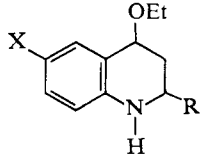


491

acetylenedicarboxylate in hot xylene gives dimethyl 5-chloroindole-2,3-dicarboxylate (**490**; R = Cl) (74%) whereas, in boiling α-picoline, methyl 6-chloro-3-(*p*-chloroanilino)-2-quinolone-4-carboxylate (**491**; R = Cl, Ar = *p*-ClC_6H_4) is obtained in 73% yield.

e. Synthesis from Anils and Vinyl Ethers. Povarov and Milkailov[1184] found that *p*-bromoaniline in benzene solution with ethyl vinyl ether in the presence of boron trifluoride–ether complex gives 6-bromo-4-ethoxy-1,2,3,4-tetrahydro-2-methylquinoline (**492**; X = Br, R = Me) (52.8%), which with hot *p*-toluenesulphonic acid *in vacuo* aromatizes to yield 6-bromo-2-methylquinoline (51.8%). The reaction is thought to involve initial formation of the anil (*p*-$BrC_6H_4N{=}CHMe$) by condensation of *p*-bromoaniline with acetaldehyde generated *in situ* by hydrolysis of the vinyl ether. In support of this idea Povarov and his co-workers[1185] demonstrated that the benzylideneanilines (*p*-$XC_6H_4N{=}CHPh$; X = Br or I) with ethyl vinyl ether under the same conditions give the halotetrahydro-2-phenylquinolines (**492**; R = Ph,



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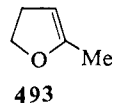

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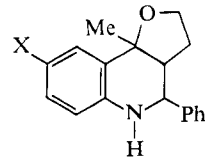


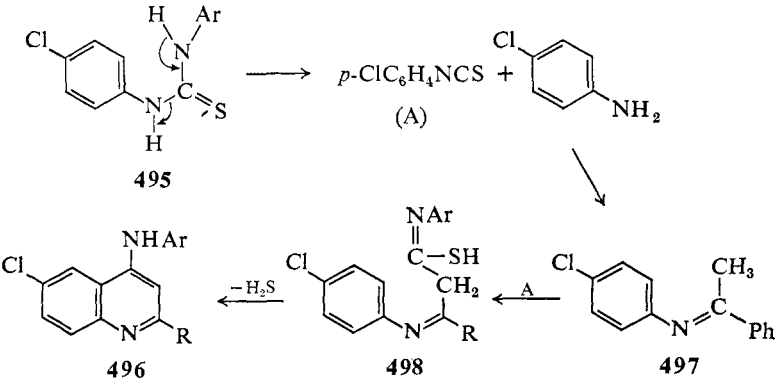
494

X = Br or I) in 44.5 and 19% yield, respectively. In an interesting variation of this reaction the *N*-benzylidene-*p*-haloanilines were treated with the cyclic vinyl ether, 2-methyl-3,4-dihydrofuran (**493**), to give the tetrahydro-2*H*-furo[2,3-*c*]quinolines (**494**; X = Cl, Br, or I) in good yields (60–80%).

A Japanese patent[1186] describes a similar reaction between ethyl vinyl ether and various anils in tetrahydrofuran solution and in the presence of an octacarbonyldicobalt catalyst. The reaction is carried out under mild conditions (4 hours at 25 °C, nitrogen atmosphere), and with benzylidene-*p*-bromoaniline a mixture of 6-bromo-2-phenylquinoline and 6-bromo-4-ethoxy-1,2,3,4-tetrahydro-2-phenylquinoline (**492**; X = Br, R = Ph) is obtained.

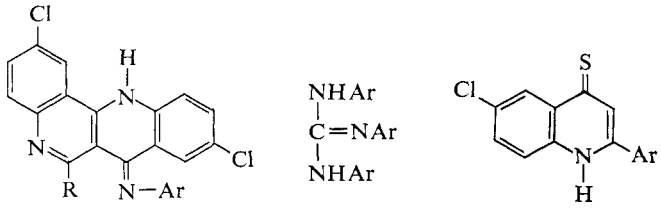
f. Synthesis from Dihalothioureas and Related Compounds. Dziewonski and Mayer[1187] observed that acetophenone and *N*,*N*′-di-(*p*-chlorophenyl)thiourea

(**495**; Ar = *p*-ClC_6H_4) at 205 °C yield 6-chloro-4-(*p*-chloroanilino)-2-phenylquinoline (**496**; R = Ph, Ar = *p*-ClC_6H_4). A mechanism involving cleavage of the thiourea to give *p*-chloroaniline and *p*-chlorophenyl isothiocyanate, as illustrated, is proposed to explain the formation of the chloroquinoline. The reaction has been extended[1188] to the preparation of other chloroanilinoquinolines.



In a similar manner the anil (**497**) reacts with 1 mol of di-*p*-(chlorophenyl)-carbodi-imide (ArN=C=NAr; Ar = *p*-ClC_6H_4) to yield the diarylquinoline (**496**; R = Ph, Ar = *p*-ClC_6H_4).[1189] With two mol of the di-imide the polycyclic compound (**499**; R = Ph, Ar = *p*-ClC_6H_4) is obtained.

The tris-(*p*-chloroanilino)guanidine (**500**; Ar = *p*-ClC_6H_4) reacts in a like manner with various aryl methyl ketones;[1189, 1190] for example, *p*-methylacetophenone and the

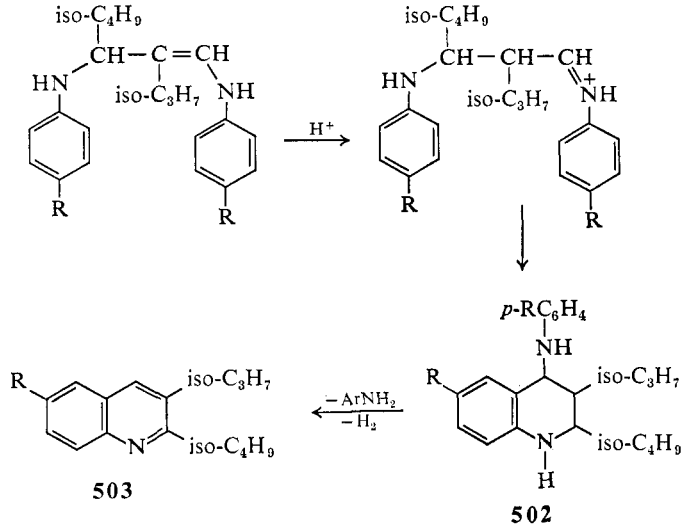


guanidine (**500**; Ar as above) yield a mixture of the anilinoquinoline (**496**; R = *p*-MeC_6H_4, Ar = *p*-ClC_6H_4) and the anil (**499**; R = Ph, Ar = *p*-ClC_6H_4).

Moszew and Nagraba[1191] have shown that thioamides of type (**498**; R = *p*-MeC_6H_4, Ar = C_6H_5) cyclize in polyphosphoric acid to give, not the anilinoquinoline (**496**; R = *p*-MeC_6H_4, Ar = C_6H_5), but the 4-thione (**501**; Ar = *p*-MeC_6H_4).

g. Decomposition of *N,N'*-Diarylpropane-1,3-diamines. *N,N'*-Diphenylpropane 1,3-diamine, $PhNH(CH_2)_3NHPh$, decomposes at 230 °C in the presence of hydrogen bromide to give a mixture of aniline, 1,2,3,4-tetrahydroquinoline, and julolidine.[1192, 1193] Further investigation of the reaction shows[1194] that *N,N'*-di(chlorophenylpropane)-1,3-diamines require higher temperatures (235–300 °C) to effect decomposition, and only poor yields of the corresponding chlorotetrahydroquinolines are produced. 1,3-Di-(*m*-chloroanilino)propane gives a 47 : 53 mixture of the 5- and 7-chloro-1,2,3,4-tetrahydroquinolines.

Russian workers[1195] have investigated the chemistry of the so-called "Schiff's base dimers" which originally[1196] were formulated as diazetidines. On acid treatment the dimers isomerize to the protonated anils (Scheme 45), which cyclize to the

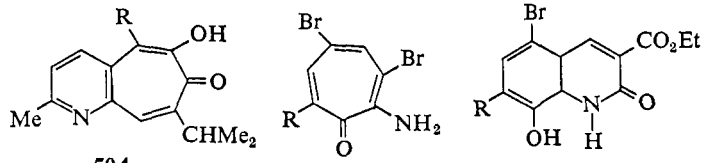


SCHEME 45

highly substituted tetrahydroquinolines (**502**); under the reaction conditions, these aromatize with loss of arylamine to give the 2,3-disubstituted 6-haloquinolines (**503**).

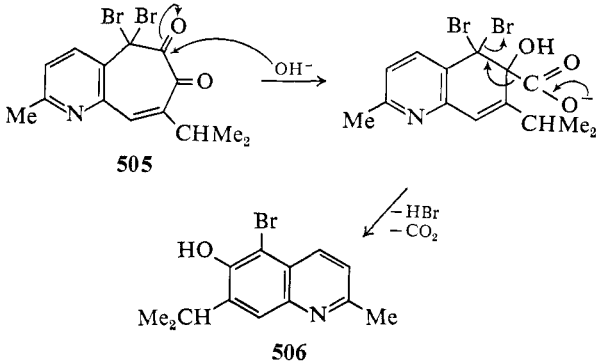
In the cases where R = F, Cl, Br, or I, good yields (44–48%) of the dialkyl-6-haloquinolines are obtained. In a similar manner *N*-butylidenearylamine dimers cyclize to give 3-ethyl-6-halo-2-(*n*-propyl)quinolines, and yields of 82–96% have been achieved.[1197]

h. RING CONTRACTION OF TROPOLONES AND TROPONES. Yamane[134] has carried out a series of interesting reactions on the pyrido[3,2-*d*]tropolone (**504**; R = H). Bromination with one equivalent of *N*-bromosuccinimide yields the monobromo-derivative (**504**; R = Br), whereas bromination with two equivalents of brominating agent yields the dibromo-compound (**505**) which, with hot alkali, undergoes ring contraction with loss of carbon dioxide, to yield 5-bromo-6-hydroxy-7-isopropyl-2-methylquinoline (**506**).



In a similar manner the monobromo-derivative (**504**; R = Br) gives 6-hydroxy-7-isopropyl-2-methylquinoline.

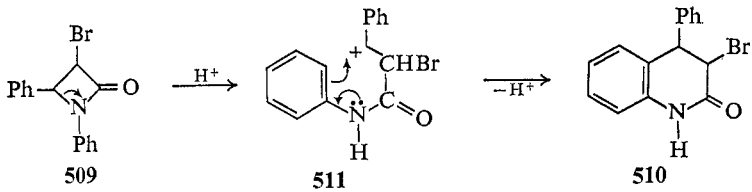
Halo-hydroxyquinoline formation is explained on the basis of a benzylic acid-type rearrangement of the α,β-diketone (**505**), followed by decarboxylation and dehydrobromination of the resulting acid as outlined in Scheme 46.



SCHEME 46

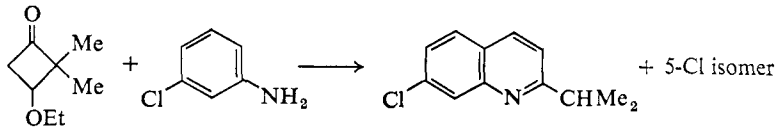
A similar reaction involving ring contraction of aminotropones has been recorded by Sato.[1198] The aminodibromotropone (**507**; R = Me_2CH) on treatment with diethyl malonate and sodium ethoxide in boiling ethanol yields ethyl 5-bromo-8-hydroxy-7-isopropyl-2-quinolone-3-carboxylate (**508**; R = Me_2CH). Likewise, other 2-quinolone-3-carboxylates (e.g. **508**; R = Me or Br) have been prepared. By using other reagents, e.g. ethyl acetoacetate, ethyl cyanoacetate, etc., in the reaction a series of halogen-substituted 2-quinolones and 2-aminoquinolines have been synthesized.[1198, 1199] No mechanistic explanation for these intriguing reactions has yet been advanced.

i. RING EXPANSION OF AZETIDINONES AND RELATED REACTIONS. Knunyants and Gambaryan[1200] have shown that 3-bromo-1,4-diphenylazetidin-2-one (**509**) in cold concentrated sulphuric acid undergoes ring expansion and rearrangement to 3-bromo-1,2,3,4-tetrahydro-2-oxo-4-phenylquinoline (**510**) in 72.5% yield. The



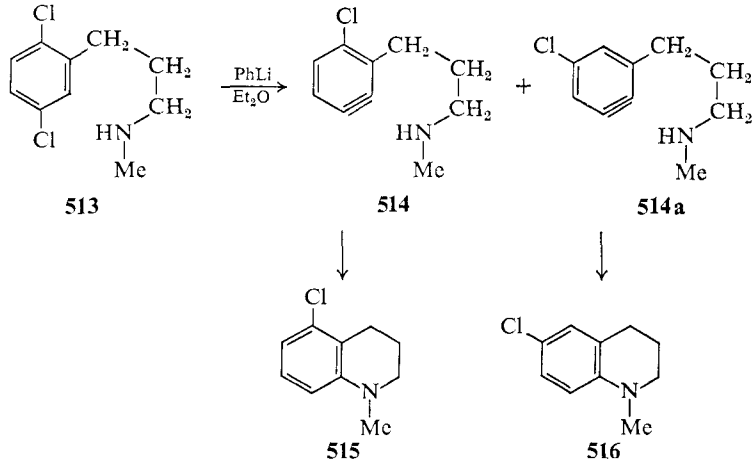
mechanism of ring-expansion is very similar to that observed by Heine[1201] for that of 1-acylaziridines to oxazolidinones, and to the ring closure of cinnamanilides in molten aluminium chloride, discussed in Section II.1.Q. Protonation of the amide-nitrogen is followed by ring opening to give the most stable carbonium ion (i.e. **511**), which then electrophilically substitutes the aryl nucleus as illustrated.

Martin and Meen[1202] found that *m*-chloroaniline with 3-ethoxy-2,2-dimethylcyclobutanone (**512**) (formed by reaction of dimethylketen with ethyl vinyl ether) in the presence of *p*-toluenesulphonic acid, yields a mixture of 5- and 7-chloro-2-isopropylquinoline. Other primary amines react in a similar manner. The mechanism of this reaction is not clear.



512

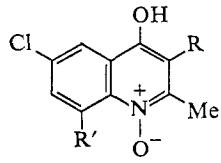
j. SYNTHESIS VIA ARYNE INTERMEDIATES. During a systematic investigation of aromatic nucleophilic substitution processes Huisgen and his co-workers[1203] found that the 3-(dichlorophenyl)propylamine (**513**) on treatment with phenyl-lithium in boiling diethyl ether undergoes cyclization to a 3 : 1 mixture of 5- and 6-chloro-1,2,3,4-tetrahydro-1-methylquinoline (**515** and **516**). The products are satisfactorily explained on the basis of amine addition to the aryne intermediates (**514** and **514a**).



513 **514** **514a**

515 **516**

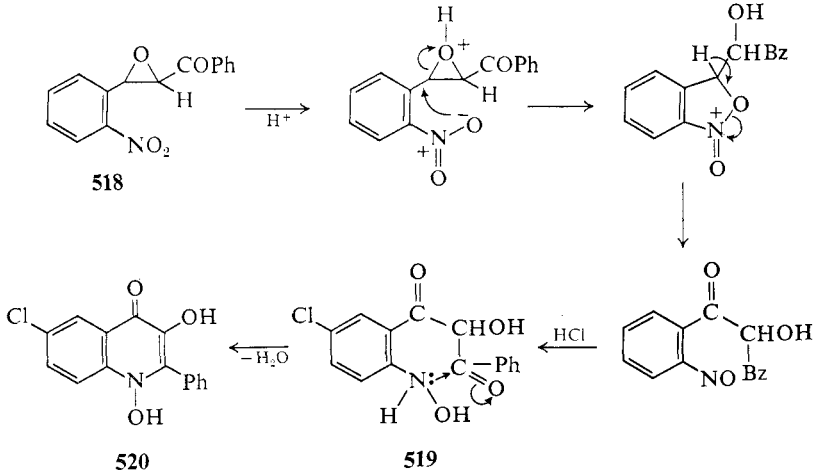
k. OTHER METHODS OF SYNTHESIS. Loudon and Wellings[1201] have obtained ethyl 6-chloro-4-hydroxy-2-methylquinoline-3-carboxylate *N*-oxide (**517**; R = CO_2Et, R′ = H) by condensing *o*-nitrobenzaldehyde with ethyl acetoacetate in the presence of hydrogen chloride. Similarly acetylacetone and diethyl acetonedicarboxylate yield



517

the products (**517**; R′ = H, R = Ac and CH_2CO_2Et, respectively). Later studies by Loudon and Tennant[1205] indicate that condensation will also occur in the presence of hydrogen bromide, but in this case nuclear halogenation is not observed. For example, 5-chloro-2-nitrobenzaldehyde and ethyl acetoacetate in the presence of hydrogen chloride give the dichloro *N*-oxide (**517**; R = CO_2Et, R′ = Cl), whereas with hydrogen bromide the monochloro-derivative (**517**; R = CO_2Et, R′ = H) is obtained. The mechanism of these reactions is still obscure.

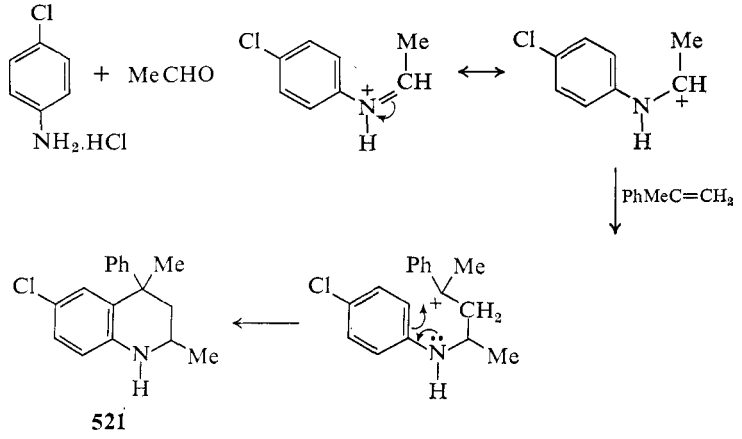
Sword[1206] has described the formation of 6-chloro-1,3-dihydroxy-2-phenyl-4-quinolone (**520**) by the action of ethereal hydrogen chloride on 3-benzoyl-2-(*o*-nitrophenyloxirane (**518**). The reaction is thought to involve nucleophilic attack by oxygen of the nitro-group at the protonated epoxide ring, followed by oxygen transfer from the nitro-group to the side chain as indicated in Scheme 47. The



SCHEME 47

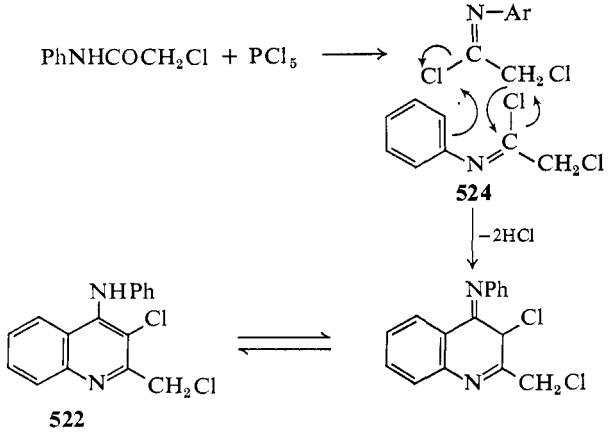
nitroso-compound so formed then suffers reduction and chlorination (by hydrogen chloride) to give the chlorohydroxylamine (**519**) which is cyclodehydrated to the product (**520**).

Work by Hesse[1207] has shown that 4,4-disubstituted 1,2,3,4-tetrahydroquinolines may be prepared by treating arylamines with aldehydes and substituted ethylenes in the presence of acetic acid. For example, *p*-chloroaniline (as the hydrochloride), acetaldehyde, and α-methylstyrene react as shown in Scheme 48 to yield 6-chloro-1,2,3,4-tetrahydro-2,4-dimethyl-4-phenylquinoline (**521**).



SCHEME 48

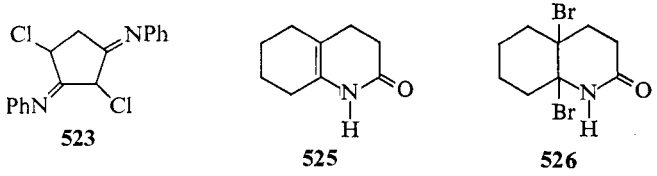
von Braun and his co-workers[599, 1208] isolated a product of molecular formula $C_{16}H_{12}Cl_2N_2.HCl$ after reaction of phosphorus pentachloride with *N*-(chloroacetyl) aniline. This product was subsequently shown to be the halogenated anilinoquinoline (**522**). Similar products had been described earlier by Wallach[1209, 1210] and Bischoff *et al.*[1211] for which they proposed structures of type (**523**). The reaction appears to proceed by initial formation of the imidoyl chloride (**524**), which condenses with itself with loss of hydrogen chloride (Scheme 49).*



SCHEME 49

In the same manner the 6-iodo-4-(*p*-iodoanilino)- and 7-chloro-(*m*-chloroanilino)-analogues of (**522**), together with several other related compounds, were prepared.

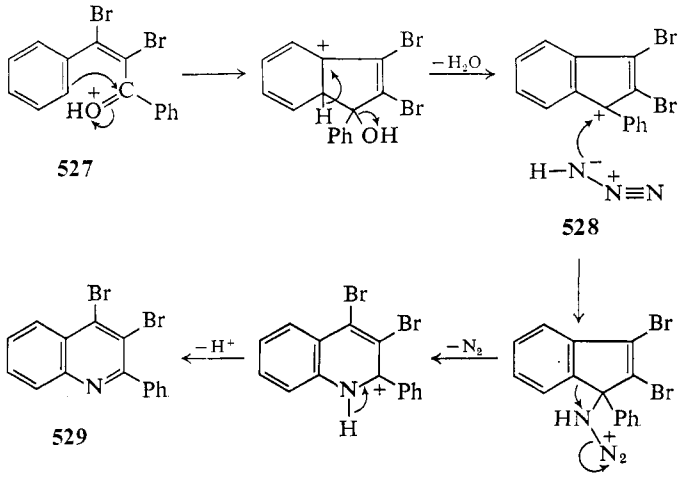
1,2,3,4,5,6,7-Octahydro-2-oxoquinoline (**525**) reacts with bromine in chloroform solution at 0 °C to give the 4*a*,8*a*-dibromo-adduct (**526**).[361]



Pratt and his co-workers[1212] have obtained 3,4-dibromo-2-phenylquinoline (**529**) in 30% yield by a Schmidt reaction (sodium azide and concentrated sulphuric acid) on the dibromochalcone (**527**). The reaction is thought to proceed via the indane (**528**), as indicated in Scheme 50, which after attack by azide ion undergoes ring expansion with loss of nitrogen to give the quinoline (**529**).

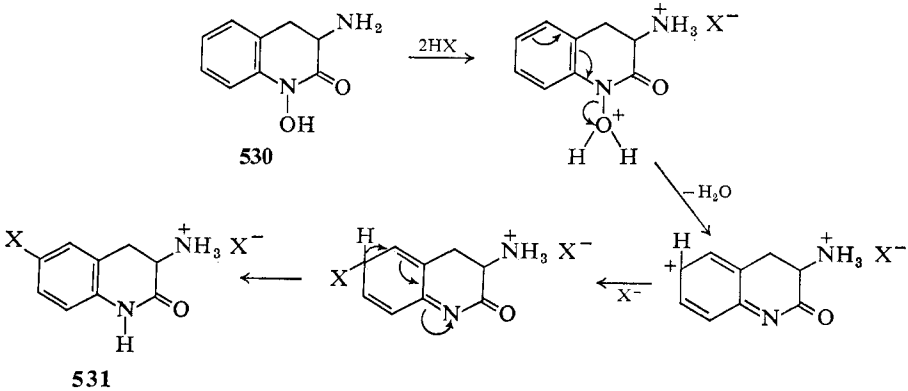
McCord and his co-workers[1176] have shown that 3-amino-1,2,3,4-tetrahydro-1-hydroxy-2-oxoquinoline (**530**), heated under reflux with concentrated hydrochloric or hydrobromic acid, undergoes halogenation at the 6-position accompanied by loss of the *N*-hydroxy-function, to give the 6-halo-2-oxoquinolines (**531**; X = Cl or Br)

* This reaction may well be a further example of a polar cycloaddition of an imidoyl halide. For review and other examples, see ref. 2101.



SCHEME 50

in high yields (90% and 66%). The reaction is thought to proceed as indicated in Scheme 51. If the reaction is carried out in boiling dilute hydrochloric acid, then the 6-hydroxy-2-oxoquinoline (**531**; X = OH) is the sole product. It appears that under these conditions nucleophilic attack by water at the electron-deficient 6-position is favoured to attack by chloride ion.



SCHEME 51

2. Properties and Reactions

A. Physical Properties

The fundamental physical properties of the haloquinolines such as melting point, boiling point, density, and refractive index are given in tables at the end of this Chapter. Special mention may be made, however, of the density and refractive-index measurements carried out by von Auwers and Kraul[1213] on 2-, 6-, 7-, and 8-chloroquinoline.

The ionization constants of most of the monohaloquinolines have been measured and are listed in Table 30 (p. 524). The first reported measurements on the ionization constant of 4-chloroquinoline, and its 6- and 8-nitro-derivatives were carried out by J. C. E. Simpson and his co-workers.[1214] Knight and his co-workers have since systematically measured, by ultraviolet-spectroscopic techniques, the dissociation constants of almost all the monofluoro-,[1215, 1216] monochloro-,[1217] and monobromo-quinolines.[1216] As expected on the basis of the electron-withdrawing inductive effect of the halogens, all the monohaloquinolines are weaker bases than quinoline itself. The base-weakening effect of the halogen is greatest when it is located in the pyridine ring, particularly at the 2- or 4-position. However, accurate measurements on the 2- and 4-halo-derivatives, particularly the 2- and 4-fluoro- and 4-bromo-compounds, are hampered by the high mobility of the halogen under the conditions employed (aqueous ethanol). As expected, the 5-, 6-, and 7-haloquinolines are only slightly weaker bases than quinoline itself, signifying that the basic strength of haloquinolines increases as the distance between nitrogen and the carbon centre bearing the halogen substituent increases. If the inductive effect were all important then the base strength should decrease as the electronegativity of the halogen increases. This, in fact, as can be seen from Table 30, appears to be the case. Thus, 3-fluoro- and 3-chloro-quinoline are weaker bases than 3-bromoquinoline, etc. The discrepancy observed with the 8-haloquinolines (i.e. 8-fluoroquinoline a stronger base than either 8-chloro- or 8-bromo-quinoline) is probably due to *peri*-type steric interactions between the halogen and the nitrogen lone-pair electrons. As expected, heptafluoro- and hepta-chloroquinoline are very weak bases.[35]

Musgrave and his co-workers[1218] have successfully prepared the hexafluoro-antimonates $[C_9F_7NH]^+SbF_6^-$ of heptafluoroquinoline and a number of other perfluoro-heterocycles. From the ^{19}F-nuclear magnetic resonance spectra of the salts the relative order of base strength for a series of polyfluoroheterocycles has been determined. Perfluoroquinoline is more basic than perfluoropyridine and perfluoro-isoquinoline. The authors suggest that the base strength of perfluoro-heterocycles is highly sensitive to the number of fluorine atoms *ortho* to the ring-nitrogen undergoing protonation.

The electric dipole moments of all the monochloroquinolines (in benzene solution) have been measured[1219] and are as follows:

Position of Cl	2	3	4	5	6	7	8
Dipole moment (D)	3.31	2.19	0.96	0.64	2.02	3.18	3.55

The authors find unsatisfactory agreement between the calculated and experimental values, and possible reasons for these errors are discussed.

The crystal structure of 2-chloroquinoline has been determined by using a least-squares method on three-dimensional intensity data obtained at -140 °C.[1220–1222] The results indicate (*a*) that the crystals are orthorhombic, (*b*) that 2-chloroquinoline molecules are almost planar, and (*c*) that the molecules are stacked in the crystal in columns of intermolecular spacing 3.43 Å. Similar measurements on 6-chloro-quinoline indicate that it also is a planar molecule with an orthorhombic crystal structure.[1223]

The influence of 8-chloro- and 8-bromo-quinoline, and of 8-chloro-5-hydroxy-quinoline on the surface properties of water have been investigated.[1224] It was demonstrated that these compounds cause a decrease in the surface potential and surface tension of an aqueous solution. 6-Fluoro-,[1225] 6-chloro-, 6-bromo-, and 6-iodo-quinoline[1226] exert similar effects.

The polarography of various quinolines including 8-chloro-2-methylquinoline has been examined.[1227]

The charge-transfer complexes formed between quinoline and the halogens are discussed in Sections III.A–C. Charge-transfer complexes of haloquinolines with other electron-acceptors are, however, known. For example, Carmody and his co-workers[1228] have investigated in some detail the charge-transfer complexes of aza-aromatic compounds with π-electron acceptors for which both n- and π-electron-donor complexes are possible. The complexes of 6-bromo- and 8-chloro-quinoline with 1,3,5-trinitrobenzene, p-benzoquinone, and tetrachloro-1,4-benzoquinone have been studied, and it is concluded that both these haloquinolines function as n-donors and yield n–π-charge-transfer complexes.

TABLE 30. Basicity of Haloquinolines

Haloquinoline	Dissociation constant	pK_a	References
4-Chloro-		2.59	1214
4-Chloro-6-nitro-		2.13	1214
4-Chloro-8-nitro-		2.64	1214
2-Chloro-	N.D.		1217
3-Chloro-	$2.1–2.5 \times 10^{-12}$	2.46	1217, 1231
4-Chloro-	$2.5–2.8 \times 10^{-11}$	3.77 ± 0.05	1217, 1232
5-Chloro-	$2.2–2.6 \times 10^{-11}$		1217
6-Chloro-	$1.0–1.1 \times 10^{-11}$	4.06 ± 0.03	1217, 1233
7-Chloro-	$3.7–4.2 \times 10^{-11}$		1217
8-Chloro-	$7.0–7.6 \times 10^{-12}$		1217
2-Bromo-	$6.0–6.2 \times 10^{-14}$		1216
3-Bromo-	$3.1–3.4 \times 10^{-12}$	2.69	1216, 1231
		2.59 ± 0.02	1233
5-Bromo-	$2.2–2.4 \times 10^{-11}$	3.68 ± 0.02	1216, 1233
6-Bromo-	$4.4–4.6 \times 10^{-11}$		1216
7-Bromo-	$3.9–4.2 \times 10^{-11}$		1216
8-Bromo-	$6.9–7.8 \times 10^{-12}$		1216
3-Fluoro-	$2.3–3.0 \times 10^{-12}$	2.46	1216, 1231
5-Fluoro-	$4.8–5.0 \times 10^{-11}$		1215, 1216
6-Fluoro-	$0.98–1.1 \times 10^{-10}$		1215, 1216
7-Fluoro-	$1.0–1.2 \times 10^{-10}$		1215, 1216
8-Fluoro-	$1.2–1.4 \times 10^{-11}$		1215, 1216
6-Bromo-8-mercapto-		2.20 ± 0.02	1233
3-Iodo-		2.69	1231
5-(Trifluoromethyl)-	1.26×10^{-11}		869
7-(Trifluoromethyl)-	1.44×10^{-11}		869
4-Chloro-6-methoxy-		3.93	1232
4-Chloro-6-ethoxy-		3.82	1232
4-Chloro-6-methyl-		3.96	1232
4-Chloro-6-fluoro-		2.95	1232
4,6-Dichloro-		2.81	1232
6-Bromo-4-chloro-		2.83	1232
4-Chloro-7-methoxy-		4.32	1234
4-Chloro-7-methyl-		4.00	1234
4,7-Dichloro-		2.80	1234
4-Chloro-7-fluoro-		3.04	1234
7-Bromo-4-chloro-		2.83	1234

N.D. = Could not be determined.

2-Chloro- and 2-iodoquinoline are reported[737, 1229] to form 1 : 1 molecular complexes with various flavan derivatives. Illuminati and Gilman,[1230] during a study on the use of haloquinolines as heteroarylating agents in the Friedel–Crafts reaction, found that 2-chloro- and 4,7-dichloro-quinoline form 1 : 1 molecular complexes with 4-chlororesorcinol.

B. Spectra

a. Ultraviolet Spectra. The ultraviolet spectra of all the monofluoro-, monochloro-, and monobromo-quinolines, with the exception of the 4-fluoro- and 4-bromo-compounds, have been measured by Knight and his co-workers.[1216, 1217, 1235] Solutions of 4-fluoro- and 4-bromoquinoline in aqueous ethanol proved to be too unstable for accurate measurements to be made.

Quinoline itself in 95% ethanol solution exhibits three maxima, at 277, 300, and and 313 nm, with molecular extinction coefficients of 3.59, 3.13, and 3.41×10^{-3}, respectively. In general, the introduction of halogen onto the quinoline nucleus produces a bathochromic shift of the absorption bands. Knight and his co-workers, however, found that the three main absorption bands were shifted by varying amounts depending on the position of the halogen substituent, and that there is a wide variation in the magnitude of the extinction coefficients. In some cases an unexplained hypsochromic shift is observed,[1235] and the shifts and variation in intensity of the absorption bands are discussed by those authors in some detail.

The ultraviolet spectra of all the monochloroquinolines have also been measured by Favini and Simonetta[1236] who obtained results in agreement with those of Knight. The vapour-phase ultraviolet spectra of 2- and 8-chloroquinoline have been reported.[1237]

Kaneko[774] has measured the ultraviolet spectra of a series of mono-, di-, tri-, and tetra-haloquinolines. He found these spectra to exhibit similar absorption maxima to those of quinoline (i.e. two main absorption maxima at around 300 and 313 nm) irrespective of the number of halogen substituents, and that in general both absorption maxima undergo a bathochromic shift of 3–6 nm. The position of the halogen substituents, however, has little influence on the position of the absorption maxima.

The ultraviolet spectrum of heptafluoroquinoline is found to resemble closely that of quinoline itself, when measured in either cyclohexane or concentrated sulphuric acid solution.[35]

The ultraviolet spectra of a large number of 4-aminoquinolines, all possessing a halogen substituent in the carbocyclic ring, have been recorded by Steck and his co-workers.[1238, 1239] They were interested in the possible effect of the position and nature of the halogen substituent on antimalarial activity and to this end the effect of pH on the ultraviolet spectra of the aminohaloquinolines was discussed in some detail. Similar studies have been carried out by Bliznyukov and Sokol.[1240]

The ultraviolet spectra of several 2,4-dichloro-3-(2-chloroethyl)quinolines[590] and of 3-bromo- and 4-chloro-quinoline *N*-oxide[1241] have been studied in some detail, as have the ultraviolet spectra of a series of quinoline–bromine charge-transfer complexes.[14]

The diffuse reflectance spectra, over the visible region, of a series of haloquinoline *N*-oxide–copper halide complexes have been reported by Hatfield and his co-workers.[1242]

b. Infrared and Raman Spectra. The infrared spectra of a whole range of substituted quinolines, including several haloquinolines, have been recorded by Lachowicz and his co-workers.[1243] The infrared spectra of 2- and 8-chloroquinoline

have been measured,[1244] as has the stimulated Raman spectrum of 8-chloroquinoline.[1245]

c. NUCLEAR MAGNETIC RESONANCE SPECTRA.* 5,7-Dichloroquinoline was one of the earliest molecules to be studied by nuclear magnetic resonance techniques, in which spin–spin splitting between protons situated in different rings of a polycyclic aromatic compound was observed.[1246]

The proton magnetic resonance spectra of 7-fluoro-, 7-chloro-, 7-bromo-, and 7-iodo-2-methylquinoline, along with those of other 5- and 7-haloquinolines, have been studied in some detail by Palmer and his co-workers,[890] who discuss at length the effect of the halogen substituent on the chemical shift of the ring protons, together with concentration and solvent effects.

The effect of various substituents located at the 6-position of the quinoline ring on the chemical shift of the ring-protons has been investigated,[1247] and 6-bromoquinoline is one of the compounds discussed.

The ^{19}F-magnetic resonance spectra of 2-fluoro-, 5,8-difluoro-, 6,8-difluoro-, and 5,6,7,8-tetrafluoroquinoline have been reported and discussed in detail by Kaslow and his co-workers.[1248] Dewar and Keleman[1249] have attempted to correlate ^{19}F-nuclear magnetic resonance chemical shifts with the local π-electron density on fluorine. For this work a whole range of fluoro-aromatic and heteroaromatic compounds including 2-, 3-, 6-, and 7-fluoroquinoline, together with 2,3,4,5,6,7,8-hepta- and 3,4,5,6,7,8-hexa-fluoroquinoline were studied. The fluorine shifts, relative to trichlorofluoromethane, were measured and are tabulated in the paper.

The ^{19}F-magnetic resonance spectra of heptafluoroquinoline and several of its derivatives have been measured by Musgrave and his co-workers.[750, 751, 1250]

d. NUCLEAR QUADRUPOLE RESONANCE SPECTRA. The theory and use of nuclear quadrupole resonance have recently been reviewed.[1251] Basically the method is a means whereby the electron distribution in a molecule may be measured, and the bulk of the measurements so far carried out have been on halogen-containing molecules. ^{35}Cl- and to a lesser extent ^{79}Br-nuclear quadrupole resonances of a variety of chloro- and bromo-quinolines have been measured.[1252–1254] Attempts have been made[1253, 1254] to correlate chlorine nuclear quadrupole resonance frequencies with the distribution of π-electron densities in conjugated systems, and Dewar and Lucken[1254] have discussed the problem, as applied to haloquinolines, in some detail.

e. MISCELLANEOUS. The fluorescence and phosphorescence spectra of 2-chloro-, 6-chloro-, and 6-bromo-quinoline have been reported.[1255]

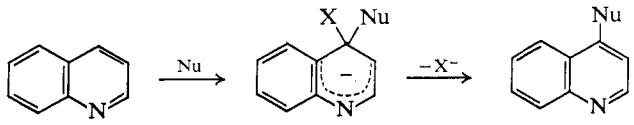
C. Nucleophilic Displacement of Halogen from Haloquinolines

a. INTRODUCTION. By far the most studied aspect of the chemistry of haloquinolines is their reactivity towards nucleophilic reagents. The ring-nitrogen, by means of both inductive and conjugative effects, activates a halogen substituent at the 2- or 4-position towards nucleophilic substitution, and favourable resonance-stabilized transition states can be envisaged for substitution at these positions.

The actual process of nucleophilic displacement of halogen can take place by various mechanisms. "Normal" substitution involves an S_N2-type transition state and can be regarded as an addition–elimination process (Scheme 52). Kinetic

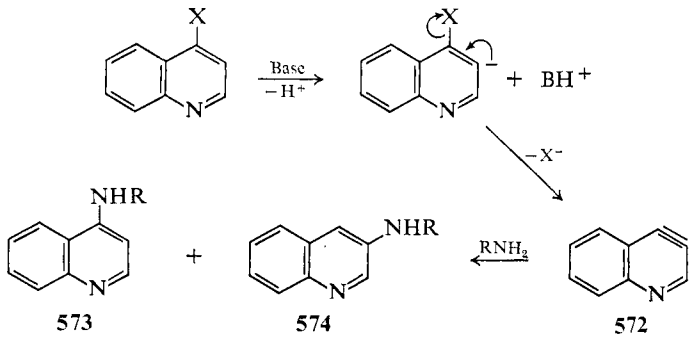
* See also Addenda, p. 689.

measurements indicate that, in general, the reaction is a genuine bimolecular process and evidence suggests that in some cases the transition state may well be a definite intermediate.



SCHEME 52

An elimination–addition mechanism (Scheme 53) has, in recent years, been shown to operate in many instances of aromatic and heteroaromatic nucleophilic substitution. An aryne intermediate (e.g. **572**) is often involved and a mixture of products (e.g. **573** and **574**) can then be isolated. For the haloquinolines it appears that, in general, the 2- and the 4-halo-compounds undergo normal addition–elimination reactions, whereas the less reactive isomers are more prone to react via an elimination–addition pathway.



SCHEME 53

As may be expected on a simple inductive-effect approach, protonation of the ring-nitrogen should increase the nucleophilic lability of the halogen atom, particularly at the 2-position, and to a lesser extent at the 4-position, of the quinoline ring. Such effects have been observed experimentally and acid-catalysed nucleophilic replacements are well documented. Autocatalysis is also observed in many reactions.

Beltrame and his co-workers[1256] have carried out molecular-orbital calculations for nucleophilic substitution in a series of halo-heteroaromatic compounds including 2- and 4-chloroquinoline. Some success is achieved in correlating experimentally determined free activation energies with reactivity indexes derived by a delocalization approach. However, as will be seen in the following Section, 4-chloroquinolines are more reactive towards weak nucleophiles (e.g. piperidine) than the 2-chloro-isomers, whereas the reverse holds with strong nucleophiles (e.g. EtO^-). A tentative theoretical explanation of these results has been offered.[4]

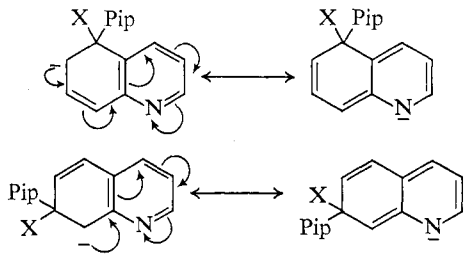
The following Section discusses the mechanistic aspects of nucleophilic displacement of halogen from haloquinolines by the addition–elimination process. Reactions involving aryne intermediates, and the synthetic implications of halogen replacement, are discussed in later Sections.

b. MECHANISTIC ASPECTS. Most of the mechanistic work on the nucleophilic displacement of halogen, not only from haloquinolines but also halogenated heterocycles in general, has been carried out over the past two decades, and an excellent review of the subject is available.[1257]

Knight and his co-workers,[1235] during some early work on the ultraviolet spectra of fluoroquinolines, observed that the spectrum of 2-fluoroquinoline in acid solution differs markedly from the spectra of the other isomeric fluoroquinolines. Subsequent studies[1258] indicate that, under the conditions employed, 2-fluoroquinoline undergoes rapid hydrolysis to 2-quinolone, and the rate of hydrolysis is found to increase with increasing acid concentration.

Early kinetic studies on the reactions of haloheterocycles with nucleophiles were carried out by Young and Amstutz.[622] They studied the rate of reaction of several chloro- and bromo-heterocycles, including 2-bromo- and 2-chloro-quinoline, with piperidine at various temperatures under pseudo-first-order conditions (i.e. in a large excess of piperidine). They found that 2-haloquinolines are more susceptible to nucleophilic displacement than 2-halopyridines and observed activation energies for the reaction of 2-bromopyridine and 2-bromoquinoline of 16.4 and 13.8 kcal/mol, respectively. The enhanced reactivity of haloquinolines over the corresponding halopyridines is explained in a later paper[1259] on the basis of the stability of the transition states. Fusion of a benzene ring to the heterocyclic nucleus allows the formation of quinonoid transition states which partially compensate for the loss of aromaticity experienced in going through to the transition state; such compensation is not possible with the parent heterocycle. In fact, experiment has shown that the activation energy for nucleophilic substitution of halogen is lowered by 3–4 kcal in going from 2-chloropyridine to 2-chloroquinoline.

Subsequently Amstutz and his co-workers[841] investigated the kinetics of the reaction of 3-, 5-, 6-, 7-, and 8-bromoquinoline, and also 4-chloroquinoline, with piperidine at temperatures of around 200 °C. The possibility of elimination–addition reactions taking place was considered but discarded on the basis of product analysis, which in each case (possibly with the exception of the 3-bromo-compound) revealed the formation of only the piperidino-compound expected from a addition–elimination process. As expected, 2- and 4-chloroquinoline show the lowest activation energies (13.8 and 16.1 kcal/mol, respectively), and the figures emphasize the greater reactivity of the 2-chloro-compound. Consideration of the transition states for the other haloquinolines predicts that resonance stabilization involving the ring-nitrogen is possible only for the 5- and 7-halo-compounds (Scheme 54). Consequently greater reactivity is



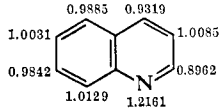
SCHEME 54

to be expected for these compounds over that of the 6- and 8-halogenated isomers. Experimental determination of the activation energies shows this to be the case (see Table 31).

TABLE 31. Activation Energy (kcal/mol) for Reaction of Haloquinolines with Piperidine[841]

Substituent	Activation energy	Substituent	Activation energy
2-Cl	13.8 ± 0.4	6-Br	23.9 ± 0.7
3-Br	21.6 ± 0.9	7-Br	21.6 ± 0.7
4-Cl	16.1 ± 1.1	8-Br	23.3 ± 0.7
5-Br	22.0 ± 0.7		

If we assume an addition–elimination process, the inductive effect of the ring-nitrogen in the 3-isomer is presumably still large enough to influence the rate of replacement of the halogen atom. The determined energies of activation reflect the reactivity of the halogen expected from electron-density measurements on quinoline (**575**).[1260]



575

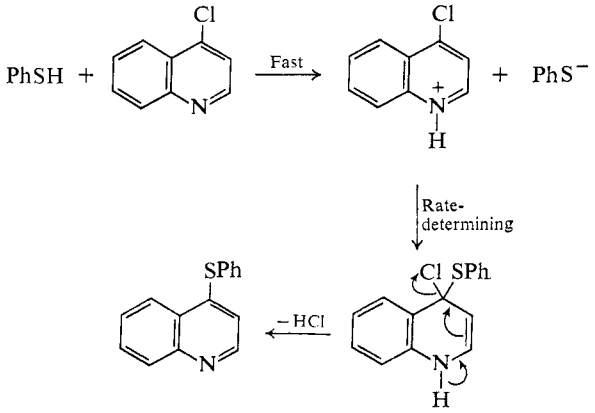
As expected, halogen situated on the carbocyclic portion of the quinoline nucleus and having an *ortho-* or *para*-electron-withdrawing group is activated towards nucleophilic displacement. Activation energies of 13.3 and 14.4 kcal/mol are reported[1261] for the reaction of 8-chloro-5-nitroquinoline with methanolic ammonia and ethanolic piperidine, respectively.

Brower[1262] studied the reaction of 2-, 6-, and 8-bromoquinoline with piperidine under high pressures (up to 1300 atmospheres) and measured the volume changes of activation. He found that the reactions are accelerated by increasing the pressure and obtained[1263] similar results for the reaction of haloquinolines with aqueous piperidine and with various alkoxides in their corresponding alcohols.

Chapman and Russell-Hill[1264–1266] have carried out nucleophilic displacement reactions on haloheterocycles in an attempt to correlate qualitatively the reactivity of aromatic systems with theoretical concepts of nucleophilic substitution. 2- and 4-Chloroquinoline were treated with piperidine and ethoxide ion at temperatures of 80–110 °C. As expected, 2-chloroquinoline displayed a larger rate constant ($k = 4.86 \pm 0.03 \times 10^{-4}$ l mol^{-1} s^{-1}) than the 4-chloro-isomer ($k = 2.62 \pm 0.02 \times 10^{-4}$ l mol^{-1} s^{-1}) when treated with ethoxide ion. It was demonstrated that the reaction between 4-chloroquinoline and piperidine in dilute solution shows an increase in rate as the reaction proceeds. No such increase is observed in an excess of piperidine or with 2-chloroquinoline. Explanation of these results lies in the fact that 4-chloroquinoline is a stronger base than the 2-chloro-isomer and can compete successfully with the attacking base for the liberated protons. Hence, acid-catalysis occurs in the former, but not in the latter, case.

A great number of kinetic studies on haloquinolines have been carried out by Illuminati and his co-workers. Early investigations[1267, 1268] by these workers were concerned with the reaction of 4,7-dichloroquinoline with *p*-thiocresol in aprotic solvents for which they found evidence of autocatalytic effects. Subsequent studies[1269] demonstrated that *p*-methylthiophenoxide ion reacts faster than methoxide ion with 4-chloroquinoline; with 2-chloroquinoline, however, the rates are reversed. In contrast, phenoxide ion reacts more slowly than methoxide ion with both isomers. A

more detailed study[1270] of these reactions reveals that *p*-thiocresol reacts very rapidly with 4-chloroquinoline in methanol solution. In fact, the reaction is faster than that observed with either *p*-methylthiophenoxide anion or with 1-methyl-4-chloroquinolinium ion. To explain this anomalous reaction a process (Scheme 55) involving fast



SCHEME 55

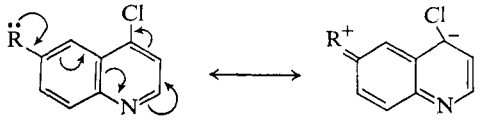
acid–base equilibration, followed by nucleophilic displacement of chloride ion from the 4-chloroquinolinium moiety by sulphide ion, was proposed.

Observations by Illuminati and his co-workers indicate that the nucleophilic lability of the 4-chloro-substituent is affected by the nature of the substituents at the 6- and 7-positions of the quinoline ring. They subsequently[1232, 1271, 1272] investigated the effect of substituents in the carbocyclic ring on the rate of reaction of 4-chloroquinolines with various nucleophiles. Methoxydechlorination* of 6- and 7-substituted 4-chloroquinolines was chosen for preliminary study since second-order kinetics are observed, free from any autocatalytic interference. The results[1272] indicate that for a 6-substituted 4-chloroquinoline the rate of methoxydechlorination varies by a factor of 1.5×10^4 on going from a strongly electron-donating (e.g. Me_2N) to a strongly electron-withdrawing (e.g. NO_2) substituent. Also in any pair of 6- and 7-isomers, the 6-isomer always displays a slower reaction (i.e. smaller rate constant and higher activation energy) than the 7-isomer.

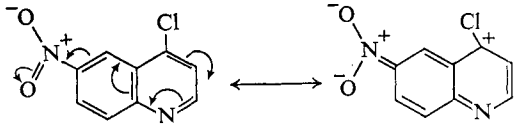
The results are in agreement with known electronic effects of the substituent groups, as it is to be expected that electron-donating substituents at the 6-position will exert a more deactivating conjugative effect on the chlorine at the 4-position than the same groups will in the 7-position. This trend, however, is reversed with the strongly electron-withdrawing nitro-group,[1272, 1274] since the 6-nitro-group can more efficiently activate the 4-position towards nucleophilic attack. These effects are illustrated in Schemes 56 and 57, respectively.

Illuminati and his co-workers[1234] pursued these ideas and have shown that the effect of substituents at the 6- and 7-positions on the rate of methoxydechlorination of 4-chloroquinolines can be correlated successfully with the Hammett equation, and a reaction constant (ρ) of 5.82 is obtained. Positive σ-values are displayed by

* This system of nomenclature is that suggested by Bunnett;[1273] the attacking nucleophile and the leaving group are grouped in one term and hence methoxydechlorination represents the displacement of a chloro-substituent by methoxide.



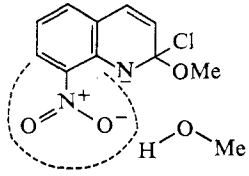
SCHEME 56



SCHEME 57

halo- and nitro-substituents at both the 6- and the 7-position, while electron-donating groups, e.g. alkoxy-, alkyl, dimethylamino-, and alkylthio-, show negative σ-values. In the case of the halogens it appears that the inductive effect is of more importance than the mesomeric effect.

The effects of substituents situated at other positions of the quinoline ring on the rate of methoxydechlorination of 2- and 4-chloroquinoline have also been studied. 4-Chloro-5-nitroquinoline reacts[1274] more slowly with methoxide ion at 30 °C than the corresponding 7-nitro-compound. Since the polar effects of the nitro-group, at either of the two positions, on the reacting carbon centre are of the same order as are the activation energies of the two reactions (18.9 and 19.4 kcal/mol, respectively), the observed decrease in rate is thought to be a consequence of steric interactions, between the 5- and the 4-position, in the transition state. Evidence for this is seen in the entropy of activation values; that of the 5-nitro-isomer is some seven units larger than for the 7-nitro-compound, indicating a more hindered transition state in the former case. The effects of substituents at the 8-position on the rate of methoxydechlorination of 2-chloroquinoline have also been investigated.[639] Comparison of the rate of methoxydechlorination of a series of 6- and 8-substituted 2-chloroquinolines reveals a faster reaction for the former compounds. Since substituents at the 6- and 8-positions are expected to exert similar polar effects on the reacting carbon centre, steric effects are held to be responsible for the decrease in reaction rate of the 8-substituted isomers. Illuminati and his co-workers propose that the bulky 8-substituent prevents efficient solvation of the transition state (see **576**) and hence lowers



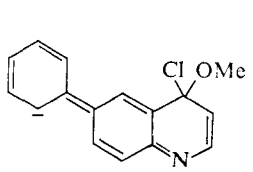
576

its stability relative to the transition state expected for the 6-nitro-compound.

Not surprisingly, the effect of substituents at the 6- and 7-positions on the rate of methoxydechlorination of 2-chloroquinoline parallels that observed for the 4-chloro-compounds.[1275] The activating effect of the substituents decreases in the order 6-NO_2 > 7-NO_2 > 7-Cl > 7-Br > 6-Cl > 6-H > 7-Me > 7-MeO. As before, an electron-withdrawing group at the 6-position greatly enhances the rate, while an electron-donating group at the 7-position exerts an opposite effect.

Having investigated the effect of substituents in the carbocyclic ring on the rate of methoxydechlorination, Illuminati and his co-workers turned their attention to the effect of substituents at the 2-position (i.e. the *meta*-position) on the rate of chloride displacement from 4-chloroquinolines, and vice versa, i.e. the reactivity of 4-substituted 2-chloroquinolines.

In a preliminary publication[1276] the reactivity of 4-chloro-2-(trifluoromethyl)-, 2-phenyl-, and 2-(dimethylamino)-quinoline was studied. As expected, only the electron-withdrawing trifluoromethyl group brings about an acceleration of methoxydechlorination. The phenyl group is of interest in that it causes deceleration of the reaction when at the 2-position but enhances the rate when at the 6-position. Stabilization of the transition state in the latter reaction is possible (**577**), whereas in the former reaction adverse conjugative effects (e.g. **578**) hinder substitution.



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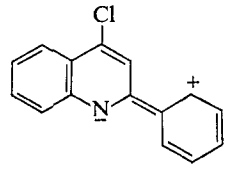
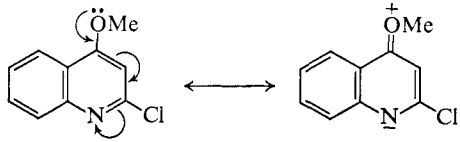


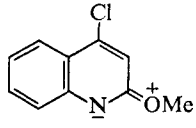
578

The rate of methoxydechlorination of 4-chlorocinnoline, which may be considered as a *meta*-aza-substituted 4-chloroquinoline, was also measured and found to be faster than the corresponding reaction with 4-chloroquinoline by a factor of 10^3. On this basis Illuminati and his co-workers were able to draw up an order of influence of *meta*-substituents on the rate of methoxydechlorination of 4-chloroquinoline of the form, 2-aza > 2-CF_3 > 2-H > 2-Ph > 2-Me_2N. Similarly, comparison of the rate of methoxydechlorination of 2-chloroquinoline reveals an order for 4-substituents of 4-aza > 4-CF_3 > 4-Ac > 4-H.[1275] Again it is observed that introduction of an aza-group at the *meta*- (i.e. 2-) position enhances the rate of reaction far more than the introduction of a strong electron-withdrawing substituent. In fact, 2-chloroquinoxaline (4-aza-2-chloroquinoline) is found to react three times faster with methoxide ion (k/k_0 2261) than 2-chloro-6-nitroquinoline (k/k_0 807.6) (where k = rate of methoxydechlorination; k_0 = rate of methoxydechlorination of 2-chloroquinoline).

A more detailed study[394] of the effect of "*meta*"-substituents on the rates of methoxydechlorination of 2- and 4-chloroquinoline confirmed the previous results but revealed some anomalous behaviour. Most striking is the surprisingly high deactivating influence of alkoxy-groups, particularly when situated at the 2-position (k/k_0 0.0579). The authors suggest that this is due to mesomeric interactions in the ground-state structures (**579–581**) rather than in the transition state, and that it



579 **580**

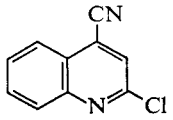


581

parallels the situation observed with the 2-phenyl group discussed above. Such structures indicate that the electron-accepting capacity of the chloroquinoline during the rate-determining step is reduced, and hence a marked decrease in rate is observed.

Halogen substituents show a rate-enhancing effect on the methoxydechlorination process, indicative of their strong electron-withdrawing tendencies.

Kinetic measurements[394] on ethoxycarbonyl-, methoxycarbonyl- and cyano-substituted 2- and 4-chloroquinoline proved troublesome. Irreproducible results with the chloroquinolinecarboxylic esters are attributed to competing attack by methoxide at the ester function. The chloro-cyano-compound (**582**) behaves normally, the cyano-group showing the expected rate-enhancing effect, whereas the isomeric



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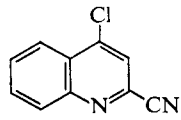

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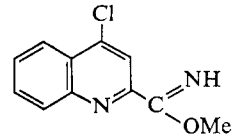


584

cyano-compound (**583**) shows an abnormally low reaction rate. Subsequent investigation reveals that competing imido-ester (**584**) formation[1277] is responsible.

A kinetic study[394, 1278] on the reaction of 2,4-dichloroquinoline with sodium methoxide in methanol reveals that the 4-chloro-substituent is slightly the more reactive. At 75 °C the partial rate constants for the 4-chloro- and 2-chloro-substituents are 74.7 and 39.3×10^{-4} l mol^{-1} s^{-1}, respectively, a factor of 1.9 : 1. It appears, therefore, that a *meta*-halogen substituent brings about a reversal in the previously reported[1266] order of reactivity of 2- and 4-chloroquinolines towards alkoxide ion.

Preliminary studies on the piperidinodechlorination of 2- and 4-chloroquinolines were carried out by Chapman *et al.*[1266] and by Bailey.[1279] Bailey obtained results substantially the same as those reported above for the methoxydechlorination reactions; i.e. electron-releasing groups depress the rate of substitution, while electron-withdrawing substituents increase the rate. Also, as before, in the case of 4-chloro-8-methylquinoline, steric factors appear to be operative in retarding the reaction.

Illuminati and his co-workers have also carried out a detailed study of the piperidinolysis of 2- and 4-chloroquinolines. Contrary to the methoxydechlorinations discussed above, they found[1280] that in methanol solution piperidinodechlorinations are subject to autocatalysis, a point noted earlier by Chapman and Russell–Hill.[1266] However, after allowance for this fact, a marked solvent-dependence of the reaction rates was observed. Thus the reactivity of 4-chloroquinoline with piperidine in methanol is some 1100 times that in toluene. The reactivity of 2-chloroquinoline, however, varies only by a factor of six on going from toluene to methanol solution. It, therefore, appears that, whereas 2- and 4-chloroquinoline are of comparable reactivity towards piperidine in methanol, under solvolytic conditions 2-chloroquinoline is by far the more reactive. The higher reactivity of the 2-chloro-substituent is a consequence of the greater sensitivity of this position to solvent effects. A "built-in" solvation process is thought to be in operation similar to that observed[1281] for the reaction of 2,4-dichloronitrobenzene with various amines.

Later work by Illuminati and Marino[1282] shows that, in contrast to 4-chloroquinoline, nucleophilic replacement of the 4-chloro-group in 2,4-dichloroquinoline by an amine is not subject to autocatalysis. This result is directly attributed to the diminished basicity of 2,4-dichloroquinoline brought about by the electron-withdrawing 2-chloro-substituent. Reaction of 2,4-dichloroquinoline with dimethylamine in methanol or toluene reveals a similar trend to that observed with piperidine, i.e. going from methanol to toluene produces a 250-fold decrease in the rate of methylaminodechlorination at the 4-position, but only an 8-fold decrease in the rate of the

corresponding reaction at the 2-position. Over a temperature range of 75–99.5 °C in methanol solution, the ratio of 4-chloro-2-(dimethylamino)quinoline to 2-chloro-4-(dimethylamino)quinoline produced is approximately 3 : 7. In toluene solution, however, over a similar temperature range, the overall rate of reaction is much slower than in methanol ($k_{99.5} = 0.780 \times 10^4$ compared with 18.2×10^4 l mol^{-1} s^{-1}), whereas the product ratio is now 19 : 1. Partial rate factors of k_α 0.737×10^4 and k_γ 0.0429×10^4 l mol^{-1} s^{-1} are observed for reaction in toluene, whereas in methanol solution values of k_α 6.24×10^4 and k_γ 11.9×10^4 l mol^{-1} s^{-1} are recorded. The figures in both cases apply to reactions carried out at 99.5 °C.

Studies[1283, 1284] on the piperidinodechlorination of a whole series of substituted 2- and 4-chloroquinolines reveal that, in all cases, under solvolytic conditions, the 2-chloro-isomer is the more reactive. More detailed investigations[1285] on the effect of solvent on the piperidinodechlorination of 2- and 4-chloroquinoline indicate that 2-chloroquinolines are not subject to autocatalytic effects unless there is a strongly electron-donating substituent (e.g. EtO) at the 4-position. In contrast, 4-chloroquinolines are prone to autocatalytic effects unless there is present a strong electron-withdrawing group (e.g. CF_3) at the 2-position, which, by virtue of its electron-withdrawing effect, decreases the basicity of the quinoline system such that protonation, and hence autocatalysis, no longer occur.

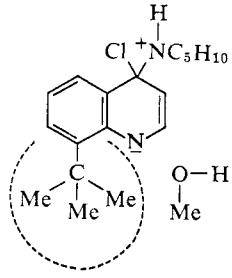
The effect of solvent, particularly the substantial increase in reaction rate brought about by dimethyl sulphoxide, has been discussed in some detail.[1284] A slight base-catalysis is detected for both chloro-compounds with piperidine under solvolytic conditions.[1285]

Both Illuminati *et al.*[639] and Bailey,[1279] as mentioned earlier, have recorded instances of steric retardation during the piperidino- and the methoxy-dechlorination of 2-chloroquinolines substituted at the 8-position. More recently, however, Illuminati and his co-workers[1286] have observed a remarkable reaction in which steric factors are believed to exert a decelerating influence on the rate of halogen replacement of an 8-substituted 4-chloroquinoline. The rates of piperidinodechlorination of 4-chloro-6-methyl- and 6-(*tert*-butyl)-4-chloro-quinoline in a series of solvents (toluene, piperidine, dimethyl sulphoxide, and methanol) were compared with those obtained for the corresponding reaction of 4-chloro-8-methyl- and 8-(*tert*-butyl)-4-chloro-quinoline in the same solvents. As expected, alkyl groups at the 6- and 8-position exert similar polar effects at the reaction centre, and in all the solvents used the ratio of the rate constants for the 6-alkyl-substituted quinolines remained virtually constant. Similarly for the 8-alkyl-4-chloroquinolines in toluene, piperidine, or dimethyl sulphoxide solution, a ratio ($k_{Me}/k_{t\text{-}Bu}$) of 2.3–3.1 is observed. However, in methanol solution the methyl and *tert*-butyl derivatives show a relative reaction rate of 24.5 : 1, the main contributor to which is the low reactivity of 8-(*tert*-butyl)-4-chloroquinoline. This decrease in reactivity is attributed to steric interactions between the bulky *tert*-butyl group and the ring-nitrogen, which decrease the efficiency of solvation of the transition state as represented in diagram (**585**) [cf. (**576**)].

A similar steric inhibition of solvation is observed during the methoxydechlorination of 8-(*tert*-butyl)-4-chloroquinoline.

An examination has been carried out to determine whether kinetic hydrogen isotope effects are operative during the piperidinodehalogenation of 2- and 4-haloquinolines.[1287] Isotope effects were found to be absent or negligible with 2- and 4-chloroquinoline and with 2-fluoroquinoline. However, a small positive isotope effect is observed with 4-fluoroquinoline, and this is taken to indicate that proton-transfer from the σ-adduct (**586**) to the reaction medium, in this case piperidine, is involved in the rate-determining step, as illustrated in Scheme 58. This result implies the possibility of base-catalysis, as noted previously.[1284] The fact that isotope

effects are observed only with the fluoro-group suggests a mechanism in which carbon–halogen bond-breakage is concerted with N—H bond cleavage.



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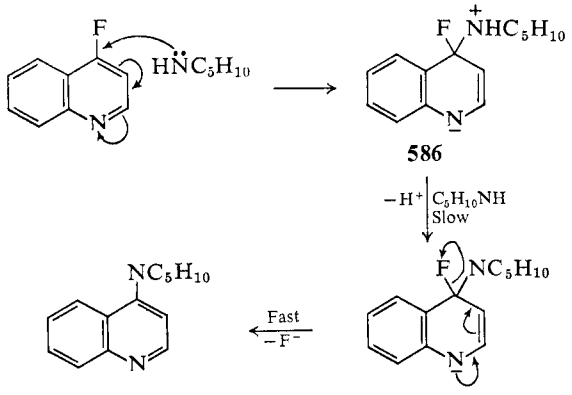
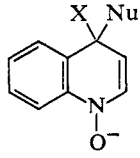


SCHEME 58

Illuminati and his co-workers[677] have determined the relative ease of displacement of chlorine and fluorine from a series of 2- and 4-haloquinolines by methoxide ion in methanol, and by piperidine in a variety of solvents. In all the reactions studied the rate of fluorine displacement is greater than that of chlorine. The results are consistent with a substitution process in which bond formation rather than bond breakage is important in determining the reaction rate, and they are in accord with current theories[1288] of the mechanism of aromatic nucleophilic substitution.

The rate constants for the reaction of 2-chloroquinoline with a series of primary and secondary amines in dimethyl sulphoxide solution have been determined[1289, 1290] and are found to decrease in the order pyrrolidine > piperidine > morpholine > benzylamine.

Comparison of the rates of piperidinodechlorination of 4-haloquinolines and their *N*-oxides reveals that the latter react more than ten times faster than the former,[731] indicating efficient stabilization of the transition state (**587**) by the *N*-oxide function. The *N*-oxide group is estimated to be of greater activating influence than a nitro group, and the observed order (Br > Cl > I) of reactivity of the haloquinolines and their *N*-oxides is again compatible with the accepted theories of aromatic nucleophilic substitution.



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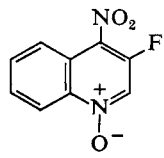


588

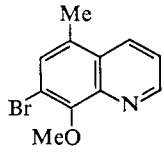
Comparison of the lability of the nitro- and the fluoro-group in 3-fluoro-4-nitroquinoline *N*-oxide (**588**) towards various nucleophiles reveals[684] that the 3-fluoro-group is more easily replaced, except under acid conditions where the former group is the more labile. With bases (e.g. aniline) the *N*-oxide reacts to give 3-anilino-4-nitroquinoline *N*-oxide, whereas with aqueous hydrochloric acid 4-chloro-3-fluoroquinoline *N*-oxide is formed. The relative rates of fluorine replacement from the *N*-oxide and from 1-fluoro-2,4-dinitrobenzene by glycine at pH 7.51 are quoted as 1.4×10^{-5} and 4.3×10^{-5} l mol^{-1} s^{-1}, respectively.

In conclusion it may be said that rigid predictions regarding the relative reactivity of 2- and 4-haloquinolines towards nucleophilic displacement are to be avoided. For example, Illuminati and his co-workers[1283] have shown that the difference in reactivity of 2-chloro- (most reactive) and 4-chloro-quinoline decreases as the electron-donating effect of a *meta*-substituent (i.e. at the 4- or 2-position, respectively) decreases. The reasons for this phenomenon are discussed but are by no means clear. Also, as these workers have emphasized, the reactivity of haloquinolines towards nucleophilic replacement depends on many factors, viz. solvent, temperature, nature of the attacking nucleophile, and position and electronic character of other substituents, as well as acid- and base-catalysis, autocatalysis, and steric effects.

c. Displacement by Nucleophilic Carbon. (*i*) *Cyanide Ion.* Jansen and Wibaut[1291] have shown that 2-bromoquinoline with potassium cyanide in aqueous alcohol at 200 °C gives 2-quinolone rather than the 2-cyano-compound. The replacement also fails with a mixture of copper and potassium cyanides. However, by employing the method used by Craig[1292] for the synthesis of 2-cyanopyridine from 2-bromopyridine, Jansen and Wibaut were able to prepare both 2-cyano- (63%) and 3-cyano-quinoline (60%) from the respective bromo-compounds; this method involves heating the bromoquinoline with copper cyanide in a fractionating flask until reaction occurs, whereupon the product is rapidly removed by distillation. As expected, 3-bromoquinoline[295, 1291] requires more prolonged heating than the 2-bromo-compound in order to bring about reaction. Gilman and Spatz[1293] were subsequently able to prepare 3-cyanoquinoline in 90% yield by using a slight modification of the Craig procedure.

Rubtsov[515] found that 2-chloro-6-methoxyquinoline with cuprous cyanide in boiling pyridine gives 2-cyano-6-methoxyquinoline; with sodium cyanide in methanol at 200 °C, however, 2,6-dimethoxyquinoline is the sole product. 4-Bromoquinoline, on being heated with cuprous cyanide, yields 4-cyanoquinoline,[1294] whereas 4-chloroquinoline and its *N*-oxide fail to react with either potassium cyanide in ethanol or with cuprous cyanide alone, or in pyridine or acetonitrile solution. 2-Chloroquinoline reacts with cuprous cyanide in boiling *N*-methylpyrrolidone to yield 2-cyanoquinoline (42%).[1295] The authors (Newman and Boden) advocate the use of *N*-methylpyrrolidone as a solvent for aryl and heteroaryl cyanide formation, since not only is it a useful medium for carrying out nucleophilic displacement reactions, but it is also a good solvent for cuprous cyanide. A whole series of 4-cyano-2-(trifluoromethyl)quinolines have been prepared, from the corresponding 4-chloro-compounds, by using this method.[627]

Other aprotic solvents have found use in the preparation of cyanoquinolines. For example, cupric cyanide in boiling dimethylformamide in the presence of sodium cyanide converts 3-bromoquinoline into 3-cyanoquinoline in 90% yield.[109] 3-Bromo-6-methoxyquinoline reacts similarly, and 3-bromo-6-chloroquinoline gives, as sole product, 6-chloro-3-cyanoquinoline, albeit in low yield (10%). Surprisingly, Kapoor and Gopalchari[156] were able to cyanodebrominate 7-bromo-8-methoxy-5-methylquinoline (**589**) using cuprous cyanide in boiling dry dimethylformamide. Bromine



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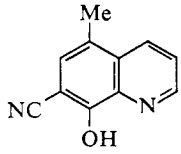

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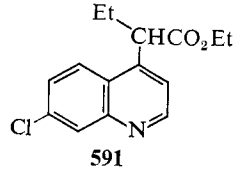
replacement is, however, accompanied by demethylation and the 8-hydroxyquinoline (**590**) is isolated in 41% yield. Demethylation appears to be subsequent to cyanide formation since 7-bromo-8-hydroxy-5-methylquinoline under identical reaction conditions yields only a trace of the 7-cyano-compound. In contrast, 8-chloro-6-methoxyquinoline yields 8-cyano-6-methoxyquinoline (43%) when fused with cuprous cyanide.[692]

(ii) *Carbanions.* An early report[1291] indicates that 2- and 3-bromoquinoline fail to react with the anion of diethyl malonate, and attempts[1294] to cause 4-chloro- and 4-bromo-quinoline and their *N*-oxides to react with the anions of diethyl malonate, ethyl acetoacetate, or malonodinitrile in *tert*-butyl alcohol were also abortive. In each case starting material and unidentifiable resinous products were obtained.

Elderfield and Serlin[1296] report that 4,7-dichloroquinoline and the sodium salt of diethyl ethylmalonate in boiling dioxan give starting material (69%), the butanoate (**591**) (16%), and 7-chloro-4-ethoxyquinoline (14%); the likely mode of formation of these products, is discussed.

In a similar manner 2-chloro-4-methylquinoline reacts[1002] with the sodium salt of diethyl malonate in absolute ethanol to give 2-ethoxy-4-methylquinoline as the sole product.



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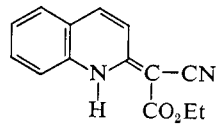

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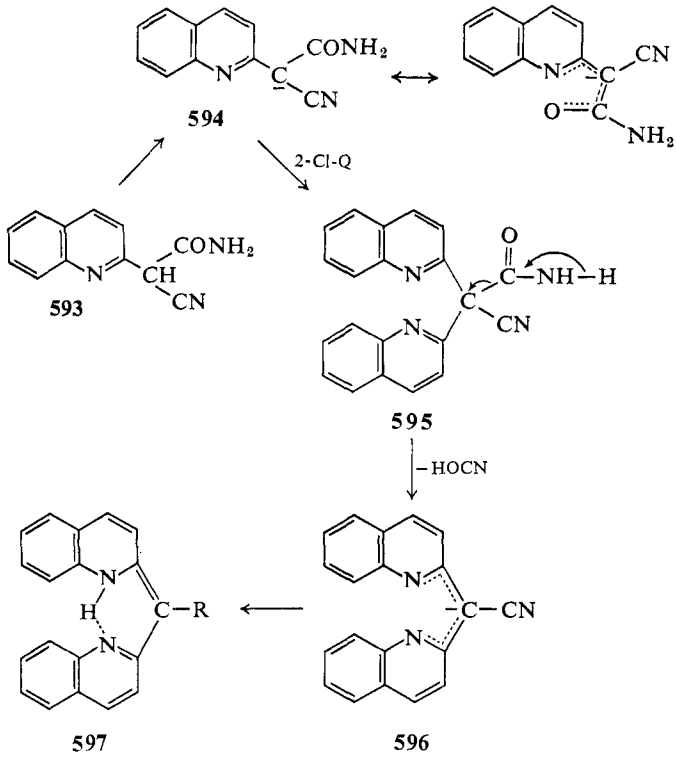
Mizuno and his co-workers[1297] have carried out a comprehensive survey of the reactivity of a wide range of halo-heterocycles, including 2-chloro- and 2-chloro-4-methylquinoline, with a series of carbanionic species. The order of ease of condensation of the reactive methylene compounds is found to decrease in the order benzyl cyanide > ethyl cyanoacetate > diethyl malonate > malonodinitrile > ethyl phenylacetate > ethyl acetoacetate > diphenylmethane. The chloroquinolines were found to react only with the most reactive carbanion source, i.e. benzyl cyanide. Bunnett and Bassett[1298] similarly report no reaction between 2-chloro-4-methylquinoline and the

sodium salt of ethyl acetoacetate in boiling tetrahydrofuran. Other workers,[1299] however, have found that ethyl cyanoacetate will react with 2-chloroquinoline in dimethylformamide solution at 120 °C, under nitrogen and in the presence of sodium hydride, to give the α-(2-quinolyl)-α-cyanoacetate derivative, the ultraviolet and infrared spectra of which favour tautomer (**592**). *tert*-Butyl cyanoacetate and malonodinitrile react similarly, whereas an abnormal reaction is observed with cyanoacetamide (see Scheme 59). Initial condensation to give the cyano-amide (**593**) proceeds normally. The amide, however, in the presence of sodium hydride yields the highly resonance-stabilized carbanion (**594**) which reacts further with 2-chloroquinoline to give the diquinolyl compound (**595**). This new cyano-amide then suffers



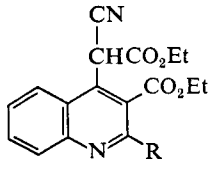
SCHEME 59

loss of HOCN to give a second resonance-stabilized carbanion (**596**), which on acidification of the reaction mixture yields the product as the hydrogen-bonded tautomer (**597**; R = CN) (34%). Hydrolysis and decarboxylation yield the known diquinolylmethane (**597**; R = H).

The diquinolyl cyanide (**597**; R = CN) has also been prepared[1300] (in 8% yield) by condensing 2-chloroquinoline with acetonitrile in boiling toluene in the presence of sodamide.

Ethyl 4-chloro- and ethyl 4-chloro-2-methyl-quinoline-3-carboxylate react with ethyl cyanoacetate and sodium hydride in dimethylformamide to give the cyanoacetates (**598**; R = H and Me, respectively) in high yield (62.5% and 81%).[520]

2-Iodoquinoline fails to react with ethyl cyanoacetate and sodium amide in dry benzene, whereas condensation occurs readily in dimethyl sulphoxide solution in the presence of potassium cyanide.[1301]



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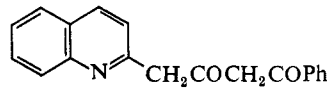

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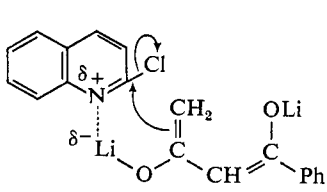
2-Chloroquinoline has been condensed with the disodium salt of benzoylacetone in liquid ammonia at -33 °C to give a moderate yield of the required diketone (**599**).[1302] The authors, on the presumption that the reaction is of the classical S_N2 type, argued that use of the dilithio-derivative may improve the yield of diketone since co-ordination with the lithium, as indicated (**600**), should increase the nucleophilic lability of the 2-chloro-substituent. An increase in yield of diketone is in fact observed



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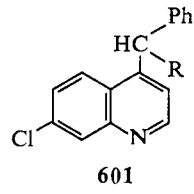
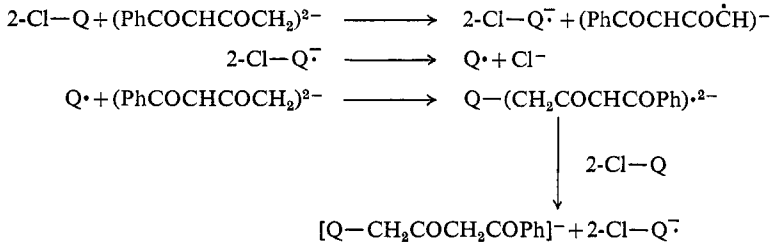


601

on going from the potassium salt (17%) to the lithium salt (71%), but the authors find that the yield of diketone drops markedly in the presence of radical-inhibitors. For example, the dilithio-salt in the presence of tetraphenylhydrazine yields only 2% of the diketone, while in the presence of oxygen the yield drops to $<1\%$. In order to explain these curious results a radical-chain mechanism SR_N1 [1303] (Scheme 60) is proposed rather, than as first expected, a polar S_N2-type displacement.*

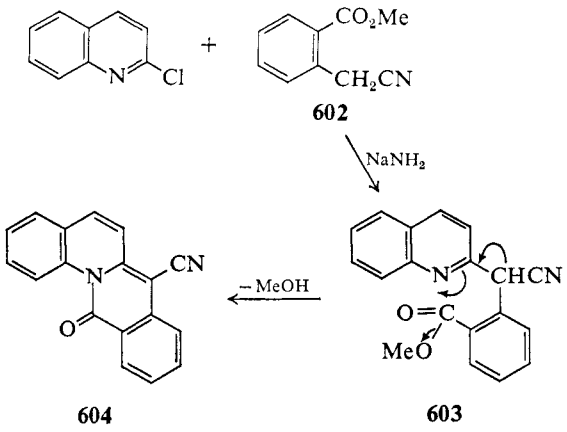


SCHEME 60

* Further work in this area indicates that the reaction of lithioacetone with 2-chloroquinoline in liquid ammonia is subject to photostimulation and entrainment,[2040] whereas secondary and tertiary lithium enolates fail to react by the expected $S_{R_N}1$ mechanism.[2041] Potassium enolates, however, react smoothly by this mechanism when photostimulated.

4,7-Dichloroquinoline in the presence of two molar equivalents of sodium amide and phenyl acetonitrile reacts to give α-(7-chloro-4-quinolyl)-α-phenylacetonitrile (**601**; R = CN) which is precipitated from the reaction mixture as the red sodium salt.[1304, 1305] In the presence of one equivalent of the reagents the acetonitrile is obtained in only 50% yield. Apparently the quinolylacetonitrile (**601**; R = CN) competes successfully with the less acidic phenylacetonitrile for the base, and hence only partial reaction occurs. Attempts to prepare the quinolyl ester (**601**; R = CO_2Et) in a like manner were fraught with difficulties. For example, 4,7-dichloroquinoline with ethyl phenylacetate and sodamide in benzene at room temperature gives the phenyl acetamide (**601**; R = $CONH_2$) (20%), the desired ester (**601**; R = CO_2Et) (1%), phenylacetamide, and as major product, ethyl α,γ-diphenylacetoacetate. The last of these products arises by Claisen condensation of ethyl phenylacetate with itself, while the amide is formed by aminolysis of the ester (**601**; R = CO_2Et) by sodamide. Replacement of sodamide by sodium hydride, however, results in the formation of only the diphenylacetoacetate (75%). Eventually a 10% yield of ester (**601**; R = CO_2Et) was realized by allowing a dilute benzene solution of ethyl phenylacetate to drip slowly into a boiling benzene solution of 4,7-dichloroquinoline containing an excess of sodium hydride. 4,7-Dichloroquinoline readily condenses with 4-(diethylamino)-2-phenylbutyronitrile in the presence of sodamide;[1304, 1306] phenyl-lithium in ether and sodium hydride in boiling benzene are also successful as condensing agents. A similar series of reactions to those outlined above were also carried out on 4,5-dichloroquinoline.[1304, 1305]

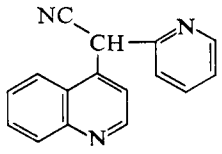
Ochiai and Suzuki[1307] treated 2-chloroquinoline with *o*-(methoxycarbonyl)benzyl cyanide (**602**) in the presence of sodium amide. Initial condensation to give the expected α-(2-quinolyl)-α-phenylacetonitrile (**603**) is followed by intramolecular



cyclization with loss of methanol to give the dibenzoquinolizinone (**604**) with 2-methoxyquinoline as a by-product. An optimum yield (43%) of the former was achieved by using a 1 : 1.4 : 5 mixture of nitrile, 2-chloroquinoline, and sodium amide in toluene solution.

α-(2-Pyridyl)acetonitrile in benzene solution containing sodamide condenses readily with 4-chloroquinoline or its *N*-oxide to give the corresponding α-(4-quinolyl)-α-(2-pyridyl)acetonitriles, e.g. (**605**).[766]

Scheibe and Rossner[1308] have found that tri-(2-quinolyl)methane can be obtained by fusing 2-chloroquinoline with 2-methylquinoline. Later work by Scheibe[1309]



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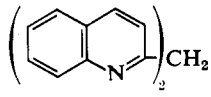
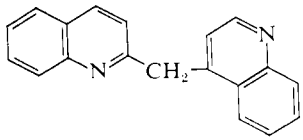


606

indicates that if the reaction is carried out at 180–200 °C in the presence of 0.5–1.0 molar excess of the 2-methyl compound, then di-(2-quinolyl)methane (**606**) is formed; subsequently[1310] the diquinolylmethane was obtained in 70% yield. More recently Scheibe and Friedrich[1311] have condensed 2-chloroquinoline with 9-methylphenanthridine and obtained only di-(9-phenanthridinyl)methane, whereas 2-methylquinoline condenses successfully with 4-chloroquinoline to yield the diquinolylmethane (**607**).



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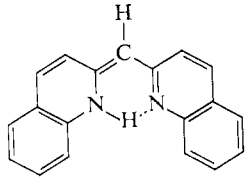

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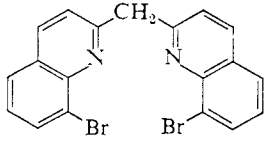
In order to account for the red colour of the diquinolylmethane (**606**) Scheibe[1309] suggested an equilibrium between the colourless alkane form (**606**) and its vinyl tautomer for which the intramolecularly hydrogen-bonded structure (**608**) was proposed.[1311]

2-Chloroquinoline condenses in a similar manner with 8-bromo-2-methylquinoline to give a mixture of the symmetrical dibromo-compound (**609**) and the unsymmetrical monobromo-compound (**610**).[926] X-ray crystallographic measurements demonstrate that the monobromo-compound exists in the *cis,cis*-form (**610**), and that this



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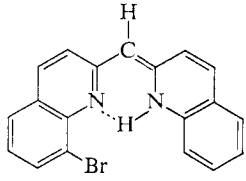

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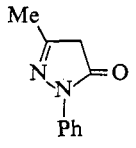
configuration is stabilized by intramolecular hydrogen bonding. However, later X-ray studies[1312] of the dibromo-compound (**609**) indicate that this molecule is non-planar with a dihedral angle of 80° between the quinoline rings. The red colour exhibited by this compound is probably due to it being a mixture of the di-*cis*-form, analogous to (**610**), and a non-planar isomer.

Meyer and Bouchet[1313] have condensed 4-chloro-2-methylquinoline with a variety of heterocyclic systems containing a reactive methylene group. For example,

3-methyl-1-phenyl-5-pyrazolone (**611**) yields a condensation product which, on account of its deep-yellow colour, is formulated as the quinonoid species (**612**). The reactions are carried out in a mixture of pyridine and acetic acid, or acetic anhydride,



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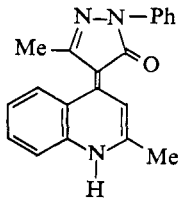
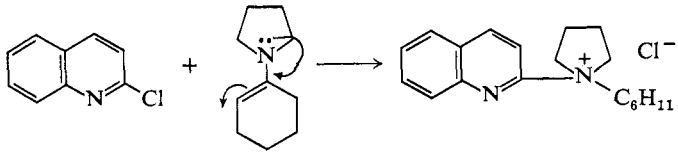


612

or, in some cases, in pyridine alone. Barbituric acid, rhodanine, and thiohydantoin fail to react.

(iii) *Miscellaneous.* The first attempts to heteroarylate enamines appear to have been carried out by Kuehne.[1314] He found that enamines react readily at the β-carbon atom with 2-chloro-5-nitro- and 4-chloro-3-nitro-pyridine in the expected manner. However, with the less reactive 2-chloroquinoline, *N*- rather than *C*-heteroarylation is observed (Scheme 61).



SCHEME 61

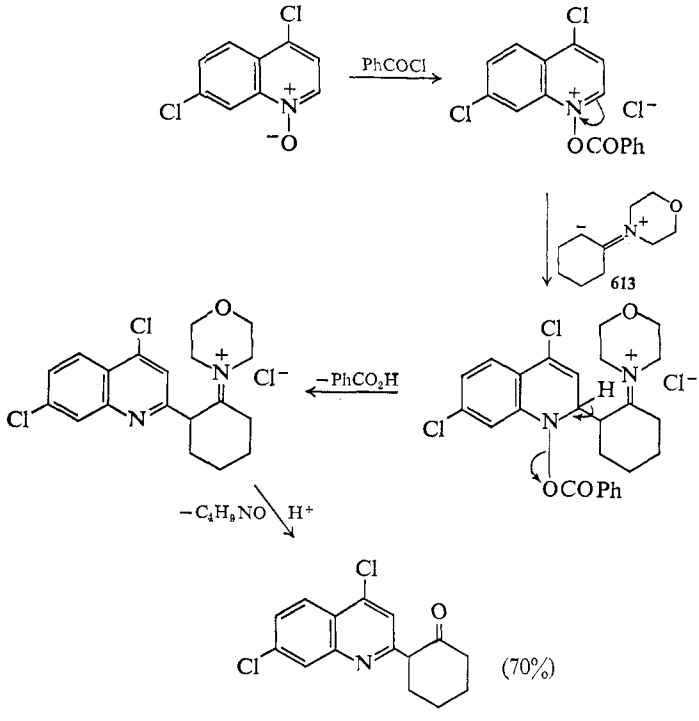
4-Chloroquinoline *N*-oxide reacts with the morpholine enamine (**613**) in boiling dioxan to give *N*-(4-quinolyl)morpholine as the sole product.[1315]

In contrast 4,7-dichloroquinoline *N*-oxide reacts in the presence of benzoyl chloride with the morpholine enamine (**613**) to give, not the product from displacement of the 4-chloro-group, but, after hydrolysis, the 2-(2-quinolyl)cyclohexanone (**614**).[1316] Other examples of this type of reaction are known[429, 1316, 1317] with both 2- and 4-chloroquinoline *N*-oxide and a mechanism, as outlined in Scheme 62, accounts for the observed products.

Chloroquinolines have been used[1230] in the Friedel–Crafts reaction as arylating agents particularly for reactive substrates. For example, 2-chloroquinoline and resorcinol in nitrobenzene solution in the presence of aluminium chloride give 2-(2,4-dihydroxyphenyl)quinoline (25%).

Ban and Seo[1318] have treated 2-chloroquinoline with 3-(2-bromoethyl)indole (**615**), obtaining 7,12-dihydro-6H-benzo[*f*]indolo[2,3-*a*]quinolizinium bromide (**616**) in 15.7% yield.

3,3-Dichloro-1,2,3,4-tetrahydro-2,4-dioxoquinoline reacts with α,α′-dibromo-*o*-xylene in a mixture of benzene and sodium hydroxide to yield the spiro-compound (**617**).[251] In a similar manner, chloroacetone reacts with 3,3-dichloro-1,2,3,4-tetrahydro-1-methyl-2,4-dioxoquinoline to give the 3,3-diacetonyl derivative (**618**), which on treatment with acid yields the spirocyclohexenone (**619**).



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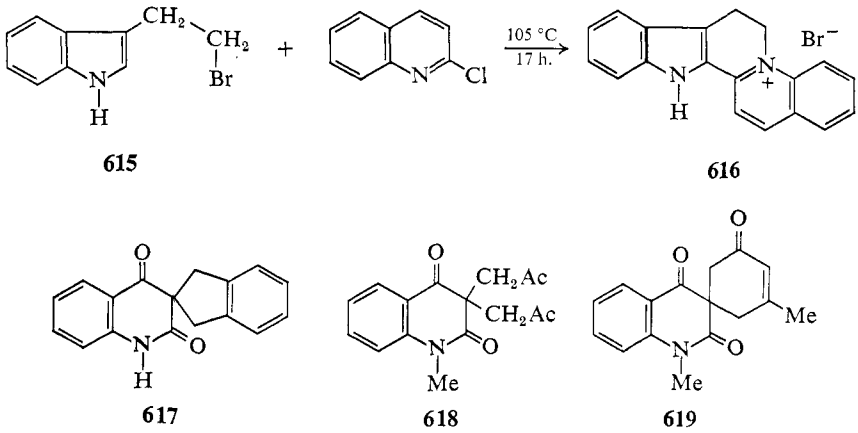
SCHEME 62



615 **616**

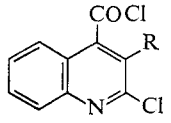
617 **618** **619**

d. DISPLACEMENT BY NUCLEOPHILIC NITROGEN.* (*i*) *Ammonia.* Nucleophilic displacement of halogen from haloquinolines by ammonia constitutes a convenient method of synthesis for a wide range of aminoquinolines. However, replacement of

* See also Addenda, p. 689.

the halogen is not always easy. For example, 4,7-dichloroquinoline remains unchanged after being heated with anhydrous ammonia at 170 °C for 3 hours, while at 240 °C after 5 hours extensive decomposition has taken place.[1319] Fusion of the dichloroquinoline with potassium phthalimide, or heating with sodamide in dry dioxan at 100 °C, yields only starting material.

Early workers employed concentrated ammonia solution under pressure as the aminating agent. 2-Chloro-6-nitro-,[405, 630] 2-chloro-5-nitro-,[630] and 2-chloro-8-nitroquinoline[630] react with ammonia solution at 120–150 °C to give the corresponding 2-amino-nitroquinolines, while 2,6- and 4,6-dichloroquinoline yield the 2- and 4-amino-derivatives, respectively, on treatment with methanolic ammonia at 105 °C.[1320] Reaction of the chloroquinoline acid chlorides (**620**; R = Me or H) with ammonia in light petroleum yields only the respective amides (**621**; R = Me or H).[657, 658] In



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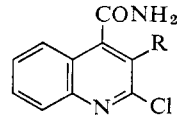

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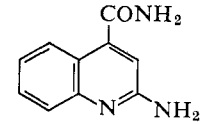
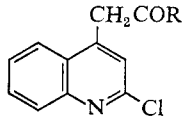


622

contrast, the 2-chloro-substituted acyl chloride (**620**; R = H) with liquid ammonia under pressure at 120 °C gives the amino-amide (**622**) in good yield (72%).[381]

Another failure to replace a 2-chloro-substituent with ammonia has been observed by Kametani and his co-workers,[856] who found that ethyl (2-chloro-4-quinolyl) acetate (**623**; R = OEt), on treatment with methanol and liquid ammonia at 75 °C for 45 hours yields only the amide (**623**; R = NH_2); the reaction also fails with a mixture of ammonia solution and ammonium chloride in the presence of zinc chloride at 160 °C; under the latter conditions hydrolysis and decarboxylation occurs to yield 2-chloro-4-methylquinoline.



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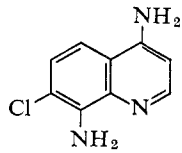

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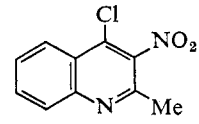
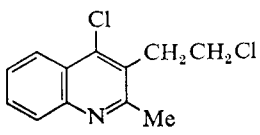


625

8-Amino-4,7-dichloroquinoline with ammonia under pressure at 180 °C gives the 4,8-diaminoquinoline (**624**).[540]

In the presence of activating groups replacement of halogen by ammonia becomes easier. 4-Chloro-2-methyl-3-nitroquinoline (**625**) yields the corresponding 4-amino-compound on treatment with boiling ethanolic ammonia.[422] Similarly, 7-chloro-8-nitroquinoline[404] and 8-chloro-5-nitroquinoline[1261] react readily with ammonia at 150–160 °C to give the corresponding nitro-amines. 4-Chloro-3-nitroquinolines react readily with anhydrous ammonia in warm (90 °C) toluene or butanol solution.[534] Quaternization of the quinoline ring also serves to activate the halogen towards nucleophilic displacement, as witnessed[634, 734] by the preparation of 2-aminoquinoline methiodide on reaction of 2-iodo-1-methylquinolinium iodide with ethanolic ammonia.

Ozawa and Nagaoka[830] have synthesized several pyrrolo[2,3-*c*]quinolines (e.g. **627**) by reaction of substituted 4-chloro-3-(2-chloroethyl)-2-methylquinolines (e.g. **626**) with ethanolic ammonia at 120 °C.



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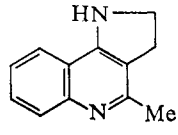
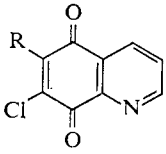


627

3-Fluoro-4-nitroquinoline *N*-oxide reacts readily with concentrated ammonia solution at 60 °C to give 3-amino-4-nitroquinoline *N*-oxide (71%).[684]

6,7-Dichloroquinoline-5,8-dione (**628**; R = Cl) reacts with hot ammonia solution to give 6-amino-7-chloroquinoline-5,8-dione (**628**; R = NH_2) in 88% yield.[257] A similar reaction is observed with 7-chloro-6-acetamidoquinoline-5,8-dione (**628**;



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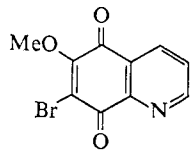


629

R = AcNH).[1321] However, the 7-bromoquinoline-5,8-dione (**629**) at room temperature, with either ammonia solution or ethanolic ammonia, suffers preferential loss of the methoxy-group.[210]

Ammonium carbonate has seen some use as a source of ammonia in ammoniade-halogenation reactions of haloquinolines.[381, 633] 2-Chloroquinoline[1322, 1323] with ammonium carbonate and ammonia solution (d = 0.880) at 210 °C gives 2-amino-quinoline, whereas ethanolic ammonia at similar temperatures yields only 2-ethoxy-quinoline.[1322] There appears to be little consistency in these reactions since in contrast to the last-mentioned result 2-chloro-8-methoxyquinoline with ethanolic ammonia at 200 °C gives the 2-amino-derivative.[633]

Occasionally mixtures of ammonia solution and zinc chloride have been used to advantage in the preparation of aminoquinolines.[633, 1323] 2-Aminoquinoline results when 2-chloroquinoline is heated with a mixture of ammonia solution, ammonium chloride, and zinc chloride at 210 °C for 8 hours.[1323] However, at temperatures above 220 °C, large amounts of 2-quinolone are formed. Presumably in these reactions the double salt $ZnCl_2.2NH_3$, which is known[1323] to be a good aminating agent particularly for 2-haloquinolines, is first formed.

Copper salts have found wide use[1324] as catalysts for the replacement of non-activated halo-substituents by ammonia, from a variety of aryl and heteroaryl systems. Studies[1325, 1326] on the reaction of 8-chloroquinoline with ammonia solution in the presence of copper salts reveal that optimum yields (69%) are obtained by using cuprous chloride at 200 °C. Copper metal and cupric sulphate are inferior catalysts and any increase in reaction temperature causes extensive decomposition of the starting material.

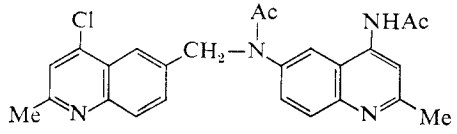
2- and 3-Bromo-quinoline react only slowly with liquid ammonia. However, in the presence of copper powder reaction is more rapid and the corresponding amino-quinolines are obtained in 50% and 60% yield, respectively.[1291] A 73% yield of 3-aminoquinoline results when 3-bromoquinoline is treated with ammonia solution (d = 0.880) and a copper sulphate catalyst at 160 °C.[299] Yields of 90% have been realized[300, 1327, 1328] for this reaction with cupric oxide as catalyst. Several other

examples of the use of copper sulphate as catalyst in the formation of 3-aminoquinolines are known,[108, 289, 320] and mention may be made of the preparation of 3-aminoquinoline *N*-oxide (32%) by the reaction of 3-bromoquinoline *N*-oxide with ethanolic ammonia in the presence of copper sulphate pentahydrate at 165 °C.[1329] Treatment of 3-bromo-6,8-dinitroquinoline with ammonia solution ($d = 0.880$) at 150 °C in the presence of copper sulphate is reported to yield only black infusible products;[289] in contrast, 3-bromo-6-nitroquinoline reacts smoothly to yield the 3-amino-compound (63%). Cupric oxide proves to be an efficient catalyst for the conversion of 6-bromoquinoline into 6-aminoquinoline (80%);[1330] 5-bromo-6,7-dimethoxyquinoline, however, fails to react with concentrated ammonia solution in the presence of cuprous oxide even after 80 hours at 160 °C.[409]

Backeberg and Marais[1331] have surveyed the various methods available for the preparation of 4-amino-2-methyl- and 2-amino-4-methyl-quinolines from the respective chloro-methyl compounds. They find that the 4-amino-compounds are best obtained by a method originally reported by Jensch[1332] in a German patent, which involves passing dry ammonia gas into a hot (180 °C) mixture of the 4-chloroquinoline and phenol; use of this technique led to virtually quantitative yields of several 4-amino-2-methylquinolines. Application of the method, however, to the preparation of 2-aminoquinolines gave only low yields (10%), the main products being 2-phenoxyquinolines. Backeberg and Marais found in fact that the best method of preparing 2-amino-4-methylquinolines is by heating the 2-chloro-compounds with zinc chloride–ammonia double salt, a method originally employed by Diepolder *et al.*[1323]

Ammonia in hot phenol has since proved to be a valuable technique for the preparation of 4-aminoquinolines. Peck and his co-workers[1333] have demonstrated that the use of phenol as a reaction medium reduces both the reaction time and temperature of halogen-replacement reactions. Subsequent work by Surrey and Cutler[1334] has clarified the role played by phenol in these condensations and the process is discussed more fully in Section II.2.C.d(iii) (p. 551). When this method is used, 4-chloroquinoline gives 4-aminoquinoline in high yield (95%)[433, 1335] and 4-aminoquinolines bearing halo-,[1319, 1333, 1336, 1337] alkoxy-,[445, 491, 1333] styryl,[445, 552] acylated amino-,[551, 552, 553, 602] nitro-,[535] aryl,[526, 551, 1333, 1338] heteroaryl,[457] alkyl,[1337, 1339, 1340] dialkylamino-,[456] and alkoxycarbonyl[526] groups have been prepared.

The monochloro-compound (**630**) fails to react with ethanolic ammonia at 120 °C whereas in phenol at 195 °C good yields of the 4,4′-diamino-derivative are obtained.[444]



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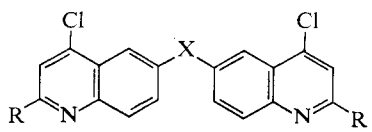

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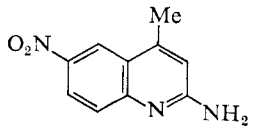

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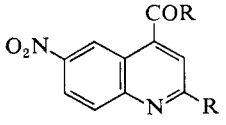
The related dichloro-compound (**631**; R = Me, X = CMe=CMe) yields the diamino-derivative (85%) on treatment with ammonia in phenol solution at 190 °C,[444] as does the dichloro-azo-compound (**631**; R = H, X = N=N).[443]

Occasionally, however, the method fails. For instance, Atkinson and Mattocks[693] report that 3-amino-4-chloro-2-phenylquinoline fails to undergo halogen replacement when either treated with ammonia in phenol at 210 °C or fused with ammonium acetate at 140 °C. In the former reaction the 4-phenoxy-compound was isolated.

Mixtures of phenol and acetamide have been employed[602, 1340] as solvents during the amination of chloroquinolines. For example, 2-chloro-4-methyl-6-nitroquinoline reacts with ammonia in such a mixture at 170 °C to give the 2-amino-derivative (**632**).[602]

(ii) *Aliphatic and Alicyclic Amines.* As with ammonia, some difficulties have been experienced[1319, 1341] in condensing haloquinolines with aliphatic primary and secondary amines of low molecular weight. Temperatures of around 190 °C are required[633] to effect successful condensation of methylamine with 2-chloro-8-methoxyquinoline, whereas 2-chloro-6-nitroquinoline-4-carbonyl chloride (**633**; R = Cl) reacts during 5 days at room temperature with *n*-butylamine or diethylamine to give the corresponding amino-amides (**633**; R = *n*-BuNH and Et_2N, respectively).[374]

The chloro-ester (**623**; R = OEt) reacts with benzylamine at 160 °C to give the acyl-(benzylamino)-benzylamine (**634**).[356]



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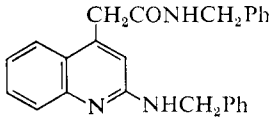

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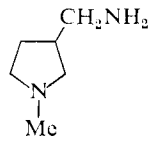

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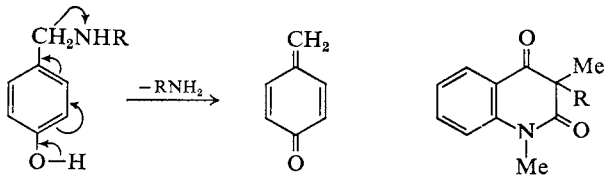
2-Chloro- and 4-chloro-quinolines have been treated at similar high temperatures with methylamine,[444, 1342, 1343] ethylamine,[444, 1344] *n*-propylamine,[1344] *n*-butylamine,[811, 982, 1344, 1345] *n*-hexylamine,[982, 1345, 1346] *n*-heptylamine,[1344–1346] *n*-octylamine,[1344] *n*-nonylamine,[1344] *n*-decylamine,[1345] *n*-hexadecylamine,[1345] cyclohexylamine,[1174, 1346] dimethylamine,[821, 1347, 1348] diethylamine,[253, 404, 444, 499, 1344] and di-isopentylamine.[689] 4-Chloroquinoline and dimethylamine hydrochloride at 170 °C are reported[821] to yield a mixture of 4-(dimethylamino)- and 4-(methylamino)-quinoline. Craig and Pearson[1348] have studied the reaction of several aliphatic amines with 4-chloro-2-methylquinoline and 4,7-dichloroquinoline under a variety of conditions. They found that in dimethyl sulphoxide solution condensation with methylamine and *n*-butylamine proceeds slowly (4–9 days) but in high yield (90%). They also found[1349] that 4-chloro-2-(tribromomethyl)quinoline in warm (60 °C) dimethylsulphoxide or dimethylformamide solution undergoes condensation, albeit in low yields (16–30%), with a range of aliphatic amines. The products, 4-alkylamino-2-(tribromomethyl)-quinolines, showed promise as antimalarial agents.

Condensation of methylamine, as the hydrochloride, with 4-chloro-2-methylquinoline in phenol at 80 °C gives inferior yields of the 4-(methylamino)-compound to those obtained by using dimethyl sulphoxide as solvent.[1348] In contrast, 4-chloro-8-methoxy-2-methylquinoline condenses readily with *n*-butylamine in phenol at 125 °C,[504] as does 2-chloro-4-methylquinoline with methylamine in phenol at 200 °C.[1350] The condensation of several 4-chloroquinolines with 3-(aminomethyl)-pyrrolidines, e.g. (**635**), in phenol solution has recently been reported.[1351–1353]

Meyer and Bouchet,[1354] in a study of the condensation of 4-chloro-2-methylquinoline with various amines, conclude that its efficiency depends on the basicity of the amine, and that with aliphatic amines condensation is accompanied by quinolone formation.

4,7-Dichloroquinoline fails to condense with *p*-hydroxy-*N*-methylbenzylamine (**636**; R = Me) in any of the common organic solvents;[1355] however, in phenol solution at 100 °C the corresponding *p*-methoxy-derivative gives a low yield of the desired condensation product. In contrast, the analogous reaction with *p*-hydroxybenzylamine (**636**; R = H) is accompanied by evolution of copious amounts of ammonia; ammonia formation is thought to be a consequence of quinone–methide (**637**) formation.

4-Chloro-2-methylquinoline condenses with dimethylamine in methanol in the presence of a copper-bronze catalyst,[1348] while cuprous chloride has been employed as a catalyst in the reaction of 8-chloroquinoline with both methylamine and ethylamine.[1326]



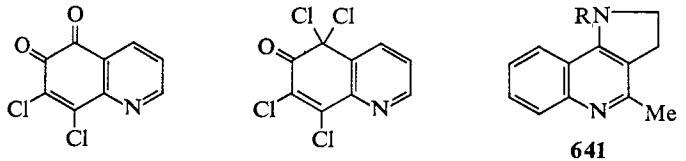
636 **637** **638**

7-Chloro- and 7-bromo-quinoline are sufficiently reactive to undergo halogen displacement with dimethylamine in aqueous solution at 250–290 °C.[699] 3-Bromo-2-phenylquinoline, however, does not react with cyclohexylamine even when heated at 200 °C for 10 hours.[1174] As expected methylamine condenses rapidly (2 h) with 4-chloro-1,2-dimethylquinolinium iodide to give 1,2-dimethyl-4-(methylamino)-quinolinium iodide in 90% yield,[736] and similar reactions are observed[634] with 2-iodo-quinolinium methiodides and a variety of amines. 2,4-Dichloroquinoline reacts with dimethylamine in toluene solution to give a mixture of 2-chloro-4-(dimethylamino) quinoline and 4-chloro-2-(dimethylamino)quinoline, the latter as the major product (83–95%);[718, 1282] in methanol solution, however, the isomer ratio is reversed (70 : 30) and 2,4-bis(dimethylamino)quinoline (14%) is also formed; the reaction conditions necessary for optimum yields of each product have been discussed.

In acetic acid solution alkylamines react with 4-haloquinolines to give 4-quinolones rather than the expected condensation products.[661] 2-Bromo- and 2-chloro-quinoline *N*-oxide, however, have been treated successfully with a variety of amines in 20% hydrochloric acid to yield the corresponding 2-(alkylamino)quinoline *N*-oxides.[1356] Condensations of 2-chloro-7-methyl-8-nitroquinoline with dialkylamines appear to be base-catalysed.[778]

3-Chloro-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxoquinoline (**638**; R = Cl) condenses easily with diethylamine in boiling ethanol to give the 3-(diethylamino)-derivative (**638**; R = NEt_2).[129]

It has been shown[60] that the dichloroquinoline-5,6-dione (**639**) and the related tetrachloro-compound (**640**) condense at the 8-position with aliphatic amines at low

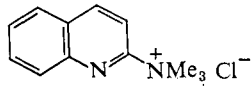


639 **640** **641**

temperatures (0 °C and −30 °C, respectively). Condensation of 6,7-dibromoquinoline-5,8-dione with various aliphatic amines proceeds smoothly in dimethylformamide solution to give the 6-(alkylamino)derivatives.[257]

Mono- and di-ethanolamine condense readily through the amino-group with a variety of 2- and 4-chloroquinolines.[739, 832, 1357, 1358] Ethanolamine and 4-chloro-3-(2-chloroethyl)-2-methylquinoline (**626**) give the tricyclic compound (**641**; R = CH_2-CH_2OH).[830] Glycine ethyl ester at 150 °C similarly condenses with the dichloro compound (**626**), but in this case loss of the ethoxycarbonyl group is observed and the (N^1-methylpyrroloquinoline (**641**; R = Me) is isolated.

3-Fluoro-4-nitroquinoline *N*-oxide undergoes fluorine displacement in high yield with both aqueous ethanolamine and methanolic glycine.[684] 2-Chloroquinoline reacts slowly (48 h) with trimethylamine at 40 °C to give the quaternary salt (**642**),[1359] which was isolated as the iodide.



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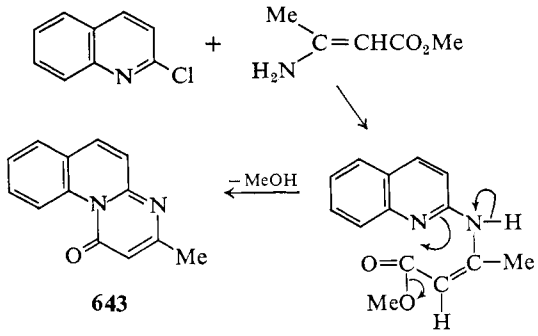
Antaki and Petrow[1360] obtained the diazaphenanthrene (**643**) by heating 2-chloroquinoline with ethyl 3-aminocrotonate in the presence of copper bronze and potassium carbonate at 200 °C. The reaction is outlined in Scheme 63.



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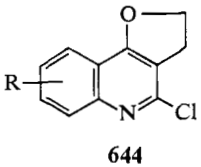
SCHEME 63

It has been shown[1361] that the 4-chloro-2,3-dihydrofuro[3,2-*c*]quinolines (**644**; R = Cl or MeO) with aliphatic amines in xylene solution in a sealed tube at 160–180 °C yield 1-substituted 2,3-dihydro-1*H*-pyrrolo[2,3-*b*]-4-quinolones (**645**; R = Cl or MeO). The reactions appear to involve initial displacement of the 2-chloro-substituent by amine, followed by cleavage of the furan ring; subsequently ring closure at the 2-position yields the pyrrole ring. Evidence for this is obtained by treating the furoquinoline (**644**; R = 7-Cl) with benzylamine under mild conditions, whereupon the benzylamino-compound (**646**) can be isolated. The tetrachloroquinoline (**647**) reacts with benzylamine (three molar equivalents) at 140–150 °C to give 1-benzyl-4,7-dichloro-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]quinoline (**648**; R = CH_2-Ph) as the sole product (37%). With an excess of benzylamine at 180–190 °C, however, other products are obtained, namely the 4-(benzylamino)-compound (**649**) (28.6%) and the 4-benzylaminopyrrolo[3,2-*c*] quinoline (**650**) (13.6%).



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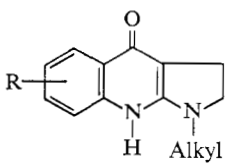

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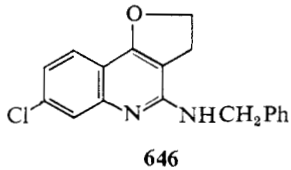

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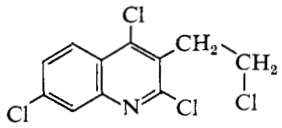

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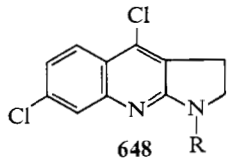

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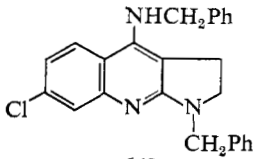

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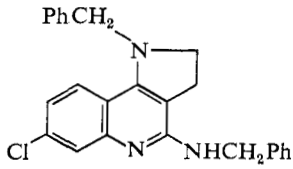

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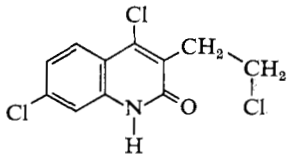
The structure of the pyrroloquinoline (**650**) was confirmed by treating the quinolone (**651**), obtained by selective acid-hydrolysis of the tetrachloro-compound (**647**), with benzylamine, and then treating the resulting pyrrolo[3,2-*c*]quinolone (**652**) with



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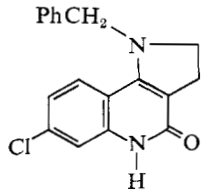

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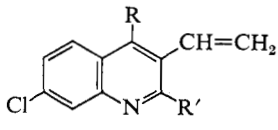
phosphorus oxychloride. The 2-chloro-compound, so formed, with benzylamine readily yields the dibenzyl derivative (**650**).

It is of interest that treatment of the tetrachloro-compound (**647**) with ethanolic ammonia in a sealed tube at 110–120 °C yields 2-amino-4,7-dichloro-3-vinylquinoline (**653**; R = Cl, R′ = NH_2) (ca. 5%) and its isomer, 4-amino-2,7-dichloro-3-vinylquinoline (**653**; R = NH_2, R′ = Cl) (15.2%), together with the expected pyrrolo-[2,3-*b*]quinoline (**648**; R = H) (40.5%).



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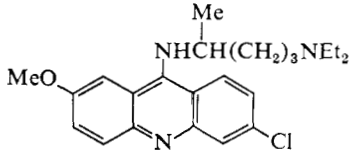

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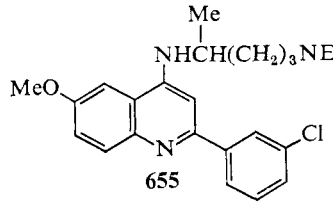
(iii) *Aliphatic Diamines.* The well-proven antimalarial activity of compounds such as "Atebrin" (**654**), which contains a diamino side chain, was instrumental in stimulating research, particularly during the period of the second world war, into the synthesis of similarly substituted quinolines, e.g. (**655**).[769] It was German workers[1362, 1363] who first reported the marked antimalarial properties of quinolines bearing the 4-diethylamino-1-methylbutylamino ("Novol diamine")* side chain,[439]



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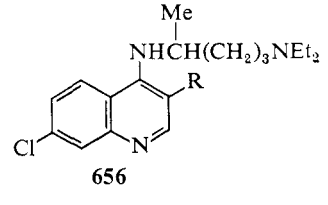

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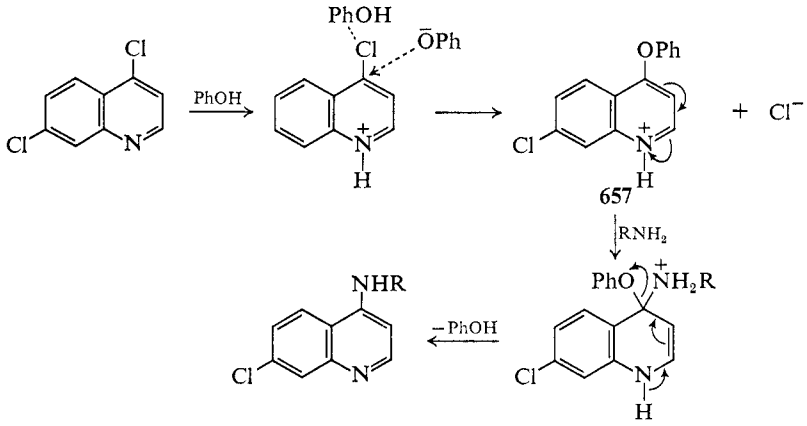
and the subseqeunt concentrated research effort by American researchers led to the development of the highly successful wartime antimalarials "Chloroquine" (**656**; R = H) and "Santochin" (**656**; R = Me). The reaction of haloquinolines with aliphatic diamines is thus of commercial interest and much effort has been spent on investigating the conditions for, and mechanism of, these reactions, and also in studying the effect of variation in the alkylamino side chain on antimalarial activity.

In general, the 4-chloroquinoline is condensed with the diamine in hot phenol solution, but in one instance[1364] β-naphthol has been employed as solvent. The commercial process for the production of "Chloroquine" involves condensing 4,7-dichloroquinoline with the diamine in the presence of phenol, and the reaction conditions have been discussed in some detail.[439] Other diamino side chains may be introduced in a similar manner, and occasionally[464] small quantities of sodium or potassium iodide are incorporated in the reaction as a catalyst. In some instances the chloroquinoline has been heated under reflux with neat diamine.[1365]

Surrey and Cutler[1334] have investigated in detail the role played by phenol in the reaction of 4,7-dichloroquinoline with 4-(diethylamino)-1-methylbutylamine. That its use is advantageous is emphasized by the significant increase in yield (45 → 85%) when the reaction is carried out in phenol rather than in neat diamine over the same time period (24 hours). Trial experiments indicate that phenol reacts faster than the diamine with the dichloroquinoline, and, therefore, the intermediacy of 4-phenoxy-7-chloroquinoline (**657**) in the reaction is a reasonable premise. Further experiments show that the phenoxy-compound (**657**) undergoes displacement of phenoxide ion by diamine only in the presence of acid. On this basis a reaction scheme involving phenol as proton-donor, solvating agent, and source of phenoxide ion is envisaged, as outlined in Scheme 64.

4-Haloquinolines bearing a wide variety of substituents have been condensed with "Novol diamine", and 4-[4-(diethylamino)-1-methylbutylamino)quinolines possessing chloro-,[122, 464, 482, 961, 1333, 1363] aryl,[471, 771, 1333, 1366] alkyl,[321, 463, 464, 482, 506, 960, 961, 990, 1333, 1367] bromo-,[118, 122, 463, 464, 482] alkoxy-,[449, 464, 471, 482, 491, 495, 506, 776, 1367] acetamido-,[1367] iodo-,[122, 960] (alkylthio)-,[118] dialkylamino-,[118] thiol,[118] sulphonamido-,[118] fluoro-,[495, 961] (trifluoromethyl),[495, 1368] heteroaryl,[449] and *N*-oxide[775] substituents have been reported. 8-Amino-4-chloro-6-methoxyquinoline and, surprisingly, 4,7-dichloro-8-nitroquinoline, failed to condense with the diamine;[540] in both these cases only tarry products were obtained. Condensation of "Novol diamine" with the sulphoxide (**187**; p. 393) was successful, but was accompanied by reduction of the sulphoxide to the sulphide.[461]

* For information on this diamine see ref. 2102.



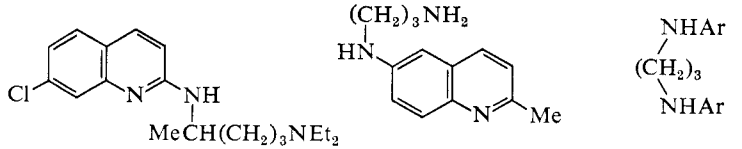
SCHEME 64

Variations in the basic side chain, which have been introduced at the 4-position of the quinoline nucleus are too numerous to be fully covered here. However, a broad survey indicates that diaminoethanes,[423, 444, 452, 488, 503, 522, 757, 1342, 1369–1372] diaminopropanes,[463, 534, 536, 691, 757, 1342, 1348, 1371–1373] diaminobutanes,[463, 534, 691, 959, 1342, 1374–1377] diaminopentanes,[770, 959, 1376] and diaminohexanes[757, 959] have all been successfully condensed with 4-chloroquinolines under conditions similar to those cited for the reaction of "Novol diamine".

In more recent years the ever-increasing emergence of resistant malaria strains has necessitated the search for more effective antimalarial agents. To this end highly modified diamino side chains have been incorporated into the quinoline nucleus. These modifications take many forms and include the following substituents; various sulphur functions,[1378] heterocyclic groups,[1379–1384] hydroxy-groups,[534, 1385–1390] aryl ethers,[1355] dialkylamino-groups,[1000] aryl groups,[1013, 1014] arenesulphonyl groups,[1391] alkyl groups,[1392] hydrazino-groups,[1393] the butenyl group,[1394] the butynyl group,[1394] and other unsaturated alkylamino-groups.[1394]

2-[4-(Diethylamino)-1-methylbutylamino]quinolines have not proved as effective antimalarial agents[366, 776, 1027] as their 4-substituted isomers. For instance, the 2-amino-7-chloroquinoline derivative (**658**), which is isomeric with "Chloroquine", is inactive against avian malarial infections.[366]

The reaction of a haloquinoline with a primary diamine sometimes results in the formation of a mixture of mono- and di-condensation products.[476, 1395, 1396] 6-Bromo-2-methylquinoline reacts with 1,3-diaminopropane in the presence of copper sulphate monohydrate at 160 °C to give the monocondensation product (**659**) in 23.6%

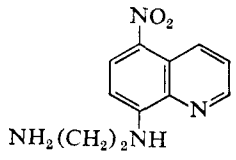


658 **659** **660**

yield.[1397] The 7-bromo-isomer reacts analogously but in lower yield (16%). Under similar reaction conditions, however, 4-chloro-2-methylquinoline yields a mixture of

the mono- (23.5%) and di- (**660**; Ar = 2-methyl-4-quinolyl) (39.5%) condensation products. In a like manner, alkylenebis-(4-aminoquinolines) have been prepared by condensing 4-chloroquinolines with 1,3-diaminopropanes,[1380] 1,4-diamino butanes,[1380] 1,5-diaminopentanes,[1380] 1,6-diaminohexanes,[1398] 1,8-diamino-octane,[1398] and *N,N'*-dimethyl-1,2-diaminoethane.[1399]

1,2-Diaminoethane reacts with 8-chloro-5-nitroquinoline to give the mono-condensation product (**661**),[404] while, somewhat surprisingly, 6-bromo-5,8-dimethoxy-2-methylquinoline (**662**) is reported to condense, in the presence of copper powder, with 1-amino-2-(diethylamino)ethane.[723]



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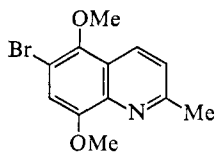

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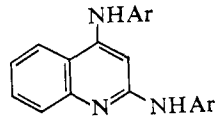
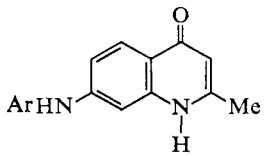


663

(iv) *Aromatic Amines.* Ephraim[1400] reported that 4-chloroquinoline condenses with aniline at 120 °C to give 4-anilinoquinoline, while at higher temperatures (130–200 °C) 2,4-dichloroquinoline reacts to give 2,4-dianilinoquinoline (**663**; Ar = Ph).[392, 1400]

The relative reactivity of the chloro-groups in 2,4-dichloroquinoline towards nucleophilic displacement by arylamines has been investigated qualitatively by Rose and his co-workers.[399] They found that the condensations are acid-catalysed and, when a mixture of dichloroquinoline and an aromatic amine is warmed, autocatalysis occurs and a violent reaction ensues. In acetic acid solution at 100 °C aniline and 2,4-dichloroquinoline react smoothly to give mainly 4-chloro-2-anilinoquinoline (53%);[399, 1401, 1402] crystallization of the mother-liquors, however, has also yielded 4-chloro-2-quinolone and 2,4-dianilinoquinoline.[1344]

Aniline has since been condensed with a variety of substituted 2- and 4-chloroquinolines, and many chloroquinolines undergo condensation on cautious heating with an arylamine at temperatures in the range 100–200 °C.[111, 388, 426, 471, 497, 500, 526, 534, 559, 600, 689, 694, 760, 794, 1036, 1298, 1403–1408] In a few cases condensation has been achieved in the presence of copper bronze.[360, 526, 626, 1409] Ethyl 4,7-dichloroquinoline-3-carboxylate reacts exothermally with aniline at room temperature,[523] as does ethyl 4-chloro-6-methoxyquinoline-3-carboxylate.[516] Little work appears to have been carried out on the replacement of halo-groups in positions other than 2 and 4 of the quinoline ring by aromatic amines. 7-Chloro-2-methyl-4-quinolone reacts with *p*-toluidine in boiling aqueous dioxan at pH 4 to give the 7-(*p*-toluidino)-derivative (**664**; Ar = *p*-MeC_6H_4) (47%).[1410] Other aromatic amines react similarly, as does the 7-chloro-8-nitro-4-quinolone (**665**).



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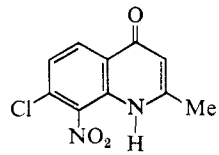

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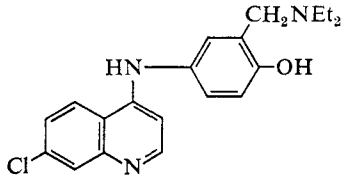
As mentioned in previous Sections, quaternization of the quinoline ring increases the reactivity of the halogen towards replacement and several aromatic amines have

been condensed smoothly with haloquinoline methiodides under relatively mild conditions.[634, 733, 734, 736, 1404]

The acid-catalysed condensation[1411] of aromatic amines and substituted 4-chloroquinolines is successful for a whole range of aromatic amines, and 4-anilinoquinolines have been prepared in which the anilino-group bears alkoxy-,[422, 519, 524, 839, 980, 983, 1407, 1412] amino-,[422, 661] alkyl,[633, 661, 689, 839] aryl,[626] acylamino-,[1408, 1413] chloro-,[422, 423, 543, 839, 982, 1336, 1414–1416] hydroxy-,[991] nitro-,[422, 1408] dialkylamino-,[770, 1404, 1417, 1418] bromo-,[1407] carboxylic acid,[1408, 1417, 1419, 1420] carboxylic ester,[1015, 1420–1428] fluoro-,[994, 1429] (trifluoromethyl),[519, 524] arsonic acid,[626] and heteroaryl[519, 1413] groups. Various naphthylamines have also been condensed with a number of 4-chloroquinolines.[523, 633, 661, 689, 1430]

Of particular interest are the 4-aminoquinolines formed by condensing 4,7-dichloroquinoline with 3-(diethylaminomethyl)-4-hydroxyaniline. The product (**666**) "Camoquin"[484] and related compounds exhibit powerful antimalarial activity.[510, 965, 991, 992, 1316, 1389, 1431–1440]



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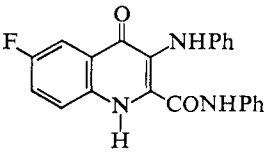

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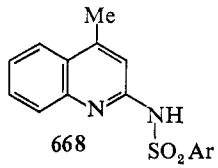
2-Chloroquinolines have been condensed successfully, in the presence of either acid or a copper catalyst, with aromatic amines bearing acylamino-,[1408] chloro-,[417 422, 423, 1414] amino-,[360, 422, 1114] dialkylamino-,[1441, 1442] alkoxy-,[422, 1443] acyl,[1043] and carboxylic acid[1408] groups. Ethyl 3-chloro-6-fluoro-4-quinolone-2-carboxylate reacts with aniline at 150 °C in the presence of a mixture of potassium and cupric acetates, to give the anilino-anilide (**667**) in 58% yield,[244] while 3-bromoquinoline condenses with anthranilic acid in the presence of copper bronze and potassium carbonate in boiling nitrobenzene to give *N*-(3-quinolyl)anthranilic acid.[1444] Special mention must be made of the reaction between *p*-aminobenzenesulphonamide and 2-chloro-4-methylquinoline;[1445] in the presence of potassium carbonate and copper powder at 250 °C condensation occurs to give the sulphonamide (**668**; Ar = *p*-$NH_2C_6H_4$), whereas at 200 °C in the absence of a catalyst condensation occurs exothermally at the amino-group to give *N*-(4-methyl-2-quinolyl)sulphanilamide in high yield (80%); presumably under the former conditions the reaction proceeds by nucleophilic attack by sulphonamide anion rather than by the primary amine function.



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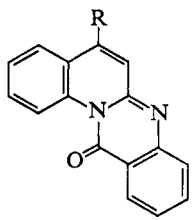

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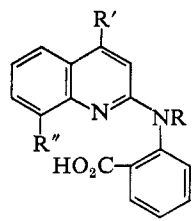

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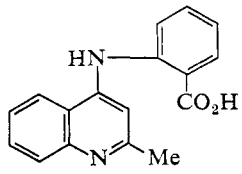
Occasionally if the aromatic amine, or the quinoline undergoing substitution, contains a reactive substituent *ortho* to the reacting centre, then secondary reactions

may be observed. For example, Bose and Sen,[1420] following earlier work by Ephraim,[1446] found that heating 2-chloroquinoline with anthranilic acid yields a mixture of 2-quinolone and a compound for which they proposed structure (**669**; R = H). Zěide and Chelintsev[1447] record an identical reaction, and the tetracycle (**669**; R = H) has also been obtained by using 2-bromoquinoline[1291] or methyl anthranilate.[1420, 1447] *N*-Methylanthranilic acid, however, condenses with 2-chloroquinoline to yield the disubstituted anthranilic acid (**670**; R = Me, R′ = R″ = H).

Similar reactions with 4-chloro-2-methylquinoline gave only the normal condensation products, i.e. 4-(*o*-carboxyphenyl)-2-methylquinoline (**671**).[1419, 1448] Backeberg,[1419]



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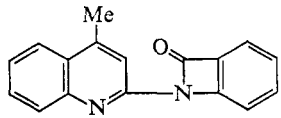
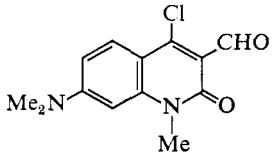


672

apparently unaware[1448] of the work of Bose and Sen, treated 2-chloro-4-methylquinoline with anthranilic acid and obtained a compound for which he proposed the benzoazetidone structure (**672**).* Structure (**672**) had originally been proposed by Ephraim[1446] and was favoured by Backeberg because this product, unlike the one obtained from 4-chloro-2-methylquinoline, i.e. (**671**), did not cyclize in concentrated acid to give an acridone. Also, on hydrolysis it gave the initially expected condensation product (**670**; R = R″ = H, R′ = Me). However, both these observations are readily explained on the basis of the quinolinoquinazolinone structure (**669**; R = Me).

5-Methylquinolino[2,1-*b*]quinazolin-12-one (**669**; R = Me), along with several other related compounds, have since been prepared[1450] in high yield (80–100%) by heating 2-chloro-4-methylquinolines with methyl anthranilate at 170–200 °C. 2-Chloro-4,8-dimethylquinoline, however, yields only the *N*-(quinolyl)anthranilic acid (**670**; R = H, R′ = R″ = Me); the authors explain this as due to the steric effect of the 8-methyl substituent which is *peri* to the point of ring closure.

Harnisch and Brack[834] have condensed the chloroquinolone-3-carbaldehyde (**673**) with *p*-anisidine and obtained a variety of products depending on the reaction conditions employed. After 15 minutes in acetic acid solution at room temperature the chloro-anil is obtained, whereas if the reactants are warmed (40 °C) in glacial



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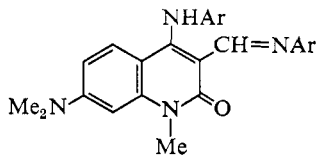

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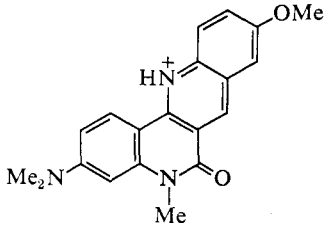
acetic acid for 3 hours and the reaction mixture then kept for several hours at room temperature, the amino-anil (**674**; Ar = *p*-$MeOC_6H_4$) is formed (82.5%). However, in boiling acetic acid the aldehyde (**673**) and *p*-anisidine give the tetracyclic compound (**675**) in 93% yield.

* This ring structure was originally named 'anthranil', a term which is now applied to the 2,1-benzisoxazole ring system.[1449]



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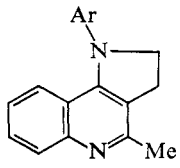

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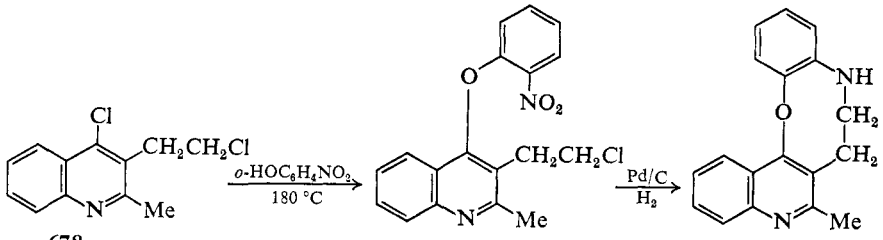
Cyclizations have also been reported during the reaction of 4-chloro-3-(2-chloroethyl)-2-methylquinoline (**678**) with aniline[830] and *o*-aminophenol.[1451] In the former case the pyrroloquinoline (**676**; Ar = Ph) is formed, whereas in the latter reaction a mixture of the pyrroloquinoline (**676**; Ar = *o*-HOC_6H_4) (74%) and the heterocycle (**677**) (22%) is obtained. The structure of the eight-membered heterocycle was confirmed by unambiguous synthesis as illustrated.



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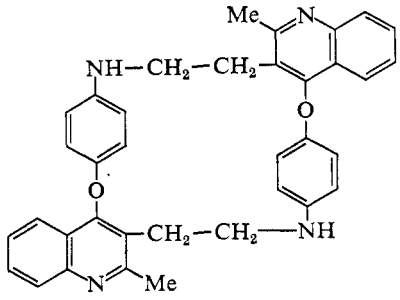
m-Aminophenol reacts with the dichloro-compound (**678**) to give the pyrroloquinoline (**676**; Ar = *m*-HOC_6H_4) (96%), whereas *p*-aminophenol yields a mixture consisting mainly (85%) of the expected pyrroloquinoline (**676**; Ar = *p*-HOC_6H_4) together with a small amount (5%) of the macrocyclic compound (**679**).



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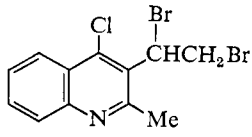
o-, *m*-, and *p*-Aminophenol condense normally with 4-chloro-2-methyl-3-vinylquinoline in boiling ethanol to give the corresponding 4-(hydroxyanilino)-2-methyl-3-vinylquinolines in high yields (85–95%).[1451]

In a slight variation of the previous reactions Nagaoka[1452] has treated the 4-chloro-3-(dibromoethyl)quinoline (**680**) with aniline in acidified ethanol. Under these

conditions condensation is followed by ring closure and dehydrobromination to yield 4-methyl-1-phenyl-1*H*-pyrrolo[3,2-*c*]quinoline (**681**).



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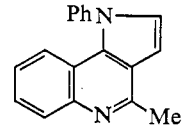

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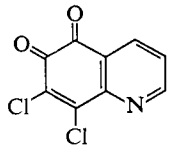
7,8-Dichloroquinoline-5,6-dione (**682**) was shown by early workers[63] to react with an excess of cold aniline to yield the 8-iminoquinolone (**683**; R = OH), whereas with aniline in boiling ethanol condensation at the 6-position also occurs to give the dianilino-derivative (**683**; R = PhNH).[59]



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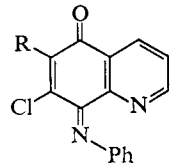

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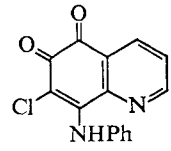

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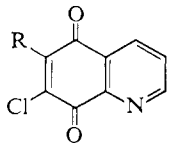
Proton magnetic resonance studies[60] reveal, however, that the products; (**683** R = OH) and related compounds exist as the amino- (**684**) rather than the imino-tautomers favoured by Zincke and his co-workers.[59, 63]

Haloquinoline-5,8-diones react readily with aromatic amines and the reactions have been studied in some detail.[1453] 7-Chloroquinoline-5,8-dione (**685**; R = H) with primary aromatic amines gives, after disproportionation of the initially formed amino-hydroquinone, the addition product (**685**; R = ArNH) rather than the substitution product (**686**). The isomeric 6-chloro-quinone (**687**; R = Cl), however,



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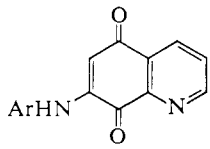

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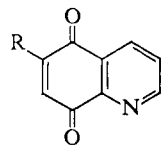

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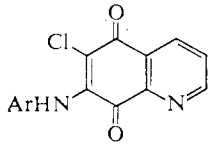

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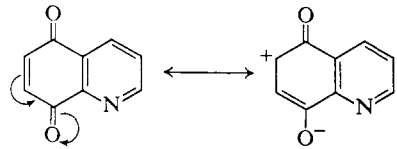


689 **690**

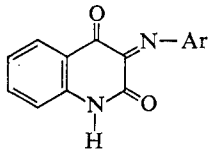
yields a mixture of substitution product (**687**; ArNH) (7%) and addition product (**688**) (76%). The difference in reactivity of the two isomers is the result of the carbonyl group at the 8-position being the more electron-deficient, owing to its position α to the ring-nitrogen. As a consequence polarization of the quinone ring is predominantly as

indicated (**689–690**) and nucleophilic attack is most favoured at position 6. The author (Pratt) shows that this effect is enhanced in the presence of acid or metal ions, since quaternization of, or complex formation with, the ring-nitrogen increases its electron-withdrawing effect. Experiment shows that in the presence of cerium ion the reaction between an arylamine and the 7-chloro-quinone (**685**; R = H) proceeds as before, whereas the 6-chloro-isomer (**687**; R = Cl) yields the substitution product (**687**; R = ArNH) exclusively (94%).

7-Bromoquinoline-5,8-dione reacts with aniline hydrochloride in the presence of sodium acetate to give 6-anilino-7-bromoquinoline-5,8-dione.[147]

These results are in accord with some early work by Schellhammer and Petersen[257] who found that 6,7-dibromoquinoline-5,8-dione condenses with a variety of amino-compounds to give the 6-amino-7-bromoquinolinediones exclusively.

3,3-Dichloro-1,2,3,4-tetrahydro-2,4-dioxoquinoline reacts with a variety of arylamines in alcohol solution to give the corresponding anils (**691**).[246, 251] With *o*-phenylenediamine, however, a double condensation involving the chloro-groups



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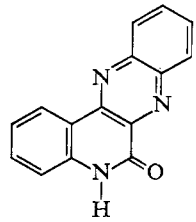

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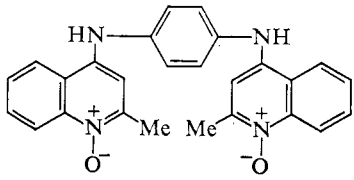
and the 4-carbonyl group occurs to give the quinolinoquinoxaline (**692**) in good yield.

p-Phenylenediamine condenses with 4-chloro-2-methylquinoline *N*-oxide in hot dioxan to give the bis(quinoline oxide) (**693**) in 56.5% yield.[1454] *m*-Phenylenediamine gives an analogous product but in lower yield (46.5%).

Slater[1455] has shown that *p*-phenylenediamine and benzidine condense with 4-chloro-6-methoxy-2-methylquinoline under a variety of conditions to give only the monocondensation products. In contrast, di-(*p*-aminophenyl)methane yields only the *N,N'*-dicondensation product even in the presence of a large excess of diamine. Attempts to condense 4,4'-diamino-3,3'-dimethyl- and 4,4'-diamino-3,3'-dimethoxy-biphenyl with the chloroquinoline failed.



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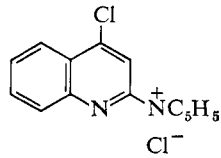

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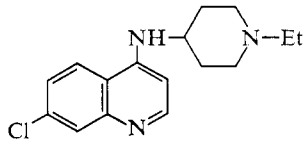
o-Phenylenediamine appears to react with 4-chloroquinolines to give only the monocondensation products[500, 600, 1409] although in one case[1409] (the reaction with 4,6-dichloroquinoline in the presence of copper powder), bis-diamine formation is noted.*

* For reaction of 4,7-dichloroquinoline with 2,3-diamino-5,6,7,8-tetrahydronaphthalene, see ref. 2054.

N-(4-Chloro-2-quinolyl)pyridinium chloride (**694**) reacts with aniline hydrochloride at 200 °C to give 2,4-dianilinoquinoline.[392]

(v) *Heterocyclic Amines.* As indicated in Section II.2.C.b. a large portion of the information available on the mechanism of heteroaromatic nucleophilic substitution has been gleaned from studies on the reaction of piperidine with haloheterocycles, and in particular 2- and 4-haloquinolines. In addition to this work many examples of the piperidinodechlorination of alkyl-,[444, 452, 1002, 1298, 1354] nitro-,[49, 91, 452, 778, 819, 1369, 1456] acylamido-,[452] heteroaryl-,[557] (trichloromethyl)-,[1456] alkoxy-,[607, 1457] and carboxy-[381] substituted haloquinolines have been reported.

4,7-Dichloroquinoline has been condensed[1458] with 4-amino-1-ethylpiperidine to give the 4-substituted 7-chloroquinoline (**695**) which is of potential interest as an antimalarial agent. The similarity of the diamine (**695**) to the 1,3-diaminopropane



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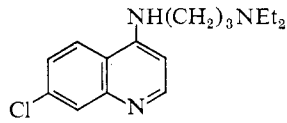


696

derivative (**696**), which is known to possess high antimalarial activity, is apparent, and several compounds of type (**695**) have since been prepared.[966, 1459]

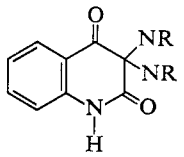
4,4′-Dichloro-2,2′-biquinoline with piperidine in boiling dimethyl sulphoxide yields the corresponding 4,4′-dipiperidino-derivative (45%).[795] A similar reaction is observed with pyrrolidine.

Bellas and Suschitzky[847] have measured qualitatively the ease of piperidinodefluorination of a series of fluoroquinoline *N*-oxides. They found that 6-fluoro- and 8-fluoro-quinoline *N*-oxide are unreactive, whereas the 3- and 7-fluoro-isomers show equal reactivity towards a variety of nucleophilic reagents, including piperidine. 5-Fluoroquinoline *N*-oxide, however, is virtually inert. The greater reactivity of the 7- than that of the 5-fluoro-isomer is best explained on the basis of stabilization of the transition state. Although both isomers can accommodate the negative charge in their transition states, it is possible to invoke a *para*-quinonoid mesomer in the case of the 7-fluoro-isomer against the *ortho*-quinonoid structure prevailing with the 5-fluoro-compound. Previous results[1266] indicate that the former structures possess greater stability than the latter. 3-Fluoro-4-nitroquinoline *N*-oxide undergoes rapid piperidinodefluorination at room temperature.[684]

Under normal conditions only the 4-chloro-substituent in 4,7-dichloroquinoline suffers nucleophilic displacement. Quaternization of the quinoline ring, however, brings about a dramatic increase in the lability of both halogens, and Schock[1460] found that 4,7-dichloro-1-methylquinoline methosulphate with piperidine at room temperature gives 7-chloro-4-piperidinoquinoline, whereas with an excess of piperidine at 100 °C the 4,7-dipiperidino-derivative is formed.

Other heterocyclic secondary amines such as pyrrolidine,[795, 1290, 1461] morpholine,[352, 381, 583, 739, 958, 1290, 1354, 1356] benzomorpholine,[1354] piperazine and *N*-substituted piperazines[347, 444, 697, 958, 1462–1466] have been condensed with haloquinolines. Piperazine depending on the molar ratio of reactants used,[347] can give rise to both mono- and di-substitution products, and several 1,4-di(7-chloroquinolyl)piperazines are to be found in the patent literature.[1467, 1468]

3,3-Dichloro-1,2,3,4-tetrahydro-2,4-dioxoquinoline reacts with piperidine and morpholine in warm dimethylformamide to give the aminals (**697**; R = C_5H_{10} and C_4H_8O, respectively) in quantitative yield.[246, 1469]



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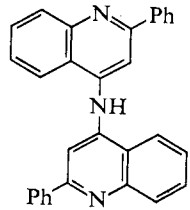
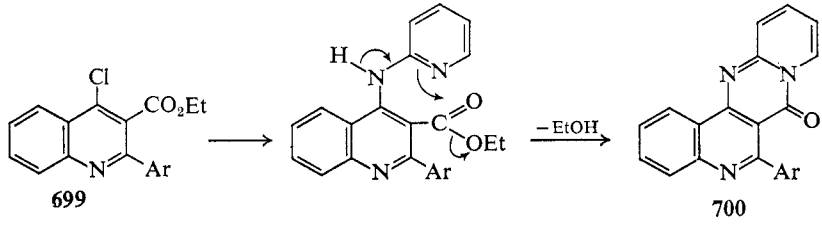


698

At high temperatures 2- and 4-haloquinolines condense with heteroaromatic primary amines. Thus at 280 °C 4-chloro-2-phenylquinoline reacts slowly (9 hours) with 4-amino-2-phenylquinoline to give the diquinolylamine (**698**).[689] Similar reactions have also been reported between 2-chloroquinoline and 2-aminoquinoline;[1323, 1470] 2-chloro-4-methylquinoline and 2-aminopyridine and 2-aminoquinoline;[1323] 4,7-dichloroquinoline and 8-amino-5-hydroxy-, 5-amino-8-hydroxy-, and 8-amino-6-hydroxy-quinoline;[913] 4-chloro-2-methylquinoline and 6-amino-[1413] and 8-amino-2-methylquinoline;[1471, 1472] and 4,7-dichloroquinoline and 2-aminopyridine.[1473, 1474] 4-Chloro-3-nitroquinoline condenses with 8-amino-6-methoxyquinoline in ethanol solution at room temperature to give 6′-methoxy-3-nitro-4,8′-diquinolylamine in high yield (87.5%), whereas 2-chloro- and 8-chloro-5-nitroquinoline yield only tars.[1000]

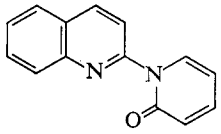
A secondary reaction occurs when 2-aminopyridine is treated with ethyl 4-chloro-2-(*o*-nitrophenyl)quinoline-3-carboxylate (**699**; Ar = *o*-$NO_2C_6H_4$) at 160 °C.[526] Nucleophilic displacement of chlorine is accompanied by loss of ethanol to give the triazabenzanthracene (**700**; Ar = *o*-$NO_2C_6H_4$) as illustrated in Scheme 65.



699 700

SCHEME 65

Hamamoto and Kubota[1475] have shown, on the basis of ultraviolet spectral data, that 2-bromoquinoline in the presence of copper powder reacts with the sodium salts of 2-pyridone and 2-quinolone to give, in each case, the *N*-heteroarylated products, e.g. (**701**), rather than the ethers, e.g. (**702**).



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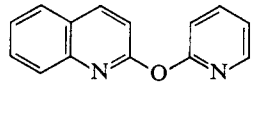
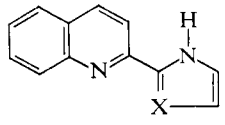


702

4,7-Dichloroquinoline has been condensed successfully with 3-aminoquinuclidine,[1476] and with 2-aminothiazole in phenol at 170 °C.[1477] However, attempts to

condense 2-aminothiazole with either 2-chloro-4-methylquinoline or 4,7-dichloro-2-methylquinoline in hot phenol resulted only in formation of the 2- and 4-phenoxy-derivatives, respectively. Under similar conditions 4,7-dichloroquinoline fails to condense with 5-amino-8-hydroxy-7-(piperidinomethyl)quinoline,[913] 3,4,5-triphenylimidazole,[1354] 2-amino-4-phenylthiazole,[1354] and 2-amino-4-chloro-6-methylpyrimidine.[1477] In the last case 7-chloro-4-phenoxyquinoline and 2-amino-6-methyl-4-phenoxypyrimidine were isolated.

2-Chloroquinoline[1478] and 2-bromoquinoline[1291] react with the potassium salt of pyrrole in a sealed tube at 230 °C to give 2-(2-pyrryl)quinoline (**703**; X = CH). 2-Chloroquinoline under similar conditions reacts also with the silver salt of imidazole to give 2-(2-imidazoyl)quinoline (**703**; X = N).[1478]* Presumably in the above reactions the *N*-quinolyl compounds are first formed but in neither case are they isolated.



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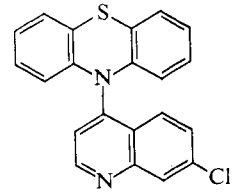
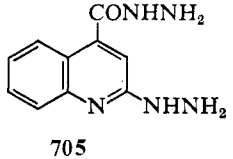


704

4-Bromo-7-chloroquinoline reacts with the sodium salt of phenothiazine in boiling ethyl methyl ketone to give the 4-(phenothiazin-10-yl)quinoline (**704**).[1479]

(vi) *Hydrazines.* In general, 2- and 4-chloroquinolines react readily with boiling hydrazine to give the appropriate hydrazinoquinolines,[448, 453, 629, 640, 689, 1480-1486] while in some cases[1480, 1487, 1488] the *N,N'*-diquinolylhydrazines are also formed. Ethyl 2-chloroquinoline-4-carboxylate† in boiling hydrazine yields the 2-hydrazinohydrazide (**705**).[368] 2-Chloro-1-methylquinolinium chloride and hydrazine give the hydrazone (**706**),[663] whereas 4-chloro-1,2-dimethylquinolinium iodide[736] and



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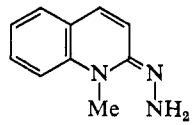

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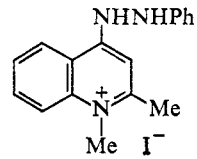


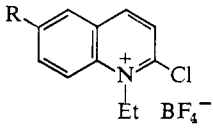
707

2-iodo-1-methylquinolinium iodide[734] react normally with phenylhydrazine to give the corresponding phenylhydrazino-1-methylquinolinium iodides, e.g. (**707**).

2-Chloro-1-ethyl-6-nitroquinolinium tetrafluoroborate (**708**; R = NO_2), prepared by treating 2-chloro-6-nitroquinoline with triethyloxonium tetrafluoroborate ($Et_3O^+BF_4^-$), reacts with benzoyl hydrazide to give the *N*-benzoyl-*N'*-(1-ethyl-1,2-dihydro-2-quinolylidene)hydrazine (**709**).[637]

* For condensation of 4,7-dichloroquinoline and related 4-chloroquinolines with imidazoles see ref. 2055.

† For more recent examples see refs. 2052 and 2053.



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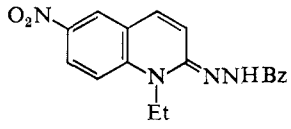
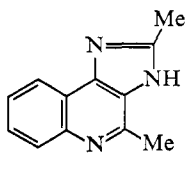


709

An anomalous reaction has been observed between hydrazine hydrate and 4-chloro-2-methylquinoline: Koenigs and von Loesch[1489] found that normal halogen-replacement occurs when the two reactants are heated in ethanol at 100 °C; in a sealed tube at 150 °C, however, a product melting at 122 °C, isomeric with 4-hydrazino-2-methylquinoline, and identical with a product previously reported by Marckwald and Chain,[1480] is obtained. Backeberg and Friedmann[598] reinvestigated these reactions and, by a process of elimination, came to the erroneous conclusion that the uncharacterized product is 3,4-diamino-2-methylquinoline. These authors state that the compound ". . . is not, however, a normal *o*-diamine", primarily because it does not undergo the usual condensation with 1,2-dicarbonyl compounds. Acetylation of the product, however, gave a diacetyl compound which with hydrochloric acid in warm ethanol cyclized to yield what was thought to be the imidazole (**710**). Backeberg[1490] also repeated the early work of Ephraim[1400] on the reaction of 4-chloro-2-methylquinoline with phenylhydrazine and found that this reaction proceeds as with hydrazine to give a product which he formulates as 4-amino-3-anilino-2-methylquinoline. Later studies by Koenigs and Freund,[1491] however, show that the product from the reaction of 4-chloro-2-methylquinoline with hydrazine is in fact 5-(*o*-aminophenyl)-3-methylpyrazole (**711**; R = H) and that the product from the corresponding reaction with phenylhydrazine is the *N*-phenyl derivative (**711**;



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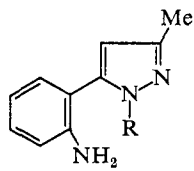

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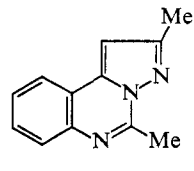


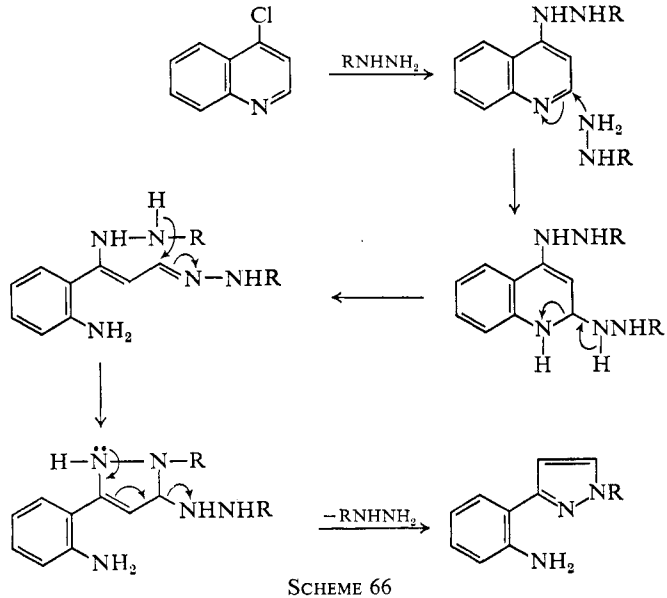
712

R = Ph). These authors suggest several possible mechanisms to explain pyrazole formation but all are without any definite supporting experimental evidence. Bowie and Wright[1492] have nevertheless extended the reaction to include other substituted 4-chloroquinolines and 4-chloro-1,8-naphthyridines and have proposed a mechanism (Scheme 66) to explain pyrazole formation.* Presumably on the basis of structure (**711**) the "imidazole" (**710**) reported by Backeberg[598] is in fact the isomeric pyrazoloquinoline (**712**).

Alberti[1493] has shown that the pyrazole (**711**) can be formed by heating 4-chloro-2-methylquinoline with hydrazine under reflux in ethylene glycol for 3 hours. However, attempts by Dey and Jouillé[453] to apply this procedure to a series of 4-chloro-2-(trifluoromethyl)quinolines failed, in that 4-hydrazinoquinolines were the sole products.

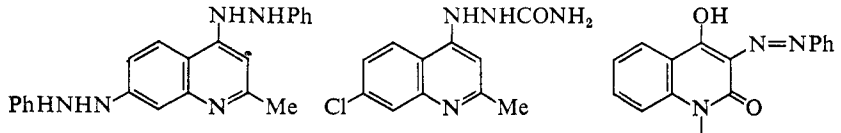
Phenylhydrazines[811, 812, 1345, 1403, 1494] and other substituted hydrazines[500, 1495, 1496] condense easily with haloquinolines. 3-Fluoro-4-nitroquinoline *N*-oxide reacts

* 2,4-Dichloroquinoline with hydrazine yields the 2,4-dihydrazino-derivative.[2057]



SCHEME 66

rapidly at room temperature with phenylhydrazine in ethanol to give 4-nitro-3-(phenylhydrazino)quinoline *N*-oxide in 79% yield.[684] 4,7-Dichloro-2-methylquinoline is reported[1497] to form the 4,7-di(phenylhydrazino)-derivative (**713**) (56%) when heated under reflux with a mixture of phenylhydrazine, ethanol, and 12N-hydrochloric acid for 30 minutes. *p*-Nitro- and 2,4-dinitro-phenylhydrazine behave in a like manner, whereas under similar conditions semicarbazide gives only the 4-semicarbazido-derivative (**714**) in 76.6% yield.



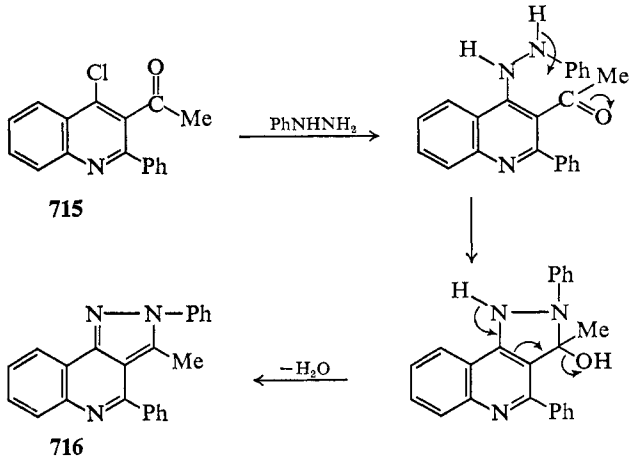
713 **714** **717**

3-Acetyl-4-chloro-2-phenylquinoline (**715**) reacts at 140 °C with phenylhydrazine to give the pyrazoloquinoline (**716**).[559] Obviously in the initial reaction nucleophilic displacement of the 4-halogeno-substituent, rather than hydrazone formation, is preferred, and the resulting hydrazine then undergoes intramolecular condensation with the adjacent carbonyl group to yield the pyrazolo-compound as indicated in Scheme 67.

As expected, 3,3,-dichloro-1,2,3,4-tetrahydro-2,4-dioxoquinoline reacts with phenylhydrazine with loss of both chlorine atoms to give a product for which the azo-structure (**717**) is preferred[246] over several other tautomeric possibilities.

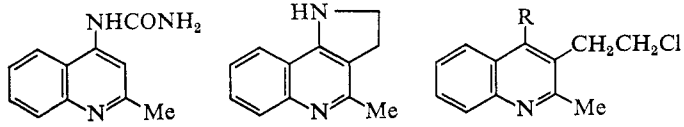
(vii) *Miscellaneous*. Meyer and Bouchet[1354] report that urea, on reaction with 4-chloro-2-methylquinoline, yields the quinolylurea (**718**),* whereas thiourea yields a product of unknown constitution.

* For other condensations involving 4-chloroquinolines with urea see ref. 2056.

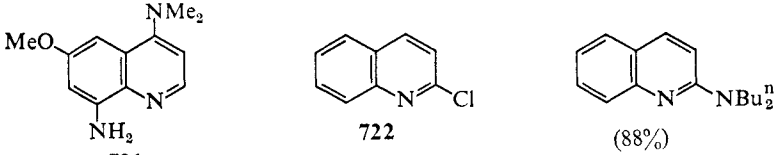


SCHEME 67

4-Chloro-3-(2-chloroethyl)-2-methylquinoline reacts with salicylamide to give the dihydropyrrolo[3,2-*c*]quinoline (**719**) (44%),[1498] identical with that obtained[830] by treating the dichloro-compound with ethanolic ammonia. The reaction proceeds by

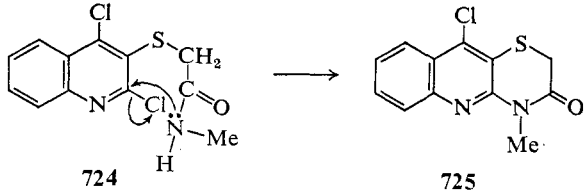


initial formation of the substituted salicylamide (**720**; R = *o*-HOC_6H_4CONH) which under the reaction conditions (180 °C for 30 minutes) undergoes ring closure with loss of the salicyloyl group. In comparison, *meta*- and *para*-hydroxybenzamides condense with the chloro-compound at the hydroxy-function to give, after hydrolysis and decarboxylation, the 4-phenoxy-derivative (**720**; R = PhO). Intramolecular hydrogen bonding in salicylamide is thought[1498] to be the cause of this difference in behaviour of the three isomers. Other examples of amides behaving as aminating agents are known. For example, Heindel and Kennewell[1499] have reinvestigated the condensation of 4-(diethylamino)-1-methylbutylamine with 8-amino-4-chloro-6-methoxyquinoline. The reaction, as earlier reported[540] fails in the absence of solvent, whereas in dimethylformamide solution a product shown[1499] to be the 4-(dimethylamino)-derivative (**721**) rather than the expected butylamino-derivative, is obtained in 65% yield. Subsequent investigations[1500] reveal that boiling dimethylformamide is



a convenient reagent for dimethylamino-dehalogenation and that the reaction is general for a whole range of *N,N'*-disubstituted, and some *N*-mono-substituted, formamides (e.g. reaction **722** → **723** in di(*n*-butyl)formamide for 12 hours under reflux). The reaction fails with *N*-methyl- and *N*-isobutylformamide, and also with formamide itself, in that only 2-quinolone (40–75%) is isolated.

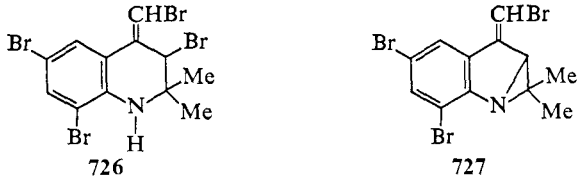
Intramolecular nucleophilic displacement of chlorine by an amide function has been observed by George and Tahilramani[262] who found that the (dichloroquinolyl)-thioglycollic amide (**724**) cyclizes, when heated with phosphorus oxychloride in



724 725

tetrachloroethane, to give the thiomorpholone (**725**). Cyclization at the 4-position is not observed, emphasizing the greater reactivity of the 2-chloro- over that of the 4-chloro-substituent.

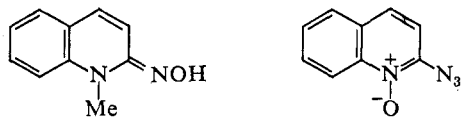
During their investigations into the preparation of the bromination products of 1,2-dihydro-2,2,4-trimethylquinoline (see p. 626) with base, Brown and Meth-Cohn[1501] observed an unusual reaction involving the tetrabromo-derivative (**726**).



726 727

With aqueous-alcoholic sodium hydroxide the tetrabromo-derivative loses elements of hydrogen bromide to give a product, which on the basis of infrared and ^{1}H-nuclear magnetic resonance studies is shown to be the aziridinoindole (**727**); this is reported to be highly unstable and decomposes exothermally even at −30 °C.

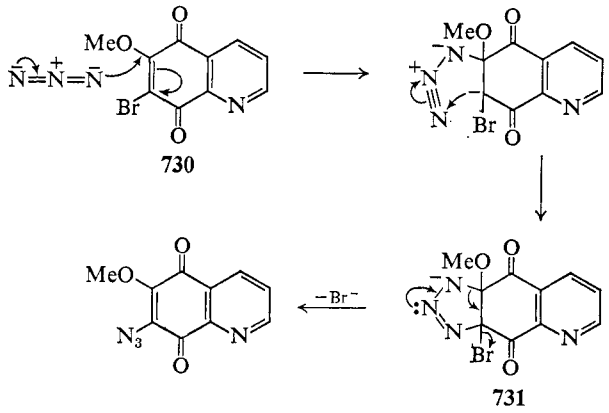
2-Chloroquinoline,[1502] 4-chloroquinoline,[821] and 4-chloroquinoline *N*-oxide[767] react smoothly with hydroxylamine hydrochloride to give the respective *N*-quinolyl-hydroxylamines. 2-Chloro-1-methylquinolinium chloride, however, reacts with hydroxylamine to yield the oxime (**728**).[663]



728 729

2-Chloroquinoline *N*-oxide with sodium azide in boiling ethanol gives 2-azido-quinoline *N*-oxide (**729**).[1488] Seemingly, a more complicated reaction takes place[210] between sodium azide and 7-bromo-6-methoxyquinoline-5,8-dione (**730**). With ethanolic or aqueous ammonia the quinone, for reasons previously outlined (p. 557)

undergoes displacement of the methoxy-rather than the bromo-group. However, with sodium azide in aqueous ethanol 7-azido-6-methoxyquinoline-5,8-dione is obtained in quantitative yield. The reaction is explained on the basis of azide attack at the 6-position followed by cyclization to the triazole (**731**), which then ring opens with loss of bromide ion, as indicated in reaction Scheme 68.



SCHEME 68

A series of 6-substituted 2-azidoquinolines has been synthesized by treating the *N*-ethyl tetrafluoro borates (**708**; R = Me, Ph, Cl, Br, NH_2, or CO_2Et) with sodium azide in methanol or buffered (Na_2HPO_4) aqueous-methanol solution.[637]

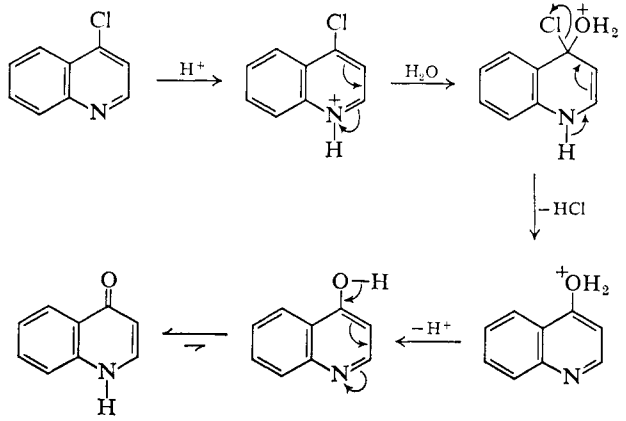
The reactions of haloquinolines with nitrite ion have been little investigated. Fatutta and Furlan[748] have shown that 2-iodo- and 4-chloro-quinoline react with sodium nitrite in dimethylformamide to give 2- and 4-nitroquinoline, respectively, in unspecified yields. More recently[1301] 2-nitroquinoline has been obtained by heating 2-iodoquinoline with sodium nitrite in either dimethylformamide or dimethyl sulphoxide solution at 160 °C for 3 hours.

e. DISPLACEMENT BY NUCLEOPHILIC OXYGEN.* (*i*) *Acid Hydrolysis.* As has been discussed in Section II.2.C.b. protonation of the quinoline ring brings about a large increase in the reactivity of halogen substituents, particularly at the 2- and 4-positions, towards nucleophilic displacement. In acid solution, therefore, replacement of halogen by hydroxyl is expected to be easy and many examples have been described. The reactions in general proceed as outlined in Scheme 69 and involve nucleophilic attack by water molecules on the protonated quinoline ring.

Early workers[111, 171, 351, 605, 633, 651, 1403] found that the 2- and 4-haloquinolines undergo hydrolysis to the corresponding quinolones when heated under pressure with water or, better, with dilute mineral acid. Thus, 2-chloroquinoline yields 2-quinolone when heated with water in a sealed tube at 120 °C.[345] More recently[1503] this hydrolysis has been carried out quantitatively by boiling the chloroquinoline with 6N-hydrochloric acid for 24 hours.

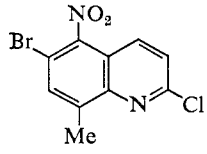
Capps and his co-workers[418, 646, 650, 653] have prepared a series of 2-quinolones by hydrolysis of 2-chloroquinolines and favour the use of 25–50% aqueous sulphuric acid, either under reflux or in an autoclave at 150–175 °C, as the hydrolysing agent.

* See also Addenda, p. 691.



SCHEME 69

Under these conditions 6-bromo-2-chloro-8-methyl-5-nitroquinoline (**732**) yields the 2-quinolone.[647] In like manner the closely related bromo-nitro-compound (**733**) yields the 2-quinolone (**734**).[644] In both these reactions, despite the presence of an activating nitro-group *ortho* or *para* to the bromo-substituent, only the 2-chloro-substituent is displaced.



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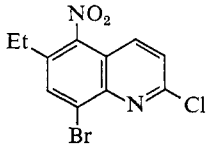

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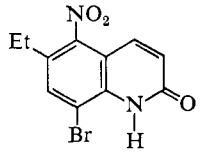
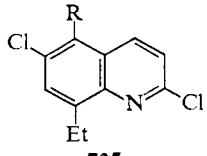


734

It appears from Capps' work that, in general, 2-chloroquinolines bearing a nitro-group require less drastic conditions for hydrolysis than those without the nitro-group. For example,[632] the dichloroquinoline (**735**; R = H) hydrolyses to the 2-quinolone (**736**; R = H) (87.5%) with a 2 : 1 concentrated sulphuric acid–water mixture in 4.5 hours at 180 °C. The nitro-compound (**735**; R = NO_2), however, hydrolyses to the quinolone (**736**; R = NO_2) (86%) with the same acid mixture in 20 minutes.



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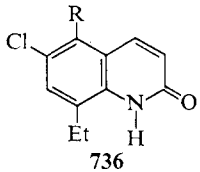

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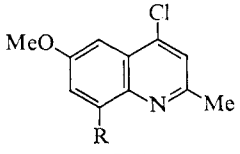


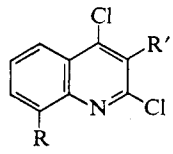
737

Acetylation of 5-amino-2-chloro-6-methylquinoline in boiling acetic acid is accompanied by hydrolysis of the 2-chloro-substituent to give what is thought to be 5-acetamido-6-methyl-2-quinolone.[641] Surprisingly, hydrolysis of the chlorodimethoxyquinaldine (**737**; R = MeO) with boiling 40% sulphuric acid brings about

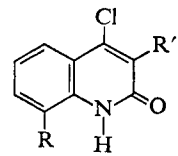
demethylation of the 8-methoxy-group to yield the 8-hydroxy-compound (**737**; R = OH) rather than displacement of the 4-chloro-substituent.[504] Another instance of non-reactive halogen is observed[274] on boiling 3-(*n*-butyl)-4-chloro-6-methoxy-2-quinolone with 48% hydrobromic acid: again ether cleavage is observed rather than halogen replacement. Friedländer and Weinberg[1504] found that 2,4-dichloroquinoline with hot hydrochloric acid yields 4-chloro-2-quinolone. Rowlett and Lutz[1505] have shown that acid-hydrolysis of 2,4,7-trichloroquinoline yields only 4,7-dichloro-2-quinolone (72%). In a similar manner 2,3,4-trichloro-6-methyl- and 2,3,4-trichloro-8-methylquinoline yield only the corresponding 3,4-dichloro-2-quinolones.[577] (The relative reactivities of 2- and 4-haloquinolines are discussed in Section II.2.C.b).

Halogens situated other than at the 2- or 4-position of the quinoline ring are virtually inert towards hydrolysis under all but the most drastic conditions. For instance, hydrolysis of 2,3-dichloroquinoline with hydrochloric acid in a sealed tube at 120 °C yields 3-chloro-2-quinolone,[1504] while 2,6,8-tribromoquinoline,[655] 2,6,8-trichloroquinoline,[648] and 2,5-dichloro-4-methylquinoline[347] yield only the respective 2-quinolones on acid hydrolysis. Claus and Howitz,[171] however, report that 3,4-dibromoquinoline will undergo hydrolysis to 3-hydroxy-4-quinolone when heated with concentrated hydrochloric acid in a sealed tube at 200 °C. 3,4-Dibromo-2-phenylquinoline, on the other hand, in boiling acetic acid yields only 3-bromo-2-phenyl-4-quinolone.[623]

Grundon and McCorkindale[570, 573] in their studies on the synthesis of dictamnine-type alkaloids found that trichloro compounds of type (**738**; R′ = CH_2CH_2Cl) are remarkably stable towards acid-hydrolysis. In fact, the methoxy-compound (**738**;



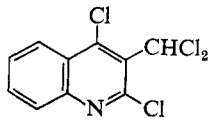
738



739

R = MeO, R′ = CH_2CH_2Cl) on treatment with 6N-hydrochloric acid in boiling dioxan yields the 2-quinolone (**739**; R = MeO, R′ = CH_2CH_2Cl) (57%). Similar results are observed during the hydrolysis of ethyl 2,4-dichloroquinoline-3-carboxylate (**738**; R = H, R′ = CO_2Et) and the ethyl ether (**738**; R = MeO, R′ = CH_2CH_2OEt).

Other workers[569, 571, 572] have recorded similar results, and Sato and Ohta[568] find that the tetrachloroquinoline (**740**) is surprisingly resistant towards nucleophilic attack by aniline, aniline in sulphuric acid, and hydroxide ion. In boiling acetic acid, however, the 2-quinolone (**741**) is formed. In view of the latter result it is rather



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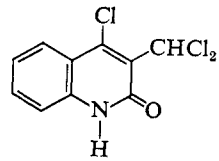

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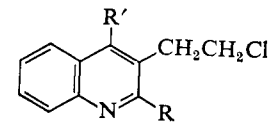
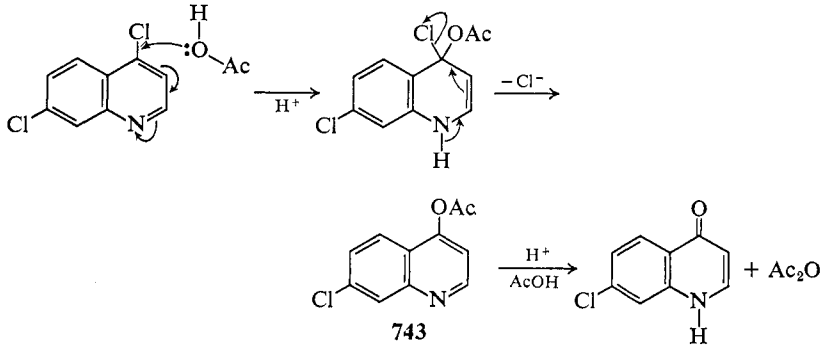


742

surprising that the closely related 2-chloro-3-(2-chloroethyl)quinoline (**742**; R = Cl, R′ = Me) remains unchanged on being heated under reflux for 3 hours with either concentrated or 6N-hydrochloric acid in dioxan solution.[354]

Although no mechanistic interpretation of these results is offered by the authors, they find that under the same conditions 2-chloro-3-ethyl-4-methylquinoline is much more difficult to hydrolyse than 2-chloro-4-methylquinoline. The position is even more confused by a report[624] that the 3-(2-chloroethyl) compound (**742**; R = Me, R′ = Cl) isomeric with the compound mentioned above hydrolyses readily in acetic acid to give 3-(2-chloroethyl)-2-methyl-4-quinolone. McCorkindale[1506] has also shown, for variously substituted 2,4-dichloro-3-ethylquinolines, that hydrolysis to the 2-quinolone proceeds smoothly in hot acetic acid.

These last results are in accord with earlier observations made by Cutler and Surrey[1507] on the reaction of 4,7-dichloroquinoline with acetic acid. They found that, in the presence of an excess of acetic acid, 4,7-dichloroquinoline is rapidly and quantitatively hydrolysed to 7-chloro-4-quinolone, and a mechanism involving the intermediacy of 4-acetoxyquinoline (**743**) is proposed (Scheme 70).



SCHEME 70

The acetoxyquinoline acts as an acetylating agent and reacts with acetic acid to yield the 4-quinolone and acetic anhydride. Various pieces of evidence, including the trapping of acetic anhydride, are put forward in support of the mechanism, and McCorkindale[1506] has isolated 4-acetoxy-3-ethyl-8-phenyl-2-quinolone in 55% yield after hydrolysis of 2,4-dichloro-3-ethyl-8-phenylquinoline in acetic acid.

These last results could well explain the hydrolysis observed during the reductive dehalogenation of some 4-chloroquinolines with palladium–charcoal and hydrogen in acetic acid solution.[455, 521]

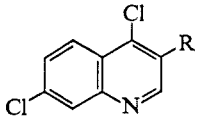
A British patent describes the acetolysis of several 4-chloroquinolines.[528]

(ii) *Hydroxide and Alkoxide.* Only on a few occasions have 2- and 4-quinolones been prepared by the action of aqueous alkali on 2- and 4-haloquinolines. Thielepape[636] observed the formation of 2-quinolone-4-carboxylic acid during the alkaline hydrolysis of ethyl 2-chloroquinoline-4-carboxylate. Alcoholic potassium hydroxide reacts with haloquinolines to give 2-alkoxyquinolines rather than 2-quinolones.[345, 1504, 1508, 1509]

Fusion of the haloquinoline with sodium or potassium hydroxide has seen sporadic use[1504, 1510] as a means of preparing quinolones. For example, 2,3-dichloroquinoline with molten potassium hydroxide gives 3-hydroxy-2-quinolone.[1510] Quinolone formation has also been observed during the attempted ammonolysis of haloquinolines with ammonia solution (d = 0.880).[618]

Until recently, acid-catalysed alcoholysis of haloquinolines was unknown. Heindel and Fine,[1511] however, have shown that, whereas 4,7-dichloroquinoline is

unreactive towards alcohols, in the presence of a catalytic amount of hydrochloric acid high yields (66–86%) of 4-alkoxy-7-chloroquinolines are obtained. In an extension of this work the authors showed[1512] that with more nucleophilically labile 4-chloroquinolines, e.g. (**744**; R = NO_2 or CO_2Et), alcoholysis is in fact autocatalytic, and attempts to crystallize these chloroquinolines from anhydrous alcohol results in the formation of 4-quinolones. Presumably the products arise from the initially formed 4-alkoxyquinolines, and the mode of cleavage of the alkoxy-compounds to the quinolones has been discussed in some detail.



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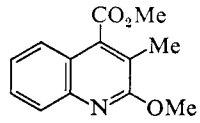

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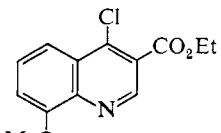


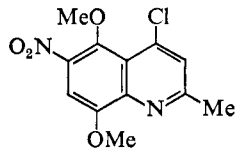
746

In light of the above results it is of interest to note the observations of previous workers, which may constitute earlier examples of acid-catalysed alcoholysis reactions. For instance, Bellas and Suschitzky[676] in their attempts to prepare the picrate of 4-fluoro-2-methylquinoline, using ethanolic picric acid, were able to isolate only the picrate of 4-ethoxy-2-methylquinoline. Also, Ornstein[658] found that 2-chloro-3-methylquinoline-4-carbonyl chloride reacts with methanol at 100 °C to give the methoxy methyl ester (**745**), while formation of ethyl 4-ethoxy-8-methoxyquinoline-3-carboxylate has been observed[525] during the hydrogenolysis of the 4-chloroquinoline (**746**) with palladium–charcoal in ethanol. The latter reaction appears to proceed normally in methanol solution.

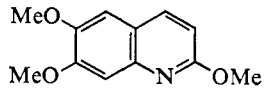
By far the most successful method of preparing alkoxyquinolines involves treating the haloquinoline with sodium alkoxide in the corresponding alcohol. As expected, 2- and 4-chloroquinolines react smoothly, and a variety of substituted quinolines have been prepared containing, *inter alia*, methoxy-,[111, 116, 259, 385, 403, 420, 446, 458, 473, 475, 530, 541, 542, 543, 760, 778, 1126, 1403, 1457, 1513–1518, 2058] ethoxy-,[124, 370, 371, 387, 542, 635, 700, 1519] *n*-propoxy-,[370, 542, 1520, 1521] *n*-butoxy-,[370, 372, 408, 462, 517, 542, 762, 1520, 1521] allyloxy-,[372, 447, 772] but-2-enyloxy-,[447] *n*-pentyloxy-,[370] *n*-hexyloxy-,[370] cyclohexyloxy-,[370] and benzyloxy-groups.[1339, 1522] The sodium salts of *N*,*N*-dialkylated ethanolamines[253, 408, 1523] and propanolamines[253] and of ethyl cellosolve[1524] have also been used to afford the corresponding ethers.

Occasionally forcing conditions are required as, for example,[545] with 4-chloro-5,8-dimethoxy-2-methyl-6-nitroquinoline (**747**) which forms the trimethoxy-derivative only on being heated with sodium methoxide in a sealed tube at 155 °C.

The failure of 4,7-dichloroquinoline-2-carboxylic acid and of its ethyl ester to yield a 4-ethoxy-compound when treated with sodium ethoxide in boiling ethanol is thought to be due to precipitation of the insoluble sodium salt of the chloro-acid during the reaction.[466]

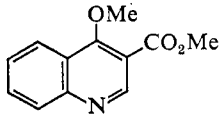


747



748

Alkoxylation is normally carried out in the appropriate alcohol solution, but recently use has been made of a variety of non-hydroxylic solvents. Pettit and Neill,[408] for example, found that 2-chloro-6,7-dimethoxyquinoline reacts poorly with sodium methoxide in methanol, whereas in dimethylformamide, diethyleneglycol dimethylether, or, surprisingly, xylene, the trimethoxy-compound (**748**) is formed in 84, 68, and 77% yield respectively. Markees and Schwab[530] observed that ethyl 4-chloroquinoline-3-carboxylate reacts exothermally with sodium methoxide in dimethylformamide; formation of the 4-methoxy-compound, however, is accompanied by ester exchange and the methyl ester (**749**) is isolated in 67% yield.



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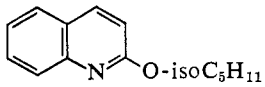

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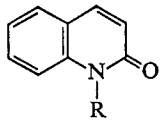
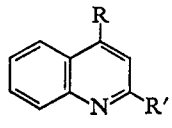


751

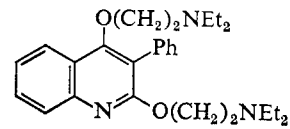
A report by Bogert and May[1519] indicates that 2-chloroquinoline with sodium isopentyl oxide gives a mixture of the 2-isopentyloxy-compound (**750**) (80%) and the *N*-isopentyl compound (**751**; R = isopentyl) (20%). Similar mixtures of *N*- and *O*-alkylated quinolines are observed after reaction of 4-chloroquinolines with sodium in allyl alcohol.[1525, 1526]

Friedländer and Weinberg[1504] report that 2,4-dichloroquinoline with ethanolic potassium hydroxide yields 4-chloro-2-ethoxyquinoline (**752**; R = Cl, R′ = OEt). Buchmann and Hamilton[583] have reinvestigated this reaction, however, and have shown that a mixture of the 2-ethoxy- (**752**; R = Cl, R′ = OEt) (32%) and the 4-ethoxy- (**752**; R = OEt, R′ = Cl) (31%) compounds is formed together with a small amount of 4-chloro-2-quinolone (5.5%).

The isomeric chloroethoxyquinolines were separated by steam-distillation, the 4-chloro-compound being the more steam-volatile. Subsequent reactions on the chloroquinolones derived from the two isomeric ethers reveal that 4-chloro-2-quinolone is unreactive towards sodium ethoxide, whereas the 2-chloro-isomer reacts readily. In contrast, 2,4-dichloroquinoline reacts smoothly with an excess of sodium ethoxide in ethanol to give 2,4-diethoxyquinoline (**752**; R = R′ = OEt).[583] Similarly, 2,4-dichloro-6- and -8-methoxyquinoline with sodium methoxide give the corresponding trimethoxyquinolines.[1527]



752

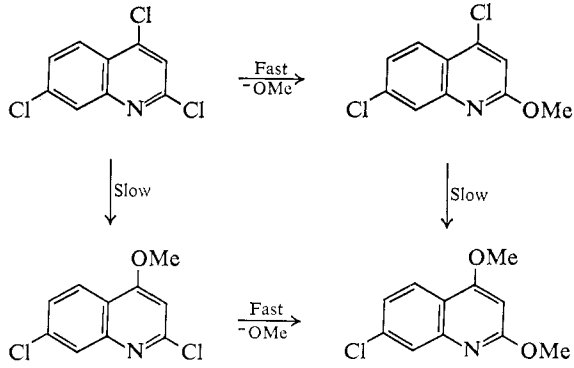


753

2,4-Dichloro-3-phenylquinoline condenses with *N*,*N*-diethylethanolamine in the presence of sodium to give the diether (**753**).[357, 1528]

The methanolysis of 2,4,7-trichloroquinoline has been studied in some detail by Rowlett and Lutz.[1505] Heating the trichloro-compound under reflux with sodium methoxide in methanol for an hour yields a mixture of 4,7-dichloro-2-methoxyquinoline (31.5%), 2,7-dichloro-4-methoxyquinoline (31%), and 7-chloro-2,4-dimethoxyquinoline (10%). A careful study of reaction conditions reveals that

maximum yields (46.5%) of the 4,7-dichloro-2-methoxy-compound are obtained with a 3-molar excess of sodium methoxide in boiling methanol for 2 hours, whereas the same conditions but a shorter (0.5 hour) reflux time favours formation of the 4-methoxy-isomer (40%). Prolonged heating, as expected, yields the 2,4-dimethoxy-derivative (100% after 22 hours). The authors conclude that the methanolysis proceeds simultaneously by two pathways as indicated in Scheme 71. One route



SCHEME 71

involves rapid formation of the 2-methoxy-4-chloro-compound which then reacts slowly with excess of methoxide to give the 2,4-dimethoxy-derivative. The other route involves slow formation of the 4-methoxy-compound which then undergoes rapid methanolysis to the diether.

2,3,4-Trichloro-6-methylquinoline reacts with sodium methoxide at 130 °C to give the 3-chloro-2,4-dimethoxy-derivative.[577]

The reaction of 4,7-dichloroquinoline with an excess of sodium methoxide has been employed[1529] as a method of determining the purity of the dichloro-compound, the displaced chloride being estimated either gravimetrically as silver chloride or volumetrically by the Volhard method.

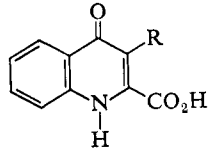
Fatutta and her co-workers[713] have studied the reaction of 4-chloro-2-iodo-, 2-chloro-4-iodo-, and 2,4-di-iodo-quinoline with methoxide ion. In each case mixtures of products are observed; the following percentage composition figures were obtained by gas–liquid chromatography:

Initial quinoline	Products		Recovered starting material
	2-MeO-	4-MeO-	
4-Chloro-2-iodo-	25.4	26.7	47.8
2-Chloro-4-iodo-	47	34	17
2,4-Di-iodo-	46.2	32.5	21.4

From the results it appears that there is little difference in halogen reactivity in the 2-iodo-4-chloro-compound, whereas in the other two compounds the halogen at the 2-position is the more labile.

As is obvious from the reactions of 4,7-dichloroquinoline already discussed, and from other literature reports,[284, 345, 697, 861, 1504, 1530, 1531] halogen other than at the 2- or

4-position of the quinoline nucleus is, in general, inert towards replacement by alkoxide or hydroxide ion. Coppini,[121] however, reports that 3-bromo-4-quinolone-2-carboxylic acid (**754**; R = Br) yields the hydroxy-derivative (**754**; R = OH) when



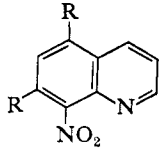
754

heated with 15% potassium hydroxide solution at 180 °C. Also Soviet workers[1532] have described in detail a process for the direct conversion of 8-chloroquinoline into 8-hydroxyquinoline; optimum conditions for the reaction require a 2.2% sodium hydroxide solution at 250 °C and 40 atmospheres for 2 hours; an 87% yield of 8-hydroxyquinoline, based on a 92.5% consumption of 8-chloroquinoline, is reported. The use of copper oxide, but not copper itself, reduces the reaction time. The reaction may in fact involve an aryne intermediate rather than an addition–elimination mechanism.

Other examples of the displacement of "non-activated halogen" are to be found in the reaction of 7-chloro-2-methyl-4-quinolone with various alkoxides;[1410] the formation of 7-methoxyquinoline from 7-bromoquinoline;[699] and the dialkoxylation of 4,7-dichloro-2-methylquinoline with a variety of sodium alkoxides in boiling alcohols.[791, 1533]

Also of interest, is the attempt to condense 2-(dimethylamino)ethanolamine with 7-bromo-6-methoxyquinoline in the presence of sodium at 180 °C.[722] Besides starting material the only other product proved to be 6-methoxyquinoline. Further investigation reveals that the 8-bromo-isomer behaves similarly, and that reductive dehalogenation rather than alkoxylation also occurs when sodium ethoxide is used.

The replacement of halogens that are activated by electron-withdrawing groups (e.g. nitro), by alkoxide or hydroxide occurs readily in most cases, and many examples[135, 136, 547, 913, 1534–1536] are to be found in the literature. 5,7-Dichloro-8-nitroquinoline (**755**; R = Cl) yields the dimethoxy-compound (**755**; R = OMe) when boiled with sodium methoxide in a mixture of methanol and pyridine.[860]



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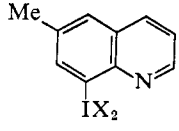

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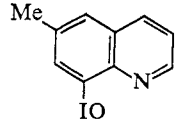

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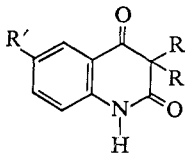
In general, 2- and 4-haloquinoline *N*-oxides react smoothly with alkoxides to give high yields of the corresponding alkoxyquinoline *N*-oxides.[695, 810–812, 1356] The order of reactivity of fluoroquinoline *N*-oxides with aqueous sodium hydroxide and sodium methoxide follows closely that observed[847] for their reaction with piperidine (see p. 559), while 3-fluoro-4-nitroquinoline *N*-oxide reacts with sodium methoxide in methanol at room temperature to give 3-methoxy-4-nitroquinoline *N*-oxide (51%).[684] In contrast to the reactions reported above of 2- and 4-chloroquinoline with sodium isopentyl oxide and sodium allyloxide, 2-chloroquinoline *N*-oxide reacts with the

potassium salt of cinnamyl alcohol to give only the *N*-alkoxylated quinolone (**751**; R = $OCH_2CH{=}CHPh$).[1537]

8-(Dichloroiodo)-6-methylquinoline (**756**; X = Cl) reacts with 10% sodium hydroxide to yield 8-iodosyl-6-methylquinoline (**757**), which on steam-distillation disproportionates to give the unstable 8-iodoyl compound (**756**; X = O) and 8-iodo-quinoline.[337]

Ziegler and his co-workers have carried out a thorough study of the reactions of 3-halo- and 3,3-dihalo-1,2,3,4-tetrahydro-2,4-dioxoquinolines with alkali. The tribromo-compound (**758**; R = R′ = Br) reacts rapidly with hot aqueous sodium hydroxide to give 6-bromo-4-hydroxy-2-quinolone (**759**),[128] whereas at room



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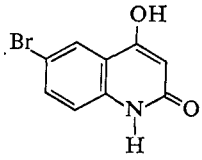

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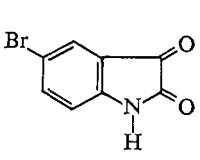
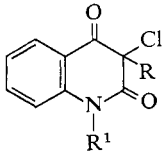


760

temperature a mixture of the quinolone and 5-bromoisatin (**760**) (37%) is slowly formed. In contrast, the 3,3-dichloro-compound (**761**; R = Cl, R′ = H) in aqueous sodium hydroxide gives a series of products, in varying yields, depending on the reaction times and temperatures employed:[1538] for example, with 2N-sodium hydroxide at 45 °C, then at room temperature for 48 hours, the 3,3′-dioxindole (**763**)



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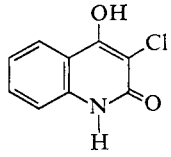

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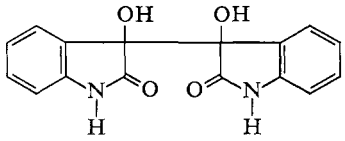
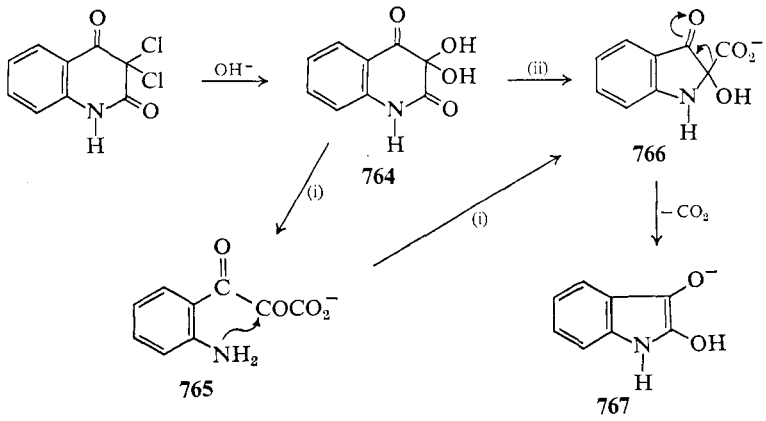


763

is obtained (89%) together with a trace of the 3-chloro-compound (**762**); at 0 °C, however, after 24 hours under a nitrogen atmosphere, the dichloro-compound yields mainly oxindole (79%) along with traces of the 3-chloro-compound (**762**), and isatin.

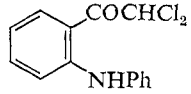
A large yield (60.5%) of isatin, accompanied by the chloroquinolone (**762**) (28.4%), is obtained on stirring the dichloro-compound with 2N-sodium hydroxide for 2.5 hours at 20 °C. 5-Chloroisatin is the main product when the trichloro-compound (**758**; R = R′ = Cl) is treated with 10% sodium hydroxide for 24 hours. The authors (Ziegler *et al.*) explain the products on the basis of Scheme 72. Initial hydrolysis of the *gem*-dichloro-compound to the *gem*-diol (**764**) is followed by either ring-opening to the amino-acid (**765**) and then recyclization (path i), or by a



SCHEME 72

benzylic acid-type rearrangement (path ii); in each case the unstable β-keto-acid (**766**) is produced which readily decarboxylates; in the absence of oxygen the hydroxy-oxindole (**767**) can be isolated, otherwise isatin is the observed product.

Ziegler, Kappe and Salvador[1539] have carried out similar reactions on 1-substituted 3,3-dichloro-compounds, e.g. (**761**; R = Cl, R′ = Ph) and were able to isolate *N*-phenylanthranilic acid, *N*-phenylisatin, and the dichloro-ketone (**768**), in varying yields, depending on the reaction conditions employed.



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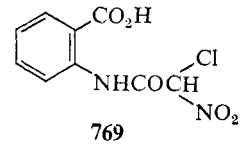
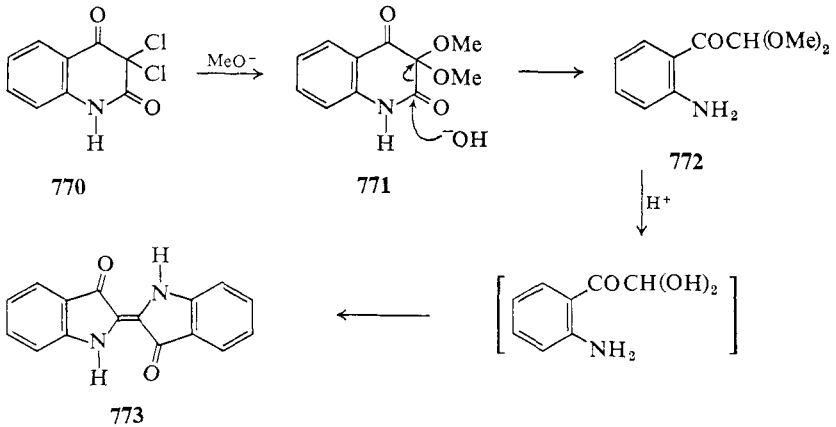


769

Hydrolysis of the chloro-nitro-compound (**761**; R = NO_2, R′ = H) with 2N-sodium hydroxide yields the α-chloro-α-nitroacetyl derivative (**769**).[263]

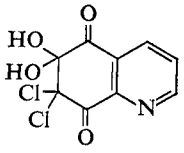
Reaction of the 3,3-dichloro-compound (**770**) with sodium methoxide has led to an interesting new synthesis of indigotin.[1540, 1541] *With sodium methoxide in*



773

methanol at 50 °C, the dimethoxy-compound (**771**) is obtained (93%), which on further treatment with warm alkali yields the acetal (**772**). In the presence of acid the acetal cyclizes quantitatively to give indigotin (**773**), as indicated. Conversion of the dichloro-compound into indigotin can be accomplished in one reaction vessel and overall yields of 90% are quoted.[1540] High yields (90–98%) of substituted indigotins have since been obtained by this method.[247]

A similar reaction to the preceding one is observed when 7,7-dichloro-5,6,7,8-tetrahydro-6,6-dihydroxy-5,8-dioxoquinoline (**774**) is boiled with water, in that ring



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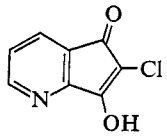
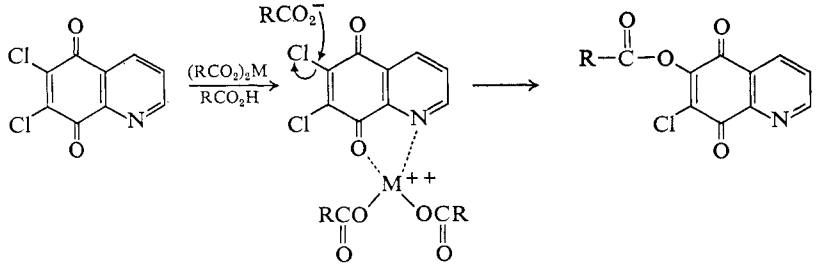


775

contraction takes place and the azaindanone (**775**) is obtained.[61] 6,7-Dichloroquinoline-5,8-dione is readily hydrolysed by 2N-sodium hydroxide to give 7-chloro-6-hydroxyquinoline-5,8-dione.[257]

Corey and König[1542] have shown that 6,7-dichloroquinoline-5,8-dione, in the presence of metal ions, is a useful system for the conversion of carboxylates into the corresponding anhydrides. During the reaction, the 6-chloro-substituent is lost from the dione, and 6-hydroxy-7-chloroquinoline-5,8-dione is obtained as the metal-complexed anion. The authors advance a mechanism for this reaction (Scheme 73)

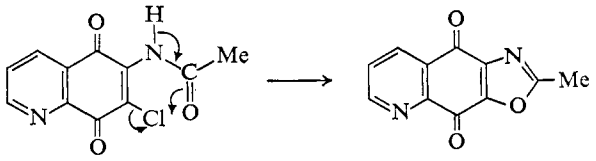


SCHEME 73

that involves initial complexing of the quinone with metal ions, and then nucleophilic displacement of the now activated 6-chloro-group by carboxylate ion. The acetoxylated quinone is itself a good acylating agent and readily reacts with more carboxylate ion to give the anhydride.

Of interest is the reaction of 6-amino-7-chloroquinoline-5,8-dione with acetic anhydride and a catalytic amount of concentrated sulphuric acid.[257] Acetylation to give the *N*-acetyl compound (**776**) is followed by ring closure to the oxazoloquinoline (**777**) (31%).

Other instances of intramolecular displacement of a 2-chloro-substituent have also been observed. For example, hydrolysis of the oxopyranoquinoline (**778**) in dilute alkaline solution leads to opening of the lactone ring followed by cyclization to 2,3-dihydrofuro[2,3-*b*]quinoline-4-carboxylic acid (**779**) in 60% yield.[363]



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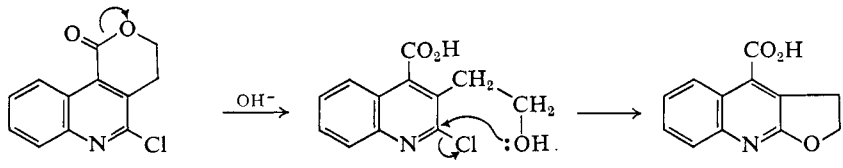
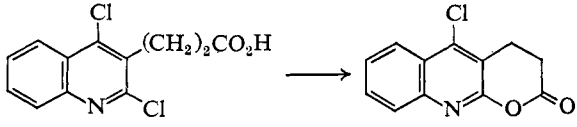


778 779

Gyul'budagyan and Durgaryan[1543] have carried out what is essentially the reverse of the preceding reaction on the 3-(dichloroquinolyl)propanoic acid (**780**). In the presence of acetic anhydride this cyclizes to give the α-pyrone system (**781**) in high yield.



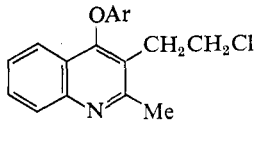
780 781

(iii). *Aryloxides.* Replacement of halogen from the 2- or 4-position of the quinoline nucleus by a phenoxy-group occurs readily in molten phenol,[381, 422, 444, 830, 1331, 1477] and in alkali–metal hydroxide–phenol mixtures.[443, 450, 498, 760, 778, 1411, 1457, 1544] Phenol–tertiary amine mixtures,[663] and phenol in aprotic solvents (e.g. dimethyl sulphoxide)[795] have also been used to effect aryloxylation. The role of phenol as a solvent in the aminolysis of haloquinolines has been discussed in Section II.2.C.d.(iii).

5-Bromo-6-methoxy-8-nitroquinoline fails to react with molten phenol, but with potassium phenoxide in boiling *n*-butylcellosolve a 51% yield of 6-methoxy-8-nitro-5-phenoxyquinoline is obtained.[911] 3-, 5-, and 7-Bromoquinoline react with phenol at 210 °C in the presence of copper powder to give the respective phenoxyquinolines.[867, 1545] Under similar conditions 7-bromo-4-chloroquinoline yields 4,7-diphenoxyquinoline (90%).[448]

4-Chloro-3-(2-chloroethyl)-2-methylquinoline with resorcinol at 165 °C gives a mixture of the mono- and di-aryloxy ethers[1546] (**782**; Ar = *m*-HOC_6H_4) and (**783**), respectively.

Catechol also reacts to give the mono- and di-condensation products, but in addition yields the cyclic diether (**784**). Mixtures of mono- and di-ethers are also formed[1454] in the reactions of 4-chloro- and 4,7-dichloro-2-methylquinoline *N*-oxide with catechol, resorcinol, and quinol. In general, the mono-ethers are formed in highest yield (50–60%). A series of diquinolyl ethers has been made[1545 1547] by treating, in every possible combination, 3-, 5-, 6-, 7-, and 8-bromoquinoline with the potassium salts of 6-, 7-, and 8-hydroxyquinoline. The reactions are carried out at 200–250 °C in the presence of copper powder. 2,2′-Diquinolyl ether results from



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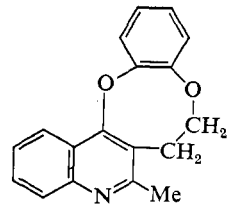

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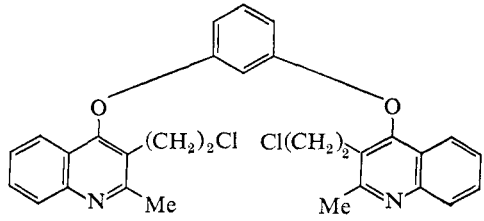
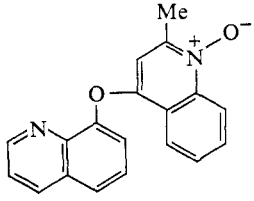


783

heating 2-quinolone with 2-chloroquinoline at 200 °C for 4 hours.[785] A low yield (19%) of the diquinolyl ether mono-*N*-oxide (**785**) is obtained[1454] on condensing 4-chloro-2-methylquinoline *N*-oxide with 8-hydroxyquinoline in the presence of ethanolic potassium hydroxide.



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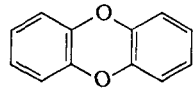

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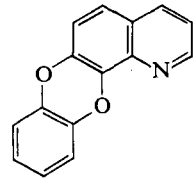

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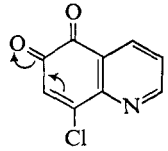
o-Bromophenol and 8-bromo-7-hydroxyquinoline as their potassium salts react on heating in the presence of copper powder to give a mixture of dibenzo-*p*-dioxin (**786**) and the quinolino[7,8]benzodioxin (**787**).[137]

During the preparation of 8-chloroquinoline-5,6-dione (**788**) from 8-chloro-5-hydroxyquinoline formation of the quinolyl ether derivative (**789**) was observed.[928]



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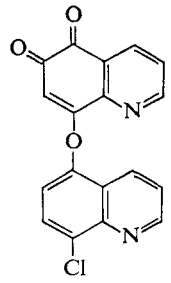


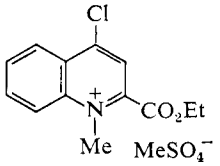
789

This ether is thought to arise via acylation of the hydroxyquinoline by the 8-chloro-substituted dione, which may be viewed as a vinylog of an acid chloride.

f. Displacement by Nucleophilic Sulphur.* (*i*) *Preparation of Thiones, Thiols, Sulphides, and Alkyl and Aryl Thioethers.* Heating 2-chloroquinoline with sodium or potassium hydrogen sulphide in the presence of base in a sealed tube at temperatures of around 150 °C has been successful for the preparation of a number of quinoline-2-[388, 631, 994] and -4-thiones.[994, 1482, 1548] Also under these conditions 8-chloroquinoline-5-sulphonic acid yields the 8-thiol albeit in low yield (13%).[1549]

Prior quaternization of the quinoline ring enables less drastic conditions than those quoted above to be employed, and a number of 4-thiones have been prepared by treating 1-methylquinolinium iodides and methosulphates with sodium hydrogen sulphide in boiling ethanol.[518] In the case of ethyl 4-chloro-1-methylquinoline-2-carboxylate methosulphate (**790**), however, all attempts to replace the 4-chloro-group using alkaline sodium hydrogen sulphide resulted solely in ester hydrolysis. The required thione was eventually obtained in moderate yield (37%) by using thiourea in place of sodium hydrogen sulphide.

Surprisingly, 4-chloro-6-ethoxy-2-methylquinoline and other alkoxy-4-chloroquinolines react with potassium hydrogen sulphide in ethanol at room temperature to give the corresponding 4-thiones, e.g. (**791**; R = EtO).[1550]



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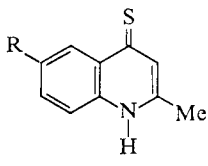

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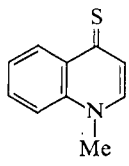


792

The thione (**791**; R = MeO) has been prepared in high yield (98%) by heating the 4-chloro-compound under reflux with an aqueous-ethanolic solution of sodium thiosulphate.[1551] Under identical conditions 4,7-dichloro-2-methylquinoline yields 7-chloro-2-methylquinoline-4-thione (94%).[1551] The isomeric 2,7-dichloro-4-methylquinoline behaves in an analogous manner.[777] 2-Chloroquinoline reacts with potassium hydrogen sulphide in ethylene glycol at 175 °C to give quinoline-2-thione (62%).[1552]

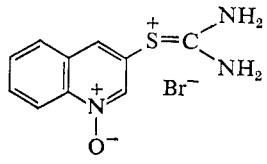
A convenient procedure for the preparation of thiones involves condensing the haloquinoline with thiourea, usually in ethanol solution, whereupon an *S*-thiouronium salt is produced. Hydrolysis of the salt under basic conditions affords the required thione. Monti and Gallo[1553] state that the method is a far superior mode of synthesis of thiones than the reaction of the quinolone with phosphorus pentasulphide, a reaction in fact, which has seen little use in the preparation of quinoline-thiones.

The use of thiourea appears to have been developed by Rosenhauer and his co-workers,[1554] who reported the preparation of 4-methylquinoline-2-thione and (under more drastic conditions) 2-methylquinoline-4-thione. In the latter case, 4,4′-disulphide formation proved troublesome especially when the reaction was carried out in hot ethanol. Renfrew[777] reinvestigated these reactions and confirmed the early observations that 4-chloroquinolines invariably yield disulphides rather than thiouronium salts. However, the method has since been used[353, 839, 994] for the

* See also Addenda, p. 693.

preparation] of a variety of 2-thiones, and several workers[839, 1555–1557] have prepared 4-thiones apparently without accompanying disulphide formation. As expected, quaternization of the quinoline ring, by either salt or *N*-oxide formation, increases the lability of the 4-halogen substituent towards nucleophilic replacement. Thus 4-chloroquinoline *N*-oxide[1558] and 4-chloro-1-methylquinolinium iodide[518] react smoothly with thiourea in hot ethanol to give 4-mercaptoquinoline *N*-oxide and 1-methylquinoline-4-thione (**792**), respectively, in high yield.

3-Bromoquinoline *N*-oxide is reported[1559] to yield the *S*-(3-quinolyl)thiouronium bromide *N*-oxide (**793**), when heated under reflux with thiourea in ethanolic potassium hydroxide for 3 hours. 8-Chloroquinoline, with thiourea in hot ethanol, appears to give a thiourea addition complex rather than the thiouronium salt.[1560]



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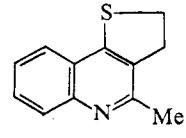


794

8-Chloro-1-methylquinolinium chloride fails to yield the required thiol when treated with thiourea in ethanol at 150 °C or with sodium hydrogen sulphide at 175 °C.[1561] 4-Chloro-3-(2-chloroethyl)-2-methylquinoline (**742**; R = Me, R′ = Cl) and related compounds react with thiourea in ethanol to give thienoquinolines, e.g. (**794**), in good yield.[1562, 1563]

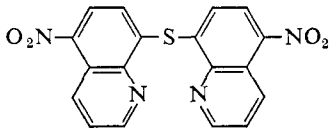
Gilman and his co-workers[840] found that sodium mercaptides react readily with chloroquinolines in boiling methyl cellosolve to give the corresponding alkyl thioethers in high yield. This method has since been used with great success for the preparation of a number of alkyl quinolyl thioethers.[49, 1564–1566] Thioethers of quinoline have also been prepared by heating the chloroquinoline with an ethanol solution of an *S*-alkylthiouronium salt, e.g. (*S*-benzylthiouronium chloride),[518, 1565] or with a mixture of the alkanethiol and sodium ethoxide in ethanol.[1356, 1457, 1567, 1568]

Thiophenols react under a variety of conditions with haloquinolines to give the arylthioquinolines. Illuminati and his co-workers in a series of papers[1267–1270] report in detail on the kinetics and mechanism of the reaction of *p*-toluenethiol with 2- and 4-chloroquinoline and their quaternary salts. They conclude[1270, 1569] on the basis of their results that the best preparative method for introducing an arylthio-group at the 2- or 4-position of the quinoline ring consists simply in heating together the thiophenol and the chloroquinoline either alone or in methanol solution. These conclusions strongly contrast with the previously employed methods of preparing arylthioethers of quinoline, which involved the use of a hot alkaline solution of the thiophenol.[49, 381, 386, 1298, 1339, 1570, 1571]

Quinolyl sulphides have already been mentioned as by-products from the reaction of thioureas with 4-chloroquinolines. They are, however, more conveniently prepared by heating the chloroquinoline in ethanolic sodium sulphide solution, and nitro-sulphides of type (**795**)[761, 896, 1572] have been obtained by this method in high yield from the appropriate chloronitroquinolines.* 4-Chloro-3-nitroquinoline behaves similarly when treated with sodium sulphide or sodium hydrogen sulphide in chloroform,[536, 761] while 4-chloro-2-phenylquinoline condenses with 2-phenyl-quinoline-4-thiones in the presence of sodium ethoxide and copper powder in a

* However, see ref. 2059 for an apparently anomalous reaction of 8-chloro-5-nitro-quinoline with sodium sulphide in ethanol.

sealed tube at 100 °C to give bis-(2-phenyl-4-quinolyl) sulphides in quantitative yield.[1548] 4-Chloroquinoline *N*-oxide with sodium thiosulphate pentahydrate in boiling aqueous ethanol gives bis-(4-quinolyl) sulphide *N,N'*-dioxide in 82% yield.[1573] The same product is obtained if 4-bromoquinoline *N*-oxide is heated under reflux with aqueous-ethanolic sodium sulphide.



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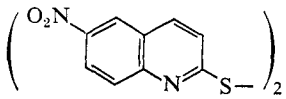
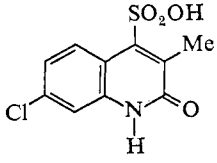


796

Bis(nitroquinolyl) disulphides, e.g. (**796**), are prepared[1574–1576] by treating the chloroquinoline with sodium disulphide in hot ethanol.*

(ii) *Preparation of Sulphonic Acids and Sulphones.* An early publication by Besthorn and Geisselbrecht[799] describes the synthesis of quinoline-2- and -4-sulphonic acid by boiling the appropriate chloroquinoline with an aqueous solution of sodium sulphite or bisulphite and this method has since been employed[483, 492, 552, 990, 1482] for the preparation of several quinolinesulphonic acids. Boiling 2,4-dichloroquinoline with a solution of sodium sulphite heptahydrate for 16 hours yields 2-quinolone-4-sulphonic acid;[990] under similar conditions 2,4,7-trichloro-3-methylquinoline yields the chloroquinolone-sulphonic acid (**797**).



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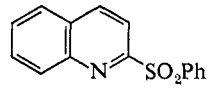

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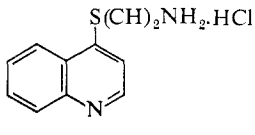
Tröger and Meinecke[386] showed that 2-chloroquinoline, treated with sodium benzenesulphinate ($PhSO_2Na$) in ethanol at 100 °C for 8 days, yields the sulphone (**798**). The direct replacement of halogen by the sulphinyl group has since become a useful preparative method for aryl quinolyl sulphones.[387, 1577, 1578]

(iii) *Miscellaneous.* 2-(Diethylamino)ethanethiol and other dialkylaminoalkanethiols have been condensed with 4,7-dichloroquinoline in boiling ethanol.[1579] The products, which are the sulphur analogues of compounds known to possess antimalarial activity, proved to be inactive, but several have found their way into the patent literature as antibacterial agents.[1580] 2-Aminoethanethiol condenses with 4-chloroquinoline in ethanol solution at pH 5.2–6.0 to give the thioether (**799**) rather than the alternative product, 4-[(2-mercaptoethyl)amino]quinoline.[1581]

4,7-Dichloroquinoline and related chloro-compounds condense in pyridine solution with thioglycollic acid to give acids such as (**800**) in high yields (90%),[1582] whereas 3-fluoro-4-nitroquinoline *N*-oxide suffers displacement of both fluoro- and nitro-groups, yielding the diacid (**801**) in 50% yield.[684]

3-Chloro-1,2,3,4-tetrahydro-2,4-dioxoquinoline with ethyl thioglycollate in the presence of sodium ethoxide gives the glycollate ester (**802**; R = OEt).[262] The amide

* See also ref. 2060.



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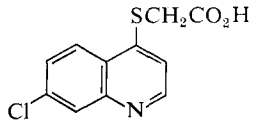

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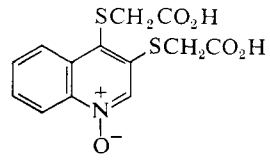
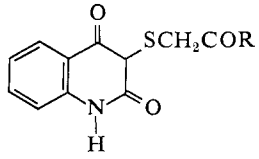


801

(**802**; R = NH_2), derived from this ester, on treatment with phosphorus oxychloride in tetrachloroethane cyclizes to give the dichloroquinolino[3,2-*b*]-1,4-thiazine (**803**).

Treatment of the acetamidochloroquinoline-5,8-dione (**804**; R = Cl) with sodium sulphide in dimethylformamide yields the thiol (**804**; R = SH).[257] However, when



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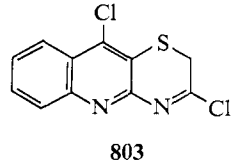

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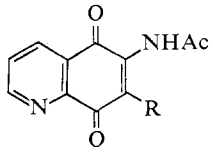

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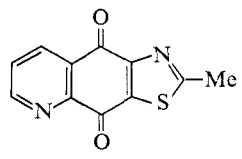
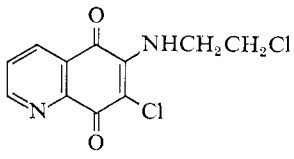


805

the dione is heated with sodium sulphide in acetic acid cyclization takes place to give the quinolinothiazole (**805**) in 59% yield.

7-Chloro-6-(2-chloroethylamino)quinoline-5,8-dione (**806**) with sodium sulphide in boiling ethanol yields the thiazine (**807**) (65%).[257]



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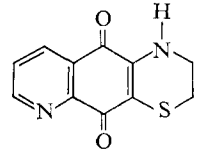
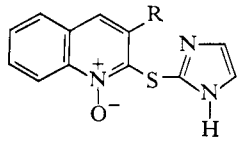


807

2-Chloroquinoline *N*-oxide with imidazole-2-thione in hot chloroform gives the imidazolyl quinolyl thioether (**808**; R = H), which has some use in the treatment of superficial mycoses.[1583] Several other quinoline *N*-oxides have been reacted similarly, including 2,3-dibromoquinoline *N*-oxide which yields, as expected, the 3-bromo-2-thioether (**808**; R = Br). 4-Chloro-6-methoxy-2-methylquinoline condenses with benzothiazole-2-thione in chloroform to give the thioether (**809**).[777]

4-Bromoquinoline *N*-oxide reacts with potassium thiocyanate or selenocyanate in boiling acetone to give 4-thiocyanato- and 4-selenocyanato-quinoline *N*-oxide (**810**; R = SCN or SeCN, respectively) in high yields (81% and 84%).[1573] An attempt



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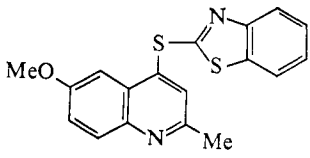

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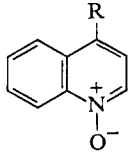

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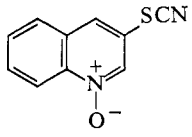
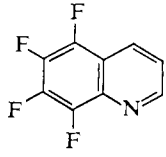


811

to prepare 3-thiocyanatoquinoline *N*-oxide (**811**) by reaction of 3-bromoquinoline *N*-oxide with potassium thiocyanate in boiling ethanol failed.[1559]

g. Nucleophilic Displacement Reactions Involving Polyhaloquinolines. The bulk of the investigations on the reactions of polychloro- and polyfluoroquinolines have been carried out by Musgrave and his co-workers. These authors have shown[271, 721] that 5,6,7,8-tetrafluoroquinoline (**812**) undergoes nucleophilic substitution solely at the 7-position. Thus, treatment of the tetrafluoroquinoline with aqueous ammonia, potassium hydroxide in *tert*-butyl alcohol, and sodium methoxide in methanol, yields 7-amino-, 7-hydroxy-, and 7-methoxy-5,6,8-trifluoroquinoline, respectively.



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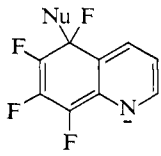

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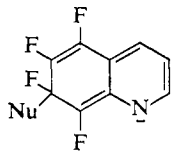


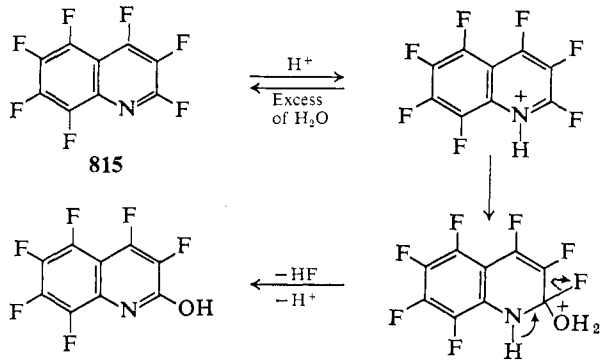
814

Nucleophilic substitution at the 5- and 7-positions is anticipated on consideration of the transition states involved (i.e. **813** and **814**), which allow delocalization of the negative charge onto the ring-nitrogen. Of the two possibilities, the transition state (**814**) is more stable as it involves the more energetically favourable[847, 1266] *para*-quinonoid structure as opposed to the *ortho*-quinonoid form involved in the transition state of the 5-isomer.

7-Bromo-5,6,8-trifluoroquinoline, prepared from the 7-amino-compound by diazotization and treatment with cuprous bromide in hydrobromic acid, undergoes metal–halogen exchange with *n*-butyl-lithium in dry tetrahydrofuran at −45 °C.[721] The resulting 7-lithio-compound reacts readily with trimethyl borate and 85% hydrogen peroxide to give 5,6,8-trifluoro-7-hydroxyquinoline, identical with the product obtained by direct hydroxylation.*

* 4,5,7,8-Tetrachloroquinolines react with sodium hydrogen sulphide or disodium sulphide to give the corresponding quinoline-4-thiones.[2063]

As may well be expected on the basis of the strong electron-withdrawing effects of the halogen substituents, both heptachloro- and heptafluoro-quinoline (**815**) are very weakly basic. They do not form salts with hydrogen chloride nor do they complex with boron trichloride.[35] They will, however, dissolve in concentrated sulphuric acid and, on dilution, the chloro-compound is recovered unchanged. Heptafluoroquinoline, however, is precipitated from the acid solution along with varying amounts of a hexafluorohydroxyquinoline, and the amount of hydroxy-compound appears to depend on the rate of dilution of the acid solution. For instance, quenching the solution into cold water yields only traces of hydroxy-compound, whereas slow dilution yields mainly polyfluorohydroxyquinoline. These results are explained in terms of initial protonation of the quinoline ring and then, in the presence of an excess of water (i.e. during quenching), rapid deprotonation. During slow dilution, however, a competing substitution process can take place as indicated in the adjacent Scheme.



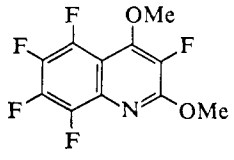
Addition of methanol to the sulphuric acid solution of the heptafluoroquinoline results in the formation of hexafluoro-2-methoxyquinoline.

In all these reactions it is presumed by the authors, on the basis of the known reactivities of 2- and 4-haloquinolines (see Section II.2.C.b), that substitution is occurring at the 2-position. A more rigorous investigation,[751] however, into the nucleophilic substitution reactions of heptafluoroquinoline reveals that with sodium methoxide at 15 °C a mixture of two isomeric hexafluoromethoxyquinolines is produced in the ratio of 3.4 : 1. The structures of these isomers were finally decided by means of ^{19}F- and ^{1}H-nuclear magnetic resonance as being hexafluoro-2- and -4-methoxyquinoline, respectively. Treatment of heptafluoroquinoline with two equivalents of sodium methoxide in boiling methanol yields 3,5,6,7,8-pentafluoro-2,4-dimethoxyquinoline (**816**) (64%).

A longer period of heating with an excess of sodium methoxide in methanol brings about the formation of a tetrafluorotrimethoxyquinoline (possibly 2,4,7-trimethoxy-), which the authors, on the basis of an unsharp melting point, suggest to be a mixture of isomers. A gas–liquid chromatogram of the product, however, shows only one component.

Heptafluoroquinoline with hydrazine hydrate in dioxan at room temperature gives hexafluoro-2-hydrazinoquinoline (76%).[36, 751] At reflux temperature, however, extensive decomposition occurs. In acetone solution heptafluoroquinoline and aqueous ammonia gave a mixture of 2- and 4-aminohexafluoroquinolines from which only the 2-amino-isomer could be obtained pure.

The tautomeric nature of polyfluoro-2- and -4-hydroxyquinolines has been investigated by Musgrave and his co-workers.[1584] On the basis of ultraviolet spectral



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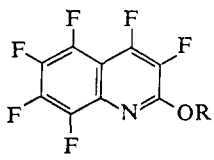

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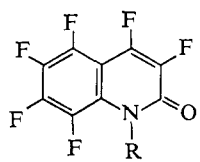
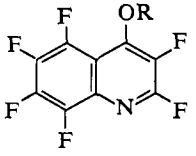


818

data and methylation and demethylation experiments they conclude that 3,4,5,6,7,8-hexafluoro-2-hydroxyquinoline exists as the tautomeric system (**817** ⇌ **818**; R = H), whereas the 4-hydroxy-isomer exists solely as the enol form (**819**; R = H).

In the presence of a molar excess of hot aqueous potassium hydroxide, heptafluoroquinoline gives a mixture of hexafluorohydroxyquinolines, methylation of which with diazomethane yields hexafluoro-2-methoxyquinoline (**817**; R = Me) (30%), hexafluoro-4-methoxyquinoline (**819**; R = Me) (20%), and hexafluoro-1-methyl-2-quinolone (**818**; R = Me) (50%).[1584] Heptafluoroquinoline on treatment with potassium hydroxide in *tert*-butyl alcohol, and then with diazomethane, gives



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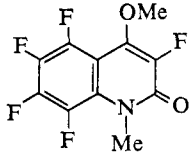


820

essentially the same products, whereas reaction with a greater amount (2-molar excess) of aqueous potassium hydroxide followed by diazomethane yields hexafluoro-2- (40%) and -4-methoxyquinoline (2%) together with the quinolone (**818**; R = Me) (38%), pentafluoro-2,4-dimethoxyquinoline (**816**) (15%), and pentafluoro-4-methoxy-1-methyl-2-quinolone (**820**) (5%).*

The acid-catalysed nucleophilic substitution reactions of perfluoroquinoline[750, 752] and of perfluoroheterocycles[752] in general have been extensively investigated by Musgrave and his co-workers. Of particular interest are the halogen-exchange reactions undergone by heptafluoroquinoline when treated with hydrogen halides and Lewis acids (e.g. AlX_3 and BX_3, where X = Cl, Br, or I). The results of these studies are discussed in Section II.1.F.e.

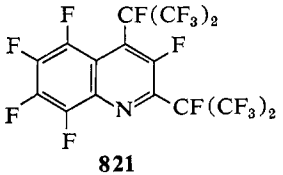
A mixture of concentrated sulphuric acid, acetic acid, and hydrogen peroxide has been shown to be an effective reagent for the conversion of perchloroheterocycles into their *N*-oxides.[1585] The method, however, fails with heptachloroquinoline, in that only a mixture of starting material and hexachloro-2-quinolone is obtained. This failure to undergo *N*-oxide formation is attributed, not only to the decreased basicity of the nitrogen, but also to *peri*-interaction of the nitrogen lone-pair with the chlorine group at the 8-position.

Musgrave and his co-workers[1586] have shown that perfluoroquinoline undergoes perfluoroalkylation when treated with hexafluoropropene in the presence of fluoride

* The reactions of perchloroquinoline with alkanethiols and sodium in propan-2-ol have also been reported.[2064]

ion.* This reaction, which has also been applied to other perfluoroheterocycles, involves attack by perfluoroisopropyl anion and is regarded by the authors as the nucleophilic equivalent of the well-known Friedel–Crafts alkylation.

The reaction tends to be complex, but hexafluoropropene in triglyme at 18 °C, and in the presence of caesium fluoride, reacts with perfluoroquinoline during 18 hours to give 2,4-bis(perfluoroisopropyl)-3,5,6,7,8-pentafluoroquinoline (**821**) (44–47%) and 2,4,6-tri(perfluoroisopropyl)-3,5,7,8-tetrafluoroquinoline (**822**) (27–32%), together with a mixture of 2- and 4-(perfluoroisopropyl)hexafluoroquinolines (4–5%).



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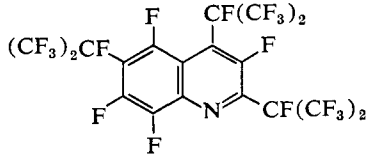

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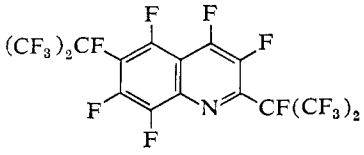


823

It appears that substitution occurs preferentially at the 2- and the 4-position and that this is followed by further attack at the 6-position. At higher temperatures the reaction becomes more complex as fluoride ion-induced rearrangements occur. For example, the bis(perfluoroisopropyl)perfluoroquinoline (**821**), heated with caesium fluoride at 160 °C, rearranges to the 2,6-isomer (**823**) (24%) together with hexafluoro-2-(perfluoroisopropyl)quinoline (13%), 3,5,7,8-tetrafluoro-2,4,6-tri-(perfluoroisopropyl)quinoline (**822**) (3%), and perfluoroquinoline (6%). An intramolecular process is favoured for these rearrangements, and the main product (**823**) is thought to arise because of the *peri*-steric crowding between the perfluoroisopropyl group at the 4-position and the fluorine at position 5; such crowding is not as intense at the 6-position and hence the 2,6-isomer is thermodynamically favoured.

h. Displacement Reactions Involving Aryne Intermediates.† Nucleophilic displacement of halogen from an aromatic substrate by an elimination–addition process is well known, and in many instances the intermediacy of an aryne is well documented. The whole field of aryne chemistry has been the subject of a book,[1587] and more specialized reviews on heteroarynes are available.[1588, 1589]

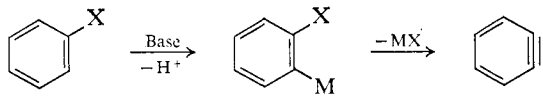
One of the main methods of generating arynes involves treating the halo-compound with strong base, e.g. potassium amide in liquid ammonia, whereupon abstraction of a proton *ortho* to the halogen substituent occurs. Elimination of MX then yields the aryne as indicated in Scheme 74.

On this basis, and unknown to the authors involved, some early work on the preparation of aminoquinolines by the action of strong base on haloquinolines may well have involved aryne intermediates. For example, Gilman and his co-workers[1590]

* Polyfluoroalkylations of perfluoroquinoline with octafluorobut-2-ene have also been described.[2037]

† See also Addenda, p. 693.

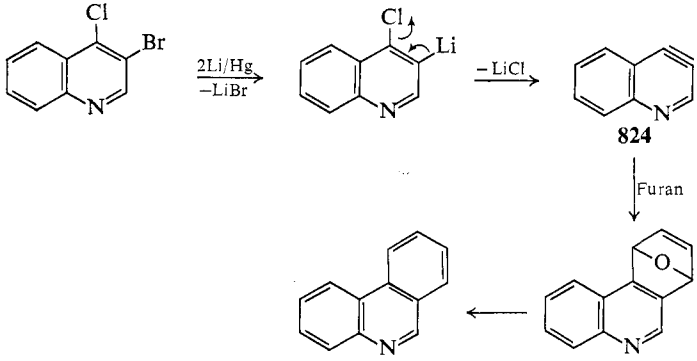
mention that, whereas 2-chloroquinoline with lithium dimethylamide and lithium ethylenimide gives 2-dimethylamino- and 2-ethyleniminoquinoline, respectively, only tars are obtained with potassium amide in liquid ammonia.



SCHEME 74

Also Hauser and Weiss[1591] have investigated the reaction of 2-chloro- and 4,7-dichloro-quinoline with sodium and potassium amides, sodium anilide ($PhNH^-Na^+$), and sodium *N*-methylanilide ($PhNMe^-Na^+$) in liquid ammonia, and in ether solution. In each case only the expected 2- and 4-amino-derivatives were isolated, albeit in low yields (15–50%). Bader,[456] however, reports that 4-amino-6-bromo-2-methylquinoline yields only tars when treated with lithium diethylamide in boiling ether. However, more recent research (see following discussion) suggests that the above-mentioned reactions are more complicated than the authors suspected.

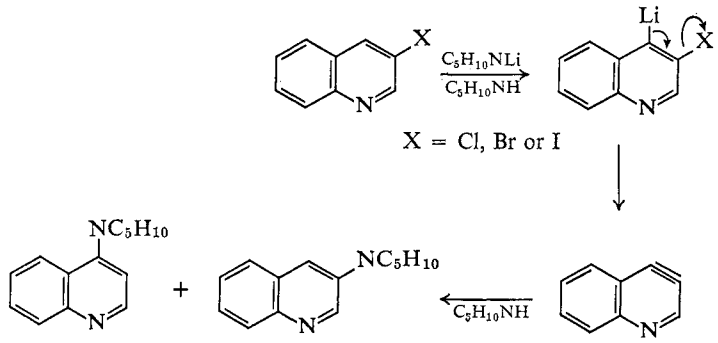
The first attempts to detect a quinolyne intermediate were carried out by Kauffmann and his co-workers who found that 3-bromo-2-chloroquinoline, on treatment with a lithium–mercury amalgam for 5 days in the presence of furan, gave traces (0.1%) of acridine.[1592] 3-Bromo-4-chloroquinoline, however, under the same reaction conditions gave phenanthridine in 9% yield.[1593] The formation of phenanthridine is best explained on the basis of a 3,4-quinolyne (**824**), intermediate as illustrated in Scheme 75.



SCHEME 75

Kauffmann and his co-workers[1593] also studied the action of lithium piperidide in piperidine on 3-fluoro-, 3-chloro-, 3-bromo-, and 3-iodo-quinoline. Except from the fluoro-compound, mixtures of 3- and 4-piperidinoquinolines were obtained in the ratios of 48 : 52 (3-chloro), 50 : 50 (3-bromo), and 49 : 51 (3-iodo). The isomeric products are again satisfactorily explained by invoking the intermediacy of a 3,4-quinolyne as outlined on p. 588.

It is of interest that for the corresponding naphthalene compound (i.e. 1,2-naphthyne) the ratio of α- to β-substituted isomers obtained is 31 : 69. This difference in isomer ratios reflects the influence of the ring-nitrogen atom on the electron-distribution in the aryne intermediate.



As with 3-halopyridines, no trace of 2-piperidinoquinoline, which could arise from a 2,3-quinolyne, could be detected. 3-Fluoroquinoline, again by analogy to 3-fluoropyridine, yields only 3-piperidinoquinoline, and it appears that, while 3-fluoroquinoline reacts by a normal addition–elimination (AEn) process, the other 3-haloquinolines react via an elimination–addition (EA) mechanism. That these reactions occur slowly via an aryne intermediate and not concomitantly with an addition–elimination process was demonstrated by repeating the reactions in the presence of a large excess of piperidine; under those conditions an addition–elimination mechanism would promote a substantial increase in the amount of 3-piperidino-isomer formed; experimentally, however, the product ratios were found to remain reasonably constant.

3-Bromoquinoline *N*-oxide reacts over a period of 3 days with boiling piperidine to give a mixture of 3- (20%) and 4-piperidinoquinoline *N*-oxide (22%).[1594] This reaction presumably involves a 3,4-quinolyne *N*-oxide intermediate and, as before, no 2-piperidino-compound (the product from a 2,3-quinolyne) could be detected. In contrast, but not surprisingly in view of the nucleophilic lability of 4-chloroquinolines, 4-chloroquinoline *N*-oxide under identical conditions undergoes an addition–elimination reaction to give 4-piperidinoquinoline *N*-oxide in quantitative yield.

Kauffmann and his co-workers[1595] have extended their work to include the reactions of 5-, 6-, 7-, and 8-haloquinolines with piperidine and lithium piperidide. In the presence of piperidine in an autoclave at 230 °C for 50 hours, 5-, 6-, 7-, and 8-chloroquinoline undergo piperidinodechlorination by an AEn mechanism to give the respective piperidinoquinolines as the sole products. However, with lithium piperidide and piperidine in boiling dry ether 5-, 6-, and 7-chloro- and 5-, 6-, and 7-bromoquinoline give mixtures of isomeric piperidinoquinolines, whereas only the 8-piperidino-derivatives are obtained from the 8-halo-compounds. The results of these experiments are listed in Table 32.

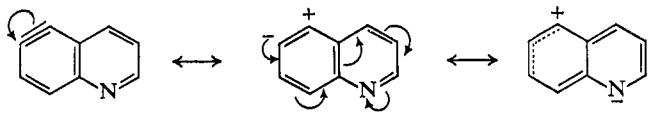
It, therefore, appears that an addition–elimination mechanism is favoured with 8-haloquinolines, whereas an aryne intermediate (i.e. an EA mechanism) is operative when the halogen is at any other position of the benzene ring. The ratio of isomers obtained with these haloquinolines is of interest and sheds light on the relative stability and preferred polarization of the quinolyne intermediates. 5-Haloquinolines can give rise to only one aryne intermediate (**825**) for which the polar structure (**826**) appears, on resonance grounds, to be the more favoured. 6-Haloquinolines can theoretically yield either the 5,6-dehydro- (**825**) or the 6,7-dehydro-intermediate (**827**). Experimentally no product arising from the 6,7-dehydro-form is observed, and the product distribution from 6-haloquinolines are almost identical with those

obtained from the 5-halo-compound. This may be due to the unfavourable loss in bond order involved in the aryne (**827**).

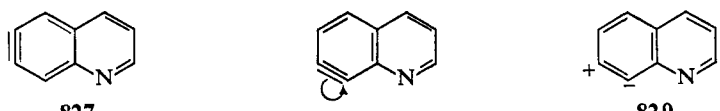
TABLE 32. Piperidinoquinolines Formed by Reaction of Haloquinolines with Lithium Piperidide in Piperidine[1595]

Starting haloquinoline	Total yield (%)	Isomer ratios of piperidinoquinolines produced	
		5- : 6-	7- : 8-
5-Cl	19	27.5 : 72.5	
5-Br	73	28 : 72	
6-Cl	62	28 : 72	
6-Br	83	30 : 70	
7-Cl	13		50 : 50
7-Br	40		52 : 48
8-Cl	76		0 : 100
8-Br	79		0 : 100
8-I	24[a]		0 : 100

[a] Extensive dehalogenation was observed, and quinoline was isolated in 65% yield.



825 **826**

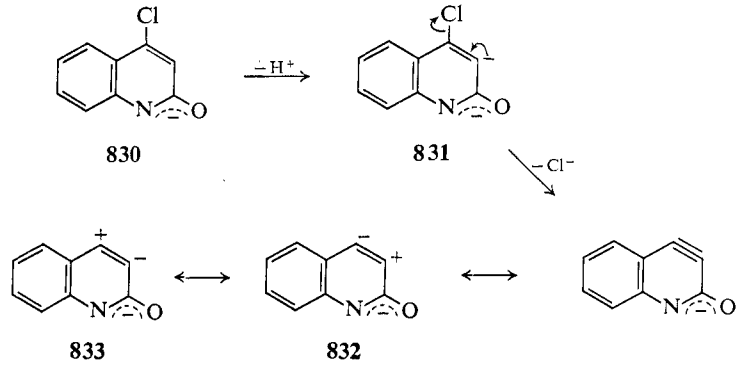


827 **828** **829**

For similar reasons 7-haloquinolines yield only one (i.e. the 7,8-dehydroquinoline; **828**) of the two possible quinolynes. However, in this case little selectivity is shown by the entering piperidino-group, which is surprising since, on the basis of the argument advanced for the 5,6-quinolyne, one would expect polar structure (**829**) to be the more favoured. However, the actual reasons for the selective polarization of the various quinolynes, and for the preference shown by 8-haloquinolines towards addition–elimination reactions, are not as yet clear. Various theories have been tentatively discussed by Kauffmann.[1589, 1595]

Kauffmann and Schulz[1596] have shown that 3-chloro- and 3-bromo-2-quinolone react with piperidine at high temperature (180 °C) to yield mixtures (54 : 46 and 52 : 48, respectively) of 3- and 4-piperidino-2-quinolone. The 1-methyl-2-quinolones behave similarly, and an elimination–addition mechanism (i.e. an aryne intermediate) is proposed. 4-Bromo-2-quinolone and its 1-methyl derivative react more quickly (4 h) at lower temperature (105 °C) to give quantitative yields of the respective

4-piperidino-2-quinolones. However, more recently Japanese workers[1597] have obtained evidence for the participation of a quinolyne intermediate in the reaction of 4-chloro-2-quinolone with potassium hydroxide. It appears that 4-chloro-2-quinolone is unattacked by potassium hydroxide at temperatures below 150 °C, whereas with molten potassium hydroxide a mixture of 3- (57%) and 4-hydroxy-2-quinolone (25%) is obtained. The authors suggest that during the reaction the quinolone is present as the resonance-stabilized anion (**830**) the effect of which is to lessen the activating influence of the ring nitrogen on the halogen at the 4-position. Hence direct substitution of the halogen by an AEn mechanism does not take place, but rather proton loss to give the dianion (**831**) occurs, with subsequent formation of the 3,4-dehydro-2-quinolone (**832**).

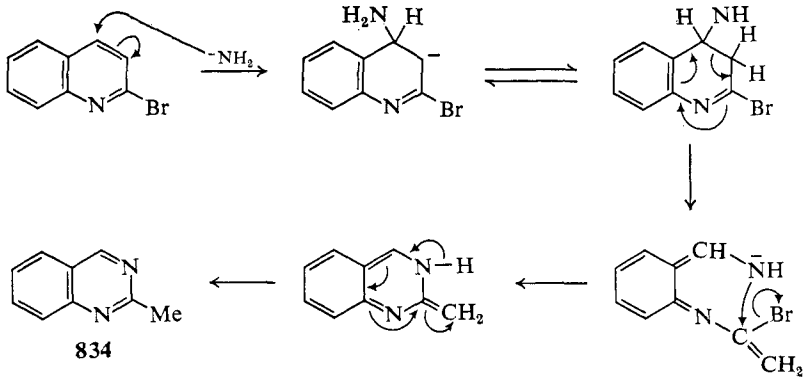


830 **831** **833** **832**

The authors also suggest that the failure of 4-halo-2-quinolones to yield quinolyne when treated with piperidine, as observed by Kauffmann,[1596] is due to the less basic character of piperidine which is not able to promote formation of anion (**830**) and hence permits the reaction to go by way of an AEn mechanism. The predominance of the 3-hydroxy-2-quinolone over the 4-hydroxy-derivative is explained on the basis of thermodynamic rather than kinetic control of the reaction of the two possible dehydro-2-quinolones (**832** and **833**), the argument being that the quinolyne (**832**) is the more thermodynamically stable as the like charges are situated further apart than in the alternate mesomer (**833**).

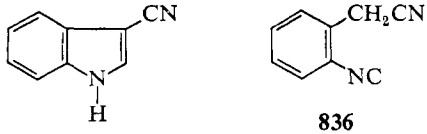
Den Hertog and Buurman[1598] have investigated the reaction of 2-, 3-, and 4-bromoquinoline with potassium amide in liquid ammonia. 3- and 4-Bromoquinoline react to give a mixture of 3- and 4-aminoquinoline. A quinolyne intermediate is indicated in each case, particularly since the ratio of products is virtually identical (1 : 1.2 and 1 : 1.25). No 2-aminoquinoline could be detected in the reaction involving 3-bromoquinoline. 2-Bromoquinoline, however, undergoes a much more complicated reaction with potassium amide. The expected 2-aminoquinoline is formed (50%) together with 2-methylquinazoline (**834**) (25%) and a small amount of quinoline (<1%). Formation of the quinazoline is accounted for on the basis of the following mechanism (Scheme 76). A similar transformation has been observed with 2,6-dihalopyridines, which with potassium amide yield aminomethylpyrimidines.[1599]

Subsequent work by den Hertog and his co-workers[620] reveals that other 2-bromoquinolines undergo similar ring transformations. For example, 3-amino-2-bromoquinoline reacts with potassium amide (4 moles) in liquid ammonia at −33 °C to give, not the expected 2,3-diaminoquinoline, but a mixture of 3-cyanoindole (**835**) (20%) and the isocyanide (**836**) (70%). The isolation of 3-cyanoindole compares



834

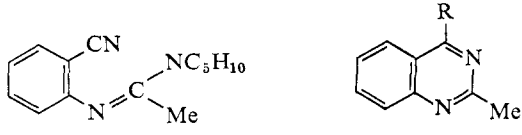
SCHEME 76



835 836

with the formation of 3-cyanopyrrole during the reaction of 3-amino-2-bromopyridine under similar conditions.[1600]

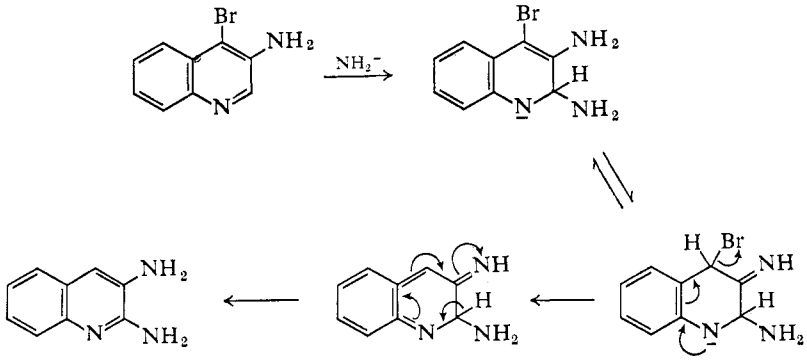
In an analogous reaction 4-amino-2-bromoquinoline on treatment with lithium piperidide in piperidine yields a 1 : 1 mixture of the *o*-cyano-compound (**837**) and the 4-piperidinoquinazoline (**838**; R = $C_5H_{10}N$).[1601]



837 838

This result prompted den Hertog and Buurman[1602] to study the action of potassium amide in liquid ammonia on all six possible isomeric aminobromoquinolines in which both substituent groups are contained on the pyridine nucleus. They found that 2-amino-3-bromo- and 2-amino-4-bromo-quinoline react via a 3,4-quinolyne to give mainly 2,3-diaminoquinoline (85–95%) together with 2,4-diaminoquinoline (3%), and, in each case, a small amount of 2-aminoquinoline (1–2%). 3-Amino-2-bromoquinoline reacts as mentioned above,[620] while 4-amino-2-bromoquinoline reacts as with lithium piperidide (see above) to give a mixture of 4-amino-2-methylquinazoline (**838**; R = NH_2) (65–70%), *o*-aminobenzonitrile (5–10%), and unchanged aminobromo-compound (25%). Of the remaining two isomers 4-amino-3-bromoquinoline is inert under the reaction conditions, while 3-amino-4-bromoquinoline, surprisingly, yields a mixture of 2,3-diaminoquinoline (10%) rather than the expected 3,4-diamino-compound, together with a small amount (2%) of 3-aminoquinoline, the bulk (85–90%) of that reaction mixture consisting of

starting material. The authors propose that 2,3-diaminoquinoline formation proceeds by addition of amide ion at the 2-position, followed by a 1,3-proton shift, and then loss of bromide ion as outlined in Scheme 77.



SCHEME 77

Other possible modes of formation including, (*a*) migration of bromine from the 4- to the 2-position followed by an addition–elimination process, and (*b*) a Chichibabin reaction to give 2,3-diamino-4-bromoquinoline followed by debromination, were considered but rejected on the basis of trial experiments.

The mechanism of these reactions remains somewhat obscure, and a recent communication by den Hertog and his co-workers[1601] highlights and summarizes the difficulties inherent in explaining the reactions of 2-halo-pyridines and -quinolines with strong nitrogenous bases. Related reactions on other halogen-substituted heterocycles have been studied extensively by van der Plas and his co-workers who have proposed a new type of nucleophilic substitution process, the so-called S_n (ANRORC)* mechanism to explain their results.

Shortly after the publication of the den Hertog work[1598] on haloquinolines a Doctoral Dissertation appeared[1603] which discussed in some detail the reactions of all possible monochloro-, monobromo-, and monoiodo-quinolines with potassium amide in liquid ammonia. A careful analysis of the reaction products was carried out by gas–liquid chromatography and infrared spectroscopic techniques. The results of this study are summarized in Table 33.

The results with the 2-, 3-, and 4-haloquinolines are essentially the same as those obtained by den Hertog except that in the case of 3- and 4-chloroquinoline, *o*-amino-phenylacetylene was detected in the products. The origin of this acetylene is not explained but van Meeteren and van der Plas[1604] have observed similar products from the reaction of 4-chloro-5-methyl-2-phenylpyrimidine with potassium amide.

Comparison of the results in Table 33 with those obtained by Kauffmann *et al.*[1595] (see Table 32) show both similarities and differences. The 5- and 6-haloquinolines show a higher percentage of product in which the amino-function is attached to the carbon that bore the halogen substituent. The authors suggest that this may be an indication of the greater nucleophilicity of potassium amide over that of lithium piperidide, a factor of importance in determining the amount of product formed by

* S_n(ANRORC) stands for substitution, nucleophilic, addition of nucleophile, ring-opening, and ring-closure reaction.[2103] For other papers on this work see A. P. Kroon and H. C. van der Plas,[2104] and references cited therein.

TABLE 33. Products formed on Reaction of Haloquinolines with Potassium Amide in Liquid Ammonia

Halo-quinoline	Quinoline (%)	Aminoquinoline; product ratio							2-Methyl-quinazoline (%)	Starting material (%)
		2	3	4	5	6	7	8		
2-Cl-	2.5	100 : 0		—	—	—	—	—	6.2	—
2-Br-	2.2	100 : 0		—	—	—	—	—	3.1	—
2-I-	1.0	100 : 0		—	—	—	—	—	5.8	—
3-Cl-*	—	—	41.3 : 58.7		—	—	—	—	—	4.8
3-Br-*	—	—	42.5 : 57.5		—	—	—	—	—	—
3-I-	—	—	38.4 : 61.6		—	—	—	—	—	—
4-Cl-*	—	—	33.5 : 66.5		—	—	—	—	—	—
4-Br-*	—	—	32.1 : 67.9		—	—	—	—	—	—
4-I-	—	—	40.7 : 59.3		—	—	—	—	—	—
5-Cl-	—	—	—	—	38.3 : 61.7		—	—	—	12.6
5-Br-	—	—	—	—	35.8 : 64.2		—	—	—	—
5-I-	8.0	—	—	—	58.6 : 41.4		—	—	—	—
6-Cl-	—	—	—	—	34.6 : 65.4		—	—	—	—
6-Br-	—	—	—	—	31.9 : 68.1		—	—	—	—
6-I-	1·5	—	—	—	23·7 : 76·3		—	—	—	—
7-Cl-	—	—	—	—	—	—	87.5 : 12.5		—	—
7-Br-	—	—	—	—	—	—	91.6 : 8.4		—	—
7-I-	2.0	—	—	—	—	—	92.4 : 7.6		—	—
8-Cl-	—	—	—	—	—	—	13.7 : 86.3		—	17–68
8-Br-	1.0	—	—	—	—	—	70.3 : 29.7		—	6.5
8-I-	4.4	—	—	—	—	—	78.8 : 21.2		—	8.5

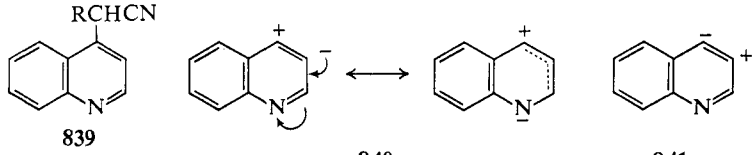
* In these reactions *o*-aminophenylacetylene was isolated in 17.0%, trace, 1.1%, and trace amounts, respectively.

an addition–elimination mechanism, which may well be competing in these reactions with the elimination–addition process.

The large differences in the reactions of 7- and 8-haloquinolines, as reported by the two groups of workers, are obvious. Potassium amide reacts with 7-chloroquinoline to give predominantly 7-aminoquinoline. This may again indicate that concomitant displacement of halogen by both EA and AEn mechanisms is taking place. The major differences in the two sets of results, however, are observed in the reactions of the 8-haloquinolines. 8-Bromo- and 8-iodo-quinoline react mainly by what appears to be an aryne mechanism, since 7-aminoquinoline is formed in approximately three times the yield of the 8-amino-isomer. The authors suggest, although without elaboration, that steric factors are of importance when considering displacement reactions of 8-haloquinolines. This postulate, however, is difficult to accept in light of the results obtained by Kauffmann, since one would expect that an AEn reaction at the 8-position, and involving a piperidide ion, would be more prone to steric interference than a similar reaction involving the far less bulky amide ion. That this is not so, is made clear from the results given in Table 32, for they indicate the formation of only 8-piperidinoquinoline. As can be seen from Table 33, 8-chloro-quinoline reacts sluggishly with potassium amide and even after several hours significant amounts of starting material are recovered, a result again at variance with the observations of Kauffmann. In order to account for the predominance of 8-amino-isomer the authors suggest, but again only tentatively, that the overall reaction with 8-chloroquinoline is slow, but that the AEn process is fast compared

with the EA process. Hence, although only poor yields are obtained, the 8-amino-isomer predominates.

An elimination–addition mechanism may well be operative in the reaction of 3-bromoquinoline with alkyl cyanides in liquid ammonia in the presence of sodamide. Kametani and co-workers[1605] found that methyl, ethyl, and *n*-propyl cyanide react under these conditions to give the 4-(cyanoalkyl)quinolines (**839**;



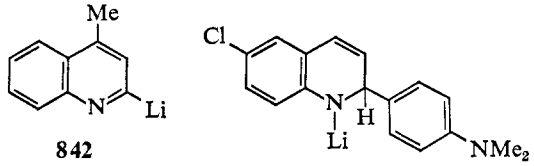
839 **840** **841**

R = H, Me, and Et, respectively) in yields of 15–50%. The absence of any 3-cyano-alkylated quinoline is attributed to the greater resonance stabilization of the polar form (**840**) over that of the alternative mesomer (**841**).

These results, however, are surprising in view of the work of den Hertog[1593] who, in the reaction of 3-bromoquinoline with potassium amide in liquid ammonia, observed formation of both 3- and 4-substituted derivatives.

*D. Reaction with Organometallic Compounds**

The formation of organometallic derivatives of quinoline has been investigated mainly by Gilman and his co-workers. In an early paper they report[1606] that 3-bromo-quinoline with *n*-butyl-lithium at −35 °C gives 3-quinolyl-lithium which on carbonation yields quinoline-3-carboxylic acid (52%). In later, more detailed study Gilman and Spatz[1293] outline the difficulties inherent in the formation of quinoline–metal compounds, particularly addition of the organometallic reagent across the azomethine bond. They found that 2-chloroquinoline was completely unreactive towards both *n*-butyl-lithium and the more reactive methyl-lithium under a variety of reaction conditions. In explanation it was suggested that the nuclear halogen may well deactivate the azomethine linkage towards addition of the organolithium reagent since quinoline under the same reaction conditions readily adds *n*-butyl-lithium. In contrast, 2-iodo-4-methylquinoline reacts with *n*-butyl-lithium at sub-zero temperatures to yield the 2-lithio-derivative (**842**).[1293]



842 **843**

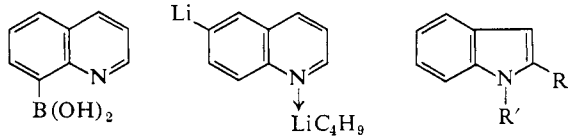
However, in a later paper[1607] Gilman and Beel showed that 2-chloroquinoline reacts with *n*-butyl-lithium to give 2-(*n*-butyl)quinoline in 11.4% yield. Higher yields (52%) were obtained by carrying out the reaction at −45 °C. In the same paper the

* See also Addenda, p. 694.

authors demonstrated that 2-chloroquinoline with phenylmagnesium bromide, and with phenyl-lithium, give 2-phenylquinoline in 31% and 66% yield, respectively. Phenylcadmium chloride, however, fails to react with 2-chloroquinoline. On the basis of these results the relative order of reactivity of 2-chloroquinoline with a series of organometallic reagents was shown to be *n*-butyl-lithium > phenyl-lithium > phenylmagnesium bromide > phenylcadmium chloride. The authors also found that 4-haloquinolines are unreactive towards phenyl-lithium if the 2-position is vacant. Thus 4,7-dichloroquinoline reacted with phenyl-lithium at 0 °C to give 4,7-dichloro-2-phenylquinoline in 85% yield; an excess of phenyl-lithium yielded only tarry products. More recently Gilman and Soddy have been able to prepare and isolate both 2-lithio-[1608] and 4-lithio-quinoline,[1609] by treating the appropriate bromo-compound with *n*-butyl-lithium in dry diethyl ether at −50 °C.

6-Chloroquinoline reacts with *p*-lithio-*N*,*N*-dimethylaniline to give the 1,2-addition compound (**843**) (44%),[1610] which, in boiling nitrobenzene, yields 6-chloro-2-(*p*-dimethylaminophenyl)quinoline (69%). 6-Bromoquinoline reacts similarly with *p*-chlorophenyl-lithium.[900] 8-Bromoquinoline with *n*-butyl-lithium in dry ether at −39 °C gives an intermediate which, on treatment with tri-(*n*-butyl) borate, yields the quinoline-8-boronic acid (**844**) (79%).[1611]

A whole range of substituted 4-chloro- and 4-bromo-quinolines have been converted into the corresponding quinoline-4-carboxylic acids by carbonation of their 4-lithio-derivatives,[627] which were obtained by treating the halo-derivative with *n*-butyl-lithium at −35 °C. A useful synthesis of quinoline-5-, 6-, and 8-carbaldehyde has recently appeared,[900] which involves the use of *n*-butyl-lithium and the corresponding haloquinoline. Reaction of 6-bromoquinoline with two equivalents of *n*-butyl-lithium at −70 °C in a 50 : 50 tetrahydrofuran–ether mixture yields the



844 **845** **846**

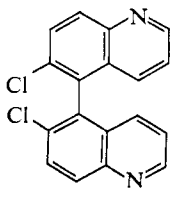
6-lithioquinoline–*n*-butyl-lithium complex (**845**). Treatment of the complex with a solution of *N*,*N*-dimethylformamide in tetrahydrofuran, which has been previously chilled to −70 °C, gives, after hydrolysis, quinoline-6-carbaldehyde (76%). The authors emphasize the need for two equivalents of *n*-butyl-lithium since with only one equivalent co-ordination with the ring-nitrogen, rather than halogen–metal exchange, takes place. Interestingly 6-bromo-8-methyl-2-phenylquinoline, a molecule in which the ring-nitrogen position is highly hindered sterically, proved to be the only halo-compound used which underwent halogen–metal exchange in the presence of one equivalent of lithium reagent. Low temperatures are necessary during reaction in order to prevent addition of the organometallic reagent to the azomethine bond, and hence to 2-(*n*-butyl)quinoline formation. However, it is found that with 6-bromo-quinolines not possessing an 8- or a 2-substituent, small amounts of the azomethine adduct are always formed.

4-Chloro- and 4-bromo-quinoline and their *N*-oxides fail to react with diethyl ethoxymagnesiomalonate, $EtOMgCH(CO_2Et)_2$.[1294] 2-Chloroquinoline and indolylmagnesium bromide (**846**; R = H, R′ = MgBr) react to give 3-(2-quinolyl)indole, while with 1-methyl-2-lithioindole (**846**; R = Li, R′ = Me) the 2-(2-quinolyl) derivative (**846**; R = 2-C_9H_6N, R′ = Me) is obtained.[429]

E. Coupling Reactions to give Biquinolines

The coupling of aryl halides in the presence of copper is a well-known process for the synthesis of biaryls,[1612] and is familiarly known as the Ullmann biaryl synthesis. It was in fact Ullmann who first synthesised 6,6′-biquinoline by causing 6-iodoquinoline to react with copper powder at 220 °C.[1613] By this method many biquinolines have since been prepared and many variations in reaction conditions have been employed.

6-Chloro-5-iodoquinoline, when heated under reflux with copper powder in nitrobenzene, couples preferentially by loss of iodine to give the 5,5′-biquinoline (**847**).[730]



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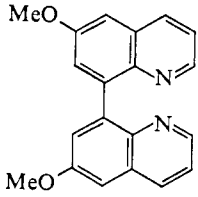


848

An attempt[692] to prepare 6-methoxy-8-(*p*-nitrophenyl)quinoline by treating 8-iodo-6-methoxyquinoline with *p*-chloronitrobenzene under Ullmann conditions failed in that only the symmetrical biquinoline (**848**) was obtained. 3-Bromo-2-methoxy-4-methylquinoline yields 2,2′-dimethoxy-4,4′-dimethyl-3,3′-biquinoline in boiling diphenyl ether solution containing copper bronze,[1614] whereas 2-chloro-4-methylquinoline yields only trace amounts of 4,4′-dimethyl-2,2′-biquinoline when heated with copper bronze in a sealed tube at 218 °C for 2 hours;[1615] the yield is not improved by using the 2-bromo- or 2-iodo-derivative.

2-Bromo-4-phenylquinoline with copper powder at 280 °C gives 4,4′-diphenyl-2,2′-biquinoline in low yield (3.1%).[615] An identical yield of 8,8′-diethyl-2,2′-biquinoline is obtained from the reaction of 2-bromo-8-ethylquinoline with copper powder at 220 °C.[617] Under the same conditions 2-bromo-8-methyl- and 2-bromo-8-phenylquinoline fail to yield the expected biquinoline even in the presence of activated[1616] copper powder. As an alternative procedure, a reductive coupling method was tried which involved heating a mixture of the haloquinoline with hydrazine hydrate under reflux in the presence of potassium hydroxide, and palladium-on-calcium carbonate. This technique was first used by Ueda,[1617, 1618] who thus prepared 7,7′- and 5,5′-biquinoline in 40% and 17% yield, respectively, and later by Busch and his co-workers[1619] who obtained 7,7′-biquinoline in 57.5% yield. However, 8,8′-dimethyl- and 8,8′-diphenyl-2,2′-biquinoline were obtained in yields of only 0.8% and 1.7%, respectively.[617] The method has, nevertheless, been used successfully by Nakano[610] and he and his co-workers in a series of publications have reported the preparation of a host of 2,2′-biquinolines bearing alkyl,[609-612, 614] aryl,[609, 612, 613] alkoxy-,[609, 611-613] and chloro-substituents;[614] in general, yields are in the region of 20–50%.

Attempts to synthesize 6,6′-dimethyl-2,2′-biquinoline, by either a Wurtz–Fittig reaction (sodium in dry ether) or a Grignard reaction on 2-bromo-6-methylquinoline, failed.[616]

*F. Nitration**

a. INTRODUCTION. The electrophilic substitution of heteroaromatics has been extensively investigated over the past few years. In particular, the process of nitration

* See also Addenda, p. 695.

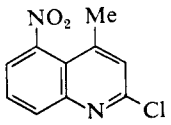
has received considerable attention and a recent text[1620] covers in excellent manner the many facets of aromatic nitration processes. In strongly acidic media quinoline is nitrated, as the quinolinium ion, at the 5- and 8-positions, whereas at lower acidities there is some evidence for the participation of the 3,4-bond during nitration and subsequent 3-nitroquinoline formation. As will be seen from the following discussion the presence of a halogen substituent in the quinoline nucleus does not seriously disturb the orientation of the nitration products. Generally a mixture of fuming nitric acid and concentrated sulphuric acid is effective for nitrating haloquinolines although, as will be mentioned below, other nitrating agents have been employed.

b. NITRATION OF 2-HALOQUINOLINES. Early reports by Claus and Pollitz[605] and Decker[1621] indicate that 2-bromoquinoline is nitrated by a mixture of fuming nitric acid and concentrated sulphuric acid to give a mixture of the 5- and 8-nitro-derivatives. Fischer and Guthmann[630] similarly obtained a mixture of 2-chloro-5-nitro- and 2-chloro-8-nitro-quinoline on nitration of 2-chloroquinoline. Deinet and Lutz[424] reinvestigated this reaction and found that separation of the nitration products by steam-distillation yields the steam-volatile 5-nitro-isomer (9.4%) together with a residue of 2-chloro-8-nitroquinoline (52%). Conditions for obtaining an optimum yield of the 8-nitro-isomer are described.

2-Chloro- and 2-bromoquinoline *N*-oxide are nitrated in 80% sulphuric acid at 70 °C with potassium nitrate to give the respective 4-nitroquinoline *N*-oxides.[741]

Nitration of 2-chloro-4-methylquinoline has led to some confusion in the literature regarding the orientation of the resulting nitro-compounds. Krahler and Burger[347] carried out the nitration as for 2-chloroquinoline (i.e. fuming nitric acid and concentrated sulphuric acid at 100 °C for 15 minutes) and obtained a mixture of 2-chloro-4-methyl-6-nitroquinoline, m.p. 213 °C (10%) (a known compound), and, as the major product, a nitro-compound, m.p. 134 °C, which, by a process of elimination, they designated as the 2-chloro-5-nitro-isomer (**849**).

Contemporary with this work, however, is a report by Johnson and Hamilton[420] who nitrated 2-chloro-4-methylquinoline at −5 °C over a period of 2 hours, using the same nitrating medium. They obtained a mixture which on fractional crystallization from ethanol gave the 6-nitro-isomer (12%) and the nitro-isomer, m.p. 135° (63%), which they regarded as being the 8-nitro-isomer (**850**); a subsequent report by



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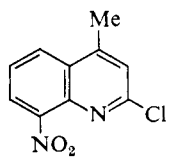

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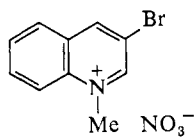

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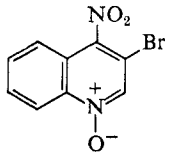
Krahler and Burger[1002] confirmed the structure of this product. In a later nitration experiment, Adams and Hey[423] were able to isolate a low yield of a third nitro-isomer, m.p. 143 °C, which they regard as the hitherto unknown, and previously[347] wrongly identified 5-nitro-isomer (**849**). Ishikawa and Kikkawa[1622] have, however, since shown that the product of m.p. 143 °C is in fact the 8-nitro-isomer (**850**), and that the product melting at 135 °C, originally thought by Johnson and Hamilton to be the 8-nitro-compound, is in fact a mixture of the 6- and the 8-nitro-compound.

2-Chloro-6-methylquinoline is easily nitrated at 100 °C to give the 5-nitro-derivative,[641] while at room temperature 2-chloro-7-methylquinoline yields 2-chloro-7-methyl-8-nitroquinoline (10%) together with other unspecified products.[652] Fischer[633]

nitrated 2-chloro-8-methylquinoline at 60 °C and obtained a mononitro-derivative, m.p. 232 °C, of unknown composition. However, when the nitration is carried out at 0 °C over 12 hours 2-chloro-5-nitro-8-methylquinoline, m.p. 119 °C is obtained in 67% yield.[418]

c. NITRATION OF 3-HALOQUINOLINES. Claus and Howitz[717] report that 3-bromoquinoline, on nitration, gives 3-bromo-5-nitroquinoline as the main product, together with the 8-nitro-isomer. Decker and his co-workers[1623] confirmed this result and quote yields of 85% and 15%, respectively, for the two isomers. 3-Chloroquinoline yields on nitration the 5-nitro-derivative (82%),[116, 237, 1121] as does 3-bromo-1-methylquinolinium nitrate (**851**).[1623]

3-Bromoquinoline *N*-oxide is slowly nitrated at −20 °C, giving a mixture consisting mainly of 3-bromo-5-nitroquinoline *N*-oxide together with a little of the 8-nitro-isomer.[1624] At 70 °C, however, the main product is the 4-nitro-compound (**852**) accompanied by smaller amounts of the 5- and 8-nitro-isomers. A more complicated reaction takes place at 130 °C in that a mixture of 3-bromo-4-nitro-, 3-bromo-5-nitro, and 3-bromo-8-nitroquinoline, together with 3,8-dibromo-5-nitroquinoline, is formed. 3-Fluoroquinoline *N*-oxide is nitrated by potassium nitrate in 79% sulphuric acid at 90 °C to give 3-fluoro-4-nitroquinoline *N*-oxide in 96.5% yield.[684]



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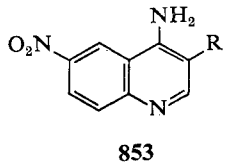

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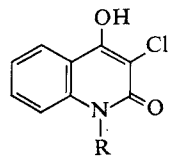

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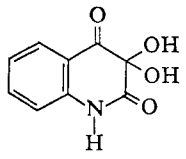
3-Iodo-2-quinolone is nitrated at the 6-position,[320] while 4-amino-3-bromoquinoline, with mixed acids, yields a mixture of the 6-nitro-compound (**853**; R = Br) (87%) together with an unidentified amino-bromodinitroquinoline, and the amino-dinitro-compound (**853**; R = NO_2) formed by displacement of bromine.[172, 173]

Nitration of 3-chloro-4-hydroxy-2-quinolone (**854**; R = H) with nitric acid (s.g. 1.4) at 45° yields a mixture of the *gem*-diol (**855**) (24%), the chloronitro-compound (**856**; R = H) (42%), and the ring-opened structure (**857**) (12%).[263]



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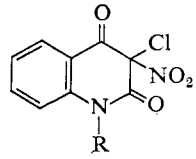

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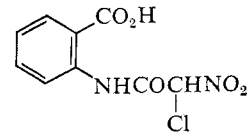

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Later studies by Wittmann[248] show that the 3-nitro-compound (**856**; R = Me) can be prepared in 50% yield from the 1-methyl-2-quinolone (**854**; R = Me) by using a mixture of concentrated nitric and acetic acid at 50 °C. The 1-phenyl-2-quinolone (**854**; R = Ph) under the same conditions yields the 3-nitro-compound (**856**; R = Ph) (57%).

d. NITRATION OF 4-HALOQUINOLINES. Baker and his co-workers[116] obtained a 40% yield of 4-chloro-8-nitroquinoline by nitrating 4-chloroquinoline at 100 °C

with a mixture of fuming nitric and concentrated sulphuric acid. Subsequent work by Mosher and his co-workers,[537] and Simpson and Wright,[760] however, reveals that nitration of 4-chloroquinoline at room temperature over a period of 3 hours yields a mixture of 4-chloro-8- and -5-nitroquinoline (40% and 20%, respectively). An improved procedure for the preparation of 4-chloro-8-nitroquinoline by direct nitration of 4-chloroquinoline has been reported.[1279]

4-Chloroquinoline *N*-oxide undergoes nitration at the 3-position (42%) with a solution of potassium nitrate in 79% sulphuric acid.[838] 4-Chloro-2-methylquinoline with a solution of potassium nitrate in oleum at room temperature gives a mixture of the 8-nitro- (main product), 5-nitro-, and 6-nitro-derivatives. Surprisingly, under the same conditions, 4-chloro-6-methoxy-2-methylquinoline is reported[475] to undergo nitration solely at the 8-position, whereas the analogous 6-ethoxy-compound with fuming nitric acid at 0 °C gives the 5-nitro-derivative in 90% yield.[498] Heindel and his co-workers, however, have shown[1625] that the former result is in error and that the 5-nitro-isomer is in fact produced in 58% yield. They also observed that 4-chloro-7-fluoro-6-methoxyquinoline, 4-chloro-6-methoxy-7-(trifluoromethyl)quinoline, and 4-chloro-6-methoxyquinoline are nitrated at the 5-position in 63%, 40%, and 83% yield, respectively.

Nitration of 4-chloro-3-methylquinoline with fuming nitric acid and concentrated sulphuric acid yields a mixture of the 5- and 8-nitro-derivatives which are difficult to separate.[543] Under similar conditions 4-chloro-7-methylquinoline is nitrated mainly at the 6-position (48%) but gives also the 8-nitro-isomer (5.5%).[778]

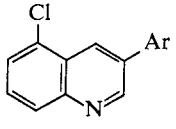
e. Nitration of 5-Haloquinolines. 5-Chloroquinoline can be nitrated at the 8-position, by a mixture of fuming nitric acid and concentrated sulphuric acid,[548, 698, 866, 959] whereas under the same conditions 5-bromoquinoline yields a mixture of the 6- and 8-nitro-derivatives.[176, 669, 715] Fuming nitric acid alone will also effect nitration of 5-bromoquinoline, but the reaction mixture has to be warmed to complete the reaction.[669] Attempts to prepare a bromodinitroquinoline failed. In fact, 5-bromo-6-nitroquinoline and a mixture of fuming nitric acid and concentrated sulphuric acid in a sealed tube at 120 °C for 20 hours yield a product which gives analyses correct for a dibromonitroquinoline and is thought to be 3,5-dibromo-8-nitroquinoline.[669] The possible mode of formation of this unexpected product is discussed in Section II.2.J. 5-Iodoquinoline on nitration yields a mixture of 5-iodo-6- and -8-nitroquinolines.[690]

5-Chloro- and 5-bromo-quinoline have been nitrated, as their nitrate salts, by potassium nitrate in 100% sulphuric acid.[1626] The 8-nitro-derivative is obtained in each case and yields of 83% and 81.3%, respectively, are claimed. Nitration of a mixture of 5- and 7-chloro-2-methylquinoline yields a mixture of the easily separable 8-nitro-derivatives.[706] 5-Chloro-2,6-dimethylquinoline can be nitrated at the 8-position in high yield (94%).[687] Nitration of 5-chloro-3-phenylquinoline, however, takes place at the phenyl ring and 5-chloro-3-(*p*-nitrophenyl)quinoline (**858**; Ar = *p*-$NO_2C_6H_4$) is the sole product.[359]

5-Chloro-8-hydroxyquinoline with a mixture of concentrated nitric and glacial acetic acid is nitrated in high yield (80%), as expected, *ortho* to the hydroxy-function.[231] 5-Bromo-6,7-dimethoxyquinoline, however, is reported[409] to undergo oxidative decomposition on attempted nitration.

It has been shown[214, 1627] that 8-hydroxy-5-iodoquinoline undergoes rearrangement during nitration to yield 8-hydroxy-7-iodo-5-nitroquinoline. The 5-bromo-compound behaves similarly and yields 7-bromo-8-hydroxy-5-nitroquinoline (90%) together with the 5-bromo-7-nitro-derivative (10%). 5-Fluoro- and 5-chloro-8-hydroxyquinoline, however, behave normally in that they give the corresponding

5-halo-8-hydroxy-7-nitroquinolines without accompanying halogen migration. The abnormal reactions appear to be examples of the so-called Reverdin rearrangement,[1628-1630] and probably involve displacement of halogen from the 5-position by nitronium ion, and subsequent halogenation of the formed 8-hydroxy-5-nitroquinoline by the liberated halonium species (I^+ and Br^+).



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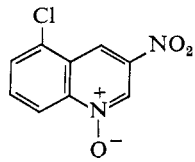

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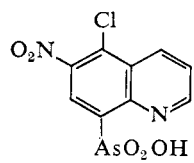

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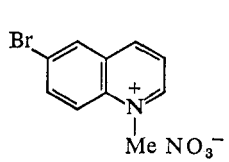
5-Chloroquinoline *N*-oxide reacts with benzoyl chloride (one equivalent) in the presence of silver nitrate to give 5-chloro-3-nitroquinoline *N*-oxide (**859**) (34.3%).[1631] Further treatment yields 5-chloro-3,8-dinitroquinoline.

5-Chloroquinoline-8-arsonic acid is nitrated readily, giving the 6-nitro-derivative (**860**).[819]

f. Nitration of 6-Haloquinolines. Early reports[716, 1632] on the nitration of 6-bromoquinolines indicate that the nitro-group enters at the 5-position. Claus and Reinhard,[836] however, using fuming nitric acid either alone or mixed with concentrated sulphuric acid obtained a mixture of 6-bromo-5- and 6-bromo-8-nitroquinoline. In a similar manner 6-chloroquinoline yields the corresponding 6-chloro-5- and 6-chloro-8-nitro-derivatives,[281] although the latter is reported to be the sole product when nitric acid alone is used as the nitrating agent. Decker *et al.*[1623] nitrated 6-bromo-1-methylquinolinium nitrate (**861**) to obtain mainly the 5-nitro-derivative (**862**).



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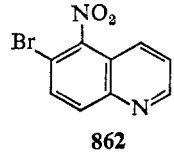

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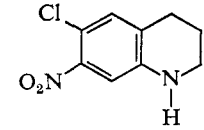


863

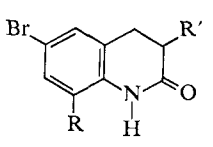
6-Iodoquinoline[147, 690] and 6-iodo-2-methylquinoline[147] with mixed acids yield their 5-nitro-derivatives. 6-Fluoroquinoline, however, under the nitrating conditions employed by Claus and Schedler,[281] i.e. heating under reflux with fuming nitric acid, yields 6-fluoro-8-nitroquinoline (25%).[846]

Nitration of 6-chloro- and 6-bromo-quinoline *N*-oxide leads solely to the formation of their 5-nitro-derivatives,[1633] and the authors comment on the fact that the *N*-oxide function does not influence the position taken up by the incoming nitro-group even though the halogen atom present has only a weak, activating, mesomeric effect.

Capps and his co-workers[632, 647, 653] have nitrated a series of 6-bromo- and 8-alkyl-6-chloro-substituted quinolines and find that nitration occurs at the 5-position in each instance. As expected, 6-chloro-8-hydroxyquinoline is nitrated smoothly at room temperature with mixed acids to give 6-chloro-8-hydroxy-5-nitroquinoline.[854] 8-Acetamido-6-chloroquinoline behaves similarly with a solution of potassium nitrate in concentrated sulphuric acid.[840] Nitration of 6-chloro-2,4-dimethylquinoline occurs in high yield (90%) at the 5-position.[91]

Nitration of 6-chloro-1,2,3,4-tetrahydroquinoline in cold sulphuric acid is reported[1634] to give 6-chloro-1,2,3,4-tetrahydro-7-nitroquinoline (**863**), which is to be expected if the cation of the secondary base is the species undergoing nitration. On the other hand, nitration of 6-bromo-1,2,3,4-tetrahydro-2-oxoquinoline (**864**; R = R′ = H) with mixed acids at 5 °C is reported[1635] to give the 8-nitro-derivative (**864**; R = NO_2, R′ = H), whereas with potassium nitrate in concentrated sulphuric acid the 3,8-dinitro-derivative (**864**; R = R′ = NO_2) is obtained.

Nitration of 6-bromo-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline (**865**; R = R′ = H) has been studied in some detail.[1636] With a mixture of sodium nitrate in concentrated sulphuric acid, initially at 0 °C, then overnight at room temperature, the 8-nitro-derivative (**865**; R = NO_2 R′ = H) is obtained. However, with mixed fuming



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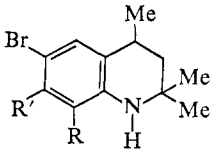

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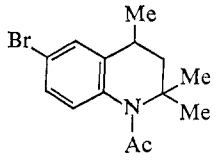
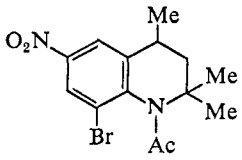


866

acids the 7,8-dinitro-derivative (**865**; R = R′ = NO_2) is formed! Nitration of the 1-acetyl derivative (**866**) proves to be a far more complicated process: unexpectedly, in a mixture of fuming nitric acid and acetic anhydride 1-acetyl-8-bromo-1,2,3,4-tetrahydro-2,2,4-trimethyl-6-nitroquinoline (**867**) is obtained. However, with a solution of sodium nitrate in concentrated sulphuric acid at 0–20 °C a mixture of the



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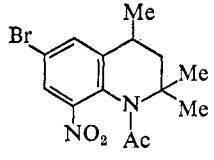


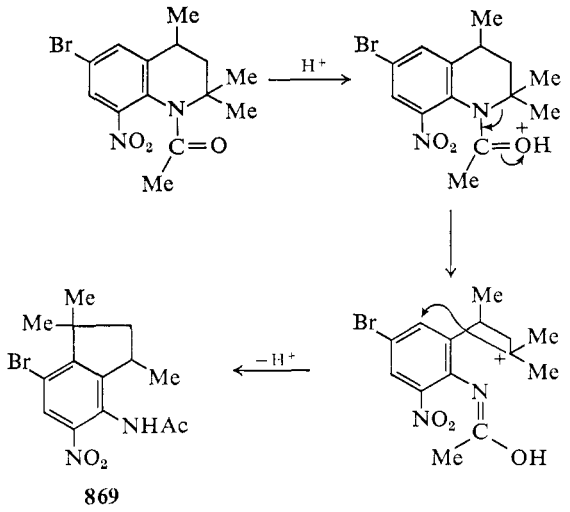
868

isomeric 1-acetyl-6-bromo-8-nitro-compound (**868**) and the bromonitroindane (**869**) is formed. The indane is thought to arise in a process outlined in Scheme 78 (p. 602).

Although no explanation is offered by the authors to account for the formation of the bromo-nitro-compound (**867**), this product could in fact arise by a route analogous to the previously mentioned Reverdin rearrangement.

g. Nitration of 7-Haloquinolines. Nitration of 7-chloroquinoline by fuming mixed acids gives a mixture of 7-chloro-8-nitroquinoline and an unidentified isomeric chloronitro-compound.[268, 866] In a similar manner 7-bromoquinoline yields 7-bromo-8-nitroquinoline plus an unidentified 7-bromonitroquinoline,[715] Both 7-chloro-2-methyl-4-quinolone[1410] and 7-chloro-2,4-dimethylquinoline[91] are nitrated in high yield at the 8-position.

h. Nitration of 8-Haloquinolines. Claus and his co-workers obtained 8-bromo-[717] and 8-chloro-5-nitroquinoline[844] on nitration of the respective 8-haloquinolines. The structure of 8-bromo-5-nitroquinoline was later confirmed by Dikshoorn,[669] who, however, failed in an attempt to dinitrate 8-bromoquinoline. 8-Iodoquinoline is also nitrated at the 5-position.[690]



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SCHEME 78

TABLE 34. Nitration Products of Di- and Tri-haloquinolines

Haloquinoline starting material	Position of entering nitro-group	M.p. (°C)	References
2,7-diBr-	5 or 8	180	618
3,8-diBr-	5	—	95
3,6,8-triBr-	5	215	95, 96
5,8-diBr-	6	155	217, 296
6,8-diBr-	5	159	96, 217
5,7-diBr-	8	198	283
5,6-diBr-	8	152	298
6,7-diBr-	5 & 8	165 & 191	298
4,7-diCl-	8	151	540, 1625
5,7-diCl-	8	168.5	49, 703, 860
5,8-diCl-	6	136	898
4,5,7-triCl-	8	114	54
6,7-diCl-2,4-diMe-	8 ?	197	91
5,6-diCl-2,4-diMe-	8 ?	152.5	91
6,8-diCl-2,4-diMe-	5 ?	123	91
5,8-diCl-2,4-diMe-	6	157	91
6-Br-2-Cl-8-Me-	5	161	647
4,7-diCl-2-Me-	8	121	957
8-Br-2-Cl-6-Et-	5	169.5	644
6-Br-2-Cl-8-Et-	5	132	653
2,6-diCl-8-Et-	5	131	632
2,8-diCl-6-Me-	5	194	646
2,8-diCl-6-Et-	5	171	645
4,7-diCl-6-MeO-	5	101	1625
4-Cl-7-F-6-MeO-	5	137	1625
6,7-diCl-Q *N*-oxide	4	192	838

The nitration of a series of 8-bromo- and 8-chloro-substituted 6-alkylquinolines has been carried out by Capps and his co-workers.[644-646, 650] In all the examples reported, nitration occurs in high yield at the 5-position. 8-Chloro-2,4-dimethylquinoline undergoes nitration at the 5-position,[1637] as do 8-chloroquinoline *N*-oxide[1633] and 8-chloro-4-methylquinoline,[1638] while 8-bromo-5-ethylquinoline yields the 6-nitro-derivative.[425]

i. NITRATION OF DI- AND TRI-HALOQUINOLINES. The position of nitration of di- and tri-haloquinolines is indicated in Table 34. Besides the examples given, Edinger and his co-workers[98, 219] have nitrated polyiodoquinolines of unknown composition. In each case nitration is accompanied by loss of an iodine atom and an unidentified iodomononitroquinoline is obtained.

G. Sulphonation

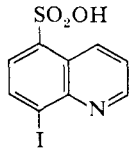
Sulphonation of haloquinolines has not been as extensively explored as nitration. Most of the haloquinolinesulphonic acids have in fact been prepared by Claus and his co-workers during their early investigations on the chemistry of quinoline. As expected, sulphonation resembles nitration in that the incoming sulphonic acid group normally enters at the 5- or 8-position. Thus 5- and 7-chloroquinoline with 30% oleum at 150 °C yield 5-[268] and 7-chloroquinoline-8-sulphonic acid,[698] respectively, while 8-chloroquinoline under similar conditions is sulphonated at the 5-position.[844] 6-Chloroquinoline with 60% oleum at 180° yields mainly 6-chloroquinoline-5-sulphonic acid together with a smaller yield of the 8-sulphonic acid;[281] at 300 °C the latter becomes the major product.

2-Bromoquinoline is sulphonated with 40% oleum at 130 °C to yield a monosulphonic acid, m.p. 290 °C, of unknown constitution,[605] 6-Bromoquinoline with oleum[297, 716] or disulphuric acid ($H_2S_2O_7$)[836] yields mainly the 6-bromo-8-sulphonic acid together with a little of the 5-sulphonic acid. 5-Bromoquinoline under these conditions gives a mixture of the 5-bromo-6- and -8-sulphonic acid, the latter as the main product.[724, 1639]

Sulphonation of 3-bromoquinoline with oleum at 250–300 °C for several hours yields 3-bromoquinoline-5-sulphonic acid as the sole product;[1640] with warm 40% oleum for 1 hour, however, a mixture of 3-bromoquinoline-5- and -8-sulphonic acid is formed; on prolonged heating the 8-sulphonic acid rearranges to the 5-isomer.

Bankovskis and his co-workers[1641] report that sulphonation of 3-bromoquinoline with sulphuric acid yields 3-bromoquinoline-8-sulphonic acid, whereas in a more recent paper[1642] sulphonation with oleum is reported to give the 5-sulphonic acid. 60% Oleum sulphonates 6-bromoquinoline mainly at the 8-position,[1643] as it does 5-bromoquinoline.[1644]

3-Fluoro-,[683] 5-fluoro-,[685] 5-chloro-,[1645] and 5-iodo-quinoline,[728] on treatment with 45–65% oleum, readily undergo sulphonation at the 8-position, while, predictably, 8-iodoquinoline with 40% oleum at 100 °C yields 8-iodoquinoline-5-sulphonic acid (**870**).[690]



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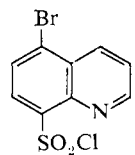

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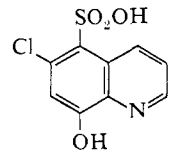

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5-Bromoquinoline with chlorosulphonic acid at 150 °C yields the chlorosulphonyl chloride (**871**),[1646] Similarly, 7-fluoro-, 7-chloro-, 7-bromo-, and 7-iodo-quinoline yield the corresponding 8-sulphonyl chlorides when treated with chlorosulphonic acid at 150–175 °C for 3 hours.[1647]

5,7-Dichloroquinoline is sulphonated readily at the 8-position by 25% oleum at 140 °C.[1648]

6-Chloro-8-hydroxyquinoline, as expected, undergoes sulphonation under milder conditions than those so far discussed: Treatment with 5% oleum at 75 °C for one hour is sufficient to give a good yield of the 5-sulphonic acid (**872**).[232]

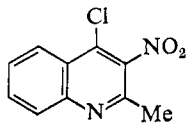
*H. Dehalogenation**

Dehalogenation of haloquinolines may be accomplished using a wide selection of reducing agents and under a variety of reaction conditions. Basically the reducing agents fall into two categories: (*a*) chemical reducing agents, e.g. tin and hydrochloric acid, and (*b*) metal catalysts and hydrogen, e.g. palladium–charcoal or Raney nickel. Chemical methods tend to be associated with the older literature and are more liable to bring about unwanted side reactions in the haloquinoline.

The actual number of instances of dehalogenation recorded in the literature is too vast to be covered completely. Accordingly examples have been selected to show as wide an application of techniques and reagents as possible, and to highlight instances where side reactions, troublesome or otherwise, occur.

Friedländer and Ostermaier[345] observed that tin and hot hydrochloric acid reduce 2-chloroquinoline to 1,2-3,4,tetrahydroquinoline, whereas a mixture of fuming hydriodic acid and acetic acid at 240 °C yields only quinoline. In general it appears that reduction of the pyridine ring is a common occurrence during reductive dehalogenations employing zinc or tin and hydrochloric acid.[281, 388, 595, 698, 732, 844, 849, 862, 864, 1634, 1639] However, 2-chloro-4-methylquinoline is reduced successfully, and in high yield, by tin and hydrochloric acid at 80 °C to 4-methylquinoline.[346, 348, 349] Under similar conditions 4-chloro-6-methoxy-2-methylquinoline[515] and 2-chloro-4,6-dimethylquinoline[888] also undergo dechlorination without accompanying reduction of the pyridine nucleus.

Stannous chloride and hydrochloric acid reduce the chloronitroquinoline (**873**) to 3-amino-2-methylquinoline,[1649] whereas reduction with ferrous sulphate and hydrochloric acid at room temperature gives the 3-amino-4-chloro-derivative. 4,7-Dichloroquinoline undergoes monodechlorination with tin in boiling hydrochloric acid to 7-chloroquinoline.[959]



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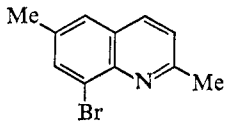

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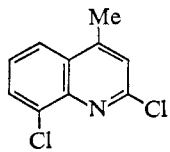

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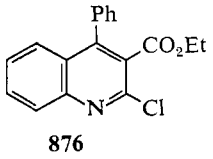
Attempts to synthesize 8-bromo-1,2,3,4-tetrahydro-2,6-dimethylquinoline by tin and hydrochloric acid reduction of the bromodimethylquinoline (**874**) failed.[929] Only the dehalogenated quinoline could be isolated. Tin and hydrochloric acid reduction of the dichloromethylquinoline (**875**) results in the formation of 8-chloro-4-methylquinoline (54%).[401]

* See also addenda, p. 695

Mixtures of potassium iodide, hydriodic acid and red phosphorus,[410, 427, 625, 643, 1650] and of hydriodic and acetic acid,[643, 1403, 1651] have proved useful as dehalogenating agents. With the latter mixture 6-chloro-5-iodoquinoline undergoes selective dehalogenation to 6-chloroquinoline,[730] whereas 2,3-dichloroquinoline[383] and 2,3,4-trichloroquinoline[576] undergo complete dechlorination. It is of interest that 2-chloro-4-ethyl-3-methylquinoline is dehalogenated on treatment with hydriodic acid and acetic acid whereas, with a mixture of phosphorus, hydriodic acid, and potassium iodide, halogen exchange to give 4-ethyl-2-iodo-3-methylquinoline is observed.[643] The isomeric 4-chloro-2-ethyl-3-methylquinoline behaves similarly.

Ester hydrolysis and amine formation, respectively, accompany the dechlorination of the chloro-ester (**876**)[382] and the chloro-nitro-compound (**877**)[706] with hydriodic acid and red phosphorus.



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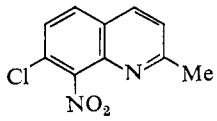

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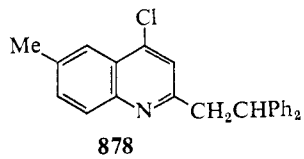

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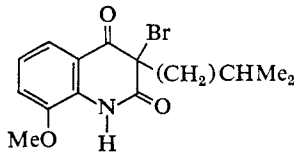
Zinc in either acid[361, 402, 416] or alkaline[180] solution is an effective dehalogenating agent. However, several 2-substituted 4-aryl-6-chloroquinolines have been reduced[1652] to the corresponding 1,2,3,4-tetrahydroquinolines by zinc in a dioxan–hydrochloric acid mixture without loss of the chlorine atom. In the case of 2,5- or 2,7-dichloro-4,6-dimethylquinoline only the 2-chloro-substituent is removed by zinc dust in warm acetic acid.[419] Distillation of the chloroquinoline (**878**) with zinc dust brings about loss of the chlorine atom,[1653] and under similar conditions 2,4-dichloroquinoline is reduced to quinoline.[562] Treatment of 6-bromo-3-methylquinoline with a zinc–copper alloy in boiling sodium hydroxide yields 3-methylquinoline.[888] Distillation of 4-chloro-2-phenylquinoline with zinc dust yields the expected 2-phenylquinoline together with 2,2′-diphenyl-4,4′-biquinoline.[689]

Other systems that have been used for dehalogenation include iron–sulphuric acid,[427] sodium or sodium amalgam in ethanol,[92, 198, 554, 1654] chromyl chloride and hydrochloric acid,[385] and aluminium powder and dilute acetic acid.[406, 1655] Boiling ethanolic potassium hydroxide causes deiodination of 8-iodo-7-(trifluoromethyl)-quinoline,[726] while the dione, (**879**) yields the 4-hydroxy-2-quinolone (**880**) on treatment with zinc and acetic acid.[313]



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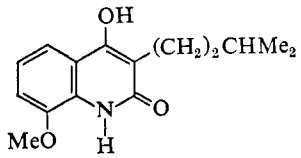

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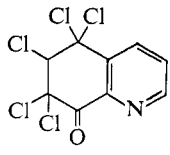
Zinc dust and acetic acid has been shown to be an effective reagent for the mono-dechlorination of 3,3-dichloro-2,4-dioxoquinolines. For example, 3,3-dichloro-1,2,3,4-tetrahydro-2,4-dioxoquinoline is reduced to 3-chloro-4-hydroxy-2-quinolone in high yield (96.5%).[57, 262] This reduction can also be accomplished using a 5%

solution of iodine in a dioxan–hydrochloric acid mixture, or a solution of thiourea in acidified ethanol at 50 °C.[57]

Early reports[59, 62, 75] indicate that polychloroquinolones, e.g. (**881**), are readily dechlorinated in warm sodium bisulphite solution to the chlorohydroxyquinolines, e.g. (**882**).



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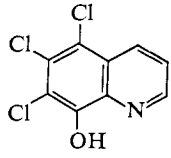

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Raney nickel is a popular reagent for bringing about catalytic dehalogenation of haloquinolines. Raney nickel and hydrogen reduce 2-chloro-4-methyl-5-nitroquinoline in ethanol solution to the corresponding 5-amino-derivative, whereas with Raney nickel in ethanolic potassium hydroxide the chloro-amine undergoes dechlorination to give 5-amino-4-methylquinoline (61%).[347] The latter method has been used on many occasions[120, 367, 399, 1656–1658] for the dechlorination of chloroquinolines.

4,7-Dichloroquinoline is selectively dechlorinated by Raney nickel and hydrogen to give 7-chloroquinoline,[494] whereas 2,4-dichloro-3-(*o*-aminophenyl)quinoline suffers dehalogenation at the 2-position with nickel in methanolic sodium hydroxide.[343]

Occasionally dehalogenations with Raney nickel are accompanied by reduction of the quinoline ring.[705, 707, 708, 901, 1659] For example, reduction of 6-chloroquinoline in ethanol solution either at room temperature, or under pressure at 160 °C, yields 6-chloro-1,2,3,4-tetrahydroquinoline.[1660, 1661]

Blankenstein and Capps[418] have reported loss of the chlorine atom during Raney nickel-catalysed reduction of 2-chloro-8-methyl-5-nitroquinoline to the corresponding amine; in acetone solution, however, the reduction proceeds smoothly without loss of halogen.

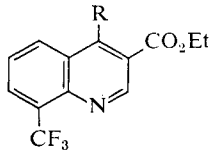
Palladium[469, 502, 533, 1317, 1662] is an effective catalyst for the dehalogenation of many haloquinolines, and a variety of catalyst supports have been employed, viz., palladium and barium sulphate in acetic acid[465, 1663] or methanol,[1003] palladium–charcoal and acetic acid,[129, 392, 403, 407, 412, 501, 1664, 1665] palladium–charcoal and sodium or potassium hydroxide[375, 409, 856, 956, 1345, 1666, 1667] palladium and calcium carbonate,[320, 435, 540, 905, 1637] and palladium–charcoal and hydrochloric acid.[58, 173, 619, 815]

On occasions, reductive dehalogenation of 2- and 4-chloroquinolines with palladium–charcoal in acetic acid are accompanied by quinolone formation.[455, 521, 1665]

Lutz and his co-workers[1668] have found that several 4-chloroquinoline-3-carboxylic esters undergo anomalous dehalogenation. For example, whereas ethyl 4-chloroquinoline-3-carboxylate and the corresponding 6,8-dimethyl-, 8-phenyl-, and 6-methoxy-derivatives are dechlorinated normally by 10% palladium–charcoal in acetic acid at 50 °C, the 8-(trifluoromethyl) derivative (**883**; R = Cl) gives a mixture of the expected dehalogenated product (**883**; R = H) and the 1,4-dihydroquinoline (**884**); the dihydroquinoline is the major product (61%) when reduction is carried out using palladium–charcoal in ethanolic potassium hydroxide.

Surprisingly, ethyl 4,6,8-trichloroquinoline-3-carboxylate is unaffected by either Raney nickel or palladium–charcoal and hydrogen.[1668]

Detailed instructions for the reductive dechlorination of a series of 2-chloro-substituted alkyl- and alkoxy-quinolines by means of palladium–charcoal in acetic



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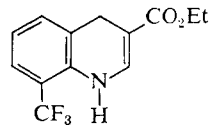
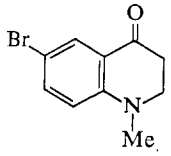


884

acid are available,[1669] and the use of palladium as a general dehalogenating agent is the subject of a brief review.[1670]

6-Amino-2,4-dichloroquinoline is reported[805] to yield 6-aminoquinoline on treatment with palladium–charcoal and hydrogen in 10% hydrochloric acid, whereas 8-amino-4,7-dichloroquinoline with 5% palladium–charcoal and hydrogen in the absence of hydrochloric acid yields 8-amino-7-chloroquinoline.[957] 6-Bromo-1,2,3,4-tetrahydro-1-methyl-4-oxoquinoline (**885**), when heated under reflux in ethylene glycol with 10% palladium–charcoal, suffers debromination and dehydrogenation to 1-methyl-4-quinolone.[126]



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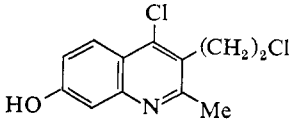

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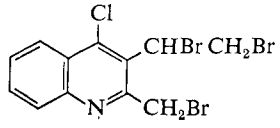
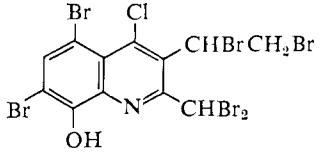


887

The dichloro-compound (**886**) in the presence of palladium–charcoal and hydrogen suffers loss of only the 4-chlorine atom,[827] whereas the chlorotribromo-compound (**887**) undergoes complete dehalogenation to give 3-ethyl-2-methylquinoline.[1452] In a similar manner the polyhaloquinoline (**888**) in the presence of hydrogen and palladium–charcoal at 80–90 °C yields the 8-hydroxyquinoline (**889**).[166]



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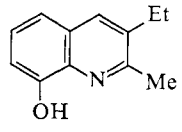
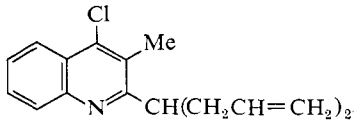


889

2-(1-Allylbut-3-enyl)-4-chloro-3-methylquinoline (**890**), on treatment with palladium–charcoal and hydrogen in ethanol solution, is reduced to 3-methyl-2-(1-propylbutyl)quinoline (**891**).[1671]



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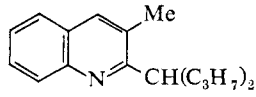


891

The reduction of 5-, 6-, 7-, and 8-bromoquinoline with palladium–charcoal and tritium provides a useful method for the synthesis of quinolines labelled with

tritium at these positions.[1672] The compounds were required for studies on the carcinogenic activity of 4-nitroquinoline *N*-oxide.

3-Bromo-4-nitroquinoline *N*-oxide yields 4-aminoquinoline *N*-oxide hydrobromide (41%) on reduction with 5% palladium–charcoal and hydrogen in ethanol solution.[1673] 4-Chloro-2-methyl-8-nitroquinoline *N*-oxide in methanol containing a trace of hydrochloric acid is reduced in the presence of palladium–charcoal to 8-amino-2-methylquinoline.[815] Similarly 4-chloro-2-phenylquinoline *N*-oxide yields 2-phenylquinoline.[837]

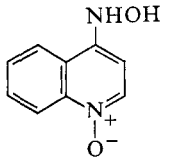
3-Acetyl-4,7-dichloroquinoline proves to be highly resistant towards reductive dehalogenation by palladium–charcoal and hydrogen under a variety of conditions.[460] 4,7-Dichloro-3-cyanoquinoline, however, readily yields 3-cyanoquinoline with palladium–charcoal in the presence of sodium acetate and ethanol.[566] Under the same conditions 4,7-dichloro-3-iodoquinoline yields 7-chloroquinoline.[122]

Palladium–charcoal in the presence of hydrazine hydrate is an effective dehalogenating agent.[1164] 2-Chloroquinoline is reduced to quinoline in 94% yield,[1674] while hydrazine hydrate in the presence of copper sulphate and sodium hydroxide brings about the dechlorination of 4-chloro-5,8-dimethoxy-2-methylquinoline.[1675]

Details for the selective dehalogenation of 4,7-dichloro-3-nitroquinoline using *p*-toluenesulphonhydrazide and sodium hydroxide have been published;[1676] loss of the 4-chloro-substituent occurs without reduction of the 3-nitro-group, and 7-chloro-3-nitroquinoline may be obtained in 62% yield.

Only scant attention seems to have been paid to the use of metal hydrides as dehalogenating agents for haloquinolines. Kawazoe and Tachibana[1677] found that 4-chloroquinoline *N*-oxide with sodium borohydride in ethanol at room temperature gives a mixture of 4-chloroquinoline (69%), quinoline (19%), and starting material (2%); in tetrahydrofuran solution a 71% yield of deoxygenated material is obtained together with starting material (13%). The authors found that 4-chloroquinoline itself is only slightly reduced by sodium borohydride (90% recovery together with 2% of 1,2,3,4-tetrahydroquinoline), indicating that the quinoline obtained in the initial experiment must arise by reduction of quinoline *N*-oxide, i.e. dehalogenation must precede deoxygenation of quinoline is to be formed.

3-Bromo-4-nitroquinoline *N*-oxide reacts as 25 °C with sodium borohydride under nitrogen to give 4-(hydroxylamino)quinoline *N*-oxide (**892**) (31%).[1673] The hydroxylamino-compound can also be obtained in 27% yield by heating the chloro *N*-oxide with phenylhydrazine at 60 °C for 1 hour.



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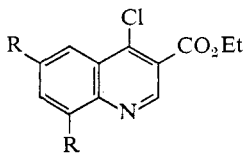

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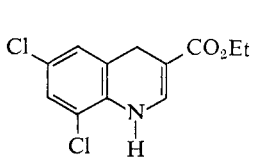


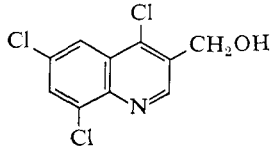
894

Lutz and his co-workers[1668] have shown that, whereas ethyl 4,6,8-trichloroquinoline-3-carboxylate (**893**; R = Cl) is unaffected by palladium–charcoal and hydrogen, with sodium borohydride in methylcellosolve reduction to the 6,8-dichloro-1,4-dihydroquinoline (**894**) (39%) and the quinolylcarbinol (**895**) is observed. In contrast, the dimethyl compound (**893**; R = Me) with sodium borohydride in methylcellosolve suffers reduction of the ethoxycarbonyl group only.

An American patent[1678] discusses in detail the electrolytic reduction of heptachloroquinoline. Reductions were carried out in a mixture of 1,2-dimethoxyethane,

methanol, and 30% aqueous sulphuric acid at 58–65 °C and 20–30 V. After 53 minutes, vapour-phase chromatographic analysis of the reaction mixture revealed the presence of heptachloro-, 2,3,5,6,7,8-hexachloro-, and 3,5,6,7,8-pentachloroquinoline in the ratio of 77.5 : 20 : 2.5. After some 3 hours the ratio was 5.8 : 78.5 : 15.7.

The polarographic reduction of 6-chloroquinoline in dimethylformamide solution has been described.[1679] Three reduction waves were observed corresponding to



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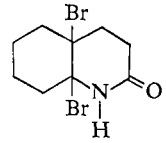
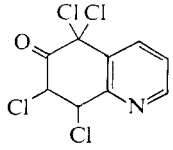


896

dehalogenation, and successive reductions of the double bonds of the pyridine ring.

4a,8a-Dibromodecahydro-2-oxoquinoline (**896**), heated with pyridine at 160 °C for 30 minutes, undergoes debromination to 5,6,7,8-tetrahydro-2-quinolone in 73% yield.[361]

The tetrachlorotetrahydro-6-oxoquinoline (**897**) undergoes reductive dehydrodehalogenation on treatment with sodium bisulphite to the dichloro-compound



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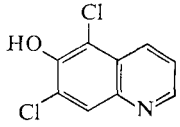
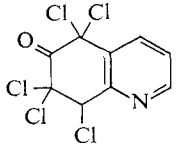


898

(**898**),[61] whereas boiling the pentachloro-6-oxoquinoline (**899**) with water yields the tetrachloro-derivative (**900**).[60]

1,5-Dichloro-2-quinolone (**901**) loses chlorine on boiling with ethanol or potassium hydroxide to give 5-chloro-2-quinolone.[341] A similar reaction is observed with 1-chloro-4-hydroxy-3-(*o*-nitrophenyl)-2-quinolone.[343]



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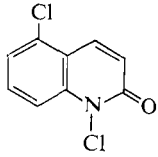
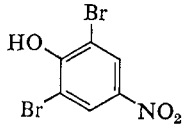


901

Fujita and his co-workers have observed debrominations during the Skraup reaction on various bromonitrophenols and bromonitroamines. For example, 2,6-dibromo-4-nitrophenol (**902**) reacts with glycerol, concentrated sulphuric acid, and phosphoric acid at 150 °C to give 7-bromo-6-hydroxyquinoline;[883] the reaction appears to be complex in that replacement of phosphoric acid by acetic acid leads to formation of the expected 5,7-dibromo-6-hydroxyquinoline, whereas in the presence of formic acid a mixture of 5,7-dibromo- and 7-bromo-6-hydroxyquinoline results.

Fujita and his co-workers[1680] have shown subsequently that, whereas 5-bromo-6-hydroxyquinoline and 8-bromo-7-hydroxyquinoline are inert towards boiling hydrobromic acid, in the presence of phenol bromine transfer to give *p*-bromophenol and 6- or 7-hydroxyquinoline is observed. Under similar conditions 5,7-dibromo-6-hydroxyquinoline yields 7-bromo-6-hydroxyquinoline together with *o*-bromophenol.[884] 7-Bromo-6-hydroxyquinoline, however, does not undergo debromination



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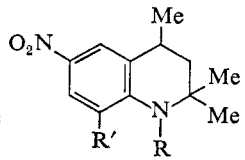
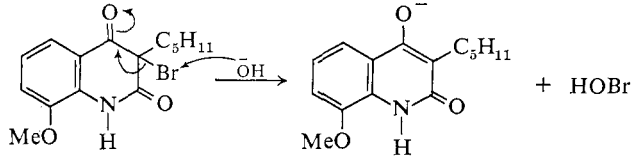


903

even in the presence of phenol.[1680] In a similar manner 6-amino-5-bromoquinoline reacts with boiling 20% hydrobromic acid in the presence of phenol to give *o*-bromophenol and 6-aminoquinoline (93%). The mechanism of these debromination reactions remains somewhat obscure.

1-Acetyl-8-bromo-1,2,3,4-tetrahydro-2,2,4-trimethyl-6-nitroquinoline (**903**; R = Ac, R′ = Br) is reported to undergo debromination to the 6-nitro-derivative (**903**; R = R′ = H) during deacetylation with boiling 40% sulphuric acid.[1636]

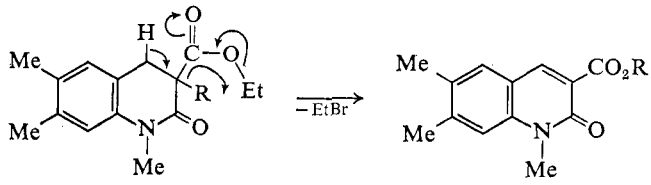
A rather unusual debromination process has been reported by Huffman,[313] who found that the bromo-compound (**879**) on treatment with base undergoes reductive



879 880

loss of bromine to yield 4-hydroxy-3-(isopentyl)-8-methoxy-2-quinolone (**880**). The authors favour a mechanism involving nucleophilic attack by hydroxide ion on the bromine atom, as indicated (**879** → **880**), giving the reduced product and hypobromous acid.

Attempts by Baker and his co-workers[199] to aromatize the tetrahydro-2-oxoquinoline (**904**; R = H) by a bromination–dehydrobromination process have led to some interesting results. Reaction of the quinolone with bromine in chloroform yields a mixture of the monobromo-derivative (**904**; R = Br), m.p. 125 °C, and an



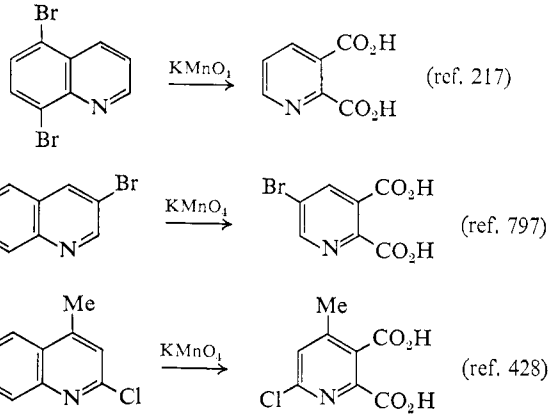
904 905

unidentified dibromo-compound, m.p. 90 °C. The former product resists dehydrobromination by sodium hydrogen carbonate, whereas the dibromo-derivative yields

the quinolone (**905**; R = Et) (29%). Further, both bromo-derivatives, if heated above their melting points, resolidify (at 135 °C and 120 °C, respectively) and then remelt at approx. 240 °C. In view of this behaviour they were thermolysed at 160 °C under reduced pressure. In each case loss of ethyl bromide was observed and a 97% yield of the 2-quinolone-3-carboxylic acid (**905**; R = H) was obtained. In order to explain loss of ethyl bromide from the monobromo-compound the authors propose a reaction sequence indicated by the arrows in (**904**). The nature of the dibromo-derivative remains obscure.

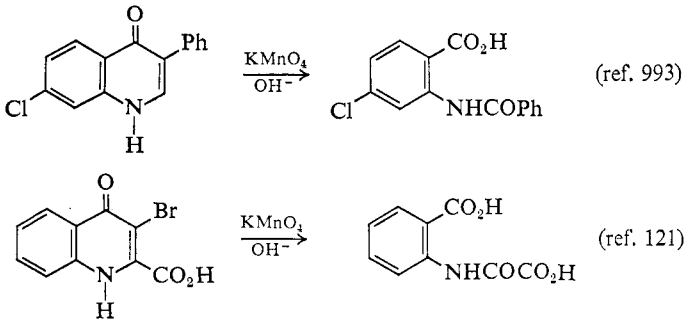
I. Oxidation of Haloquinolines

Oxidative degradation of the quinoline ring system proved to be a valuable technique for early workers in determining the position of substituents therein. In general, quinolines are oxidized by potassium permanganate and similar oxidizing agents to pyridine dicarboxylic acids, i.e. it is the carbocyclic ring that is oxidized. Halogenation of the quinoline nucleus does not appear to alter this oxidation pattern and many examples[99, 127, 131, 148, 287, 427, 716, 1681, 1682] of the oxidation of haloquinolines bearing halogen in both the benzene and the pyridine ring have been reported. The reactions given below should serve as representative examples.



Ukai and Akiya[1683] have observed that brominated quinolines are more resistant to oxidation by alkaline permanganate than are non-brominated quinolines.

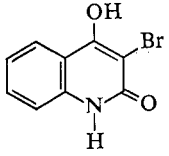
Haloquinolones, on oxidation, suffer rupture of the pyridine ring with the formation of substituted anthranilic acids.[195, 325, 993] Illustrative examples are set out below.



3-Bromo-4-hydroxy-2-quinolone (**906**) is oxidized by alkaline permanganate at 85 °C, to isatin (33%),[119] while under similar conditions 6-bromo-1,2,3,4-tetrahydroquinoline yields pyridine-2,3-dicarboxylic acid.[103]

6-Fluoro- and 8-amino-6-fluoro-quinoline, on ozonolysis, are degraded to pyridine-2,3-dicarboxylic acid in 15% and 44% yield, respectively.[1684]

Cochran and Little[704] have investigated in some detail the electrolytic oxidation of haloquinolines (halogen in the pyridine ring) in sulphuric acid solution. 3-Fluoro-, 3-chloro-, and 3-bromo-quinoline give the respective 5-halopyridine-2,3-dicarboxylic acids in yields of 26%, 54%, and 73%. 3-Iodoquinoline, however, behaves somewhat differently in that an iodine-free product, thought to be 5-hydroxypyridine-2,3-dicarboxylic acid hemihydrate, is obtained. Electrolysis of 2- and 4-chloroquinoline resulted in loss of chlorine but only red polymeric material could be isolated from the product mixtures.



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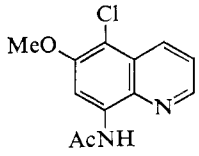


907

J. Reactions Involving Halogen Migration

Several instances are known in which halogen attached to either carbon or nitrogen of the quinoline ring undergoes migration. Such rearrangements appear, in general, to occur under acid conditions, although there are occasional examples of halogen migration under neutral conditions.

Claus and Howitz[171] demonstrated that 4-bromoquinoline, heated at 270 °C or, surprisingly, on storage at room temperature, yields 3,4-dibromoquinoline. Eisch[1685] has investigated reactions of this type more thoroughly. He argues, on the basis of the bridged bromonium ion intermediate (**10**) (p. 330), proposed by him[13] to explain the preferential 3-bromination of quinoline over 6-bromination during the decomposition of quinoline–bromine complexes, that 3-bromoquinoline should undergo debromination more readily than 6-bromoquinoline, since a common transition state, i.e. complex (**10**), should be involved. Experimentally he has shown that 3-bromoquinoline hydrobromide, heated at 300 °C for 90 minutes, yields a mixture of quinoline (38%), 3-bromoquinoline, 4-bromoquinoline, and several unidentified polybromoquinolines. Longer reaction times result in the formation of 3,4-dibromoquinoline, in agreement with the observations of Claus and Howitz, together with small quantities of 5-bromoquinoline. The formation of 4-bromoquinoline, a major product when short periods of heating are employed, cannot be explained on the basis of bromination of quinolinium bromide, which has been shown to brominate either at the 5- and 8-positions, or at the 3-position (see Section II.1.A.b). Eisch, however, contends that 4-bromination is reasonable on the basis of the bromonium complex (**10**), which can undergo transfer of bromonium ion to position 4 with accompanying proton loss. 6-Bromoquinoline hydrobromide undergoes no detectable debromination or rearrangement under the same conditions.

Halogen lability under acid conditions has been observed on several occasions. Dikshoorn[669] found, on nitrating 5-bromo-8-nitroquinoline with mixed acids at 100 °C, that 3,5-dibromo-8-nitroquinoline was the major product, along with pyridine-2,3-dicarboxylic acid. 5-Bromo-6-nitroquinoline behaved similarly. The

products are thought to arise by oxidation of the bromonitroquinoline to give the pyridinedicarboxylic acid and free bromine, with the latter product then brominating starting material to yield the dibromo-compound.

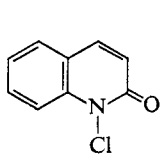
Okamoto[1624] has shown that 3-bromoquinoline *N*-oxide will react with a mixture of concentrated nitric and sulphuric acid at 130 °C to give 3-bromo-4-nitro-, 3-bromo-5-nitro-, 3-bromo-8-nitro-, and 3,8-dibromo-5-nitro-quinoline.

Deacetylation of 8-acetamido-5-bromo-6-methoxyquinoline with 10% hydrobromic acid is accompanied by bromine migration to give 8-amino-7-bromo-6-methoxyquinoline.[180] When the reaction is carried out in the presence of phenol, brominated phenols are obtained, indicating that the 5-bromo-substitutent is capable of being lost as an electrophilic bromine species. 8-Amino-5,7-dibromo-6-methoxyquinoline exhibits similar properties. Interestingly only slow bromine migration is observed when using hydrochloric acid, while comparable studies on 8-acetamido-5-chloro-6-methoxyquinoline (**907**) produced no evidence of chlorine migration.[180] A related reaction has been reported by Irving and Pinnington[169] who found that 5-bromo-8-methoxyquinoline in boiling hydrobromic acid undergoes demethylation and bromine rearrangement to give 5,7-dibromo-8-hydroxyquinoline as the major product.

Kajihara[1686, 1687] has reported a complex series of reactions between pyridine, quinoline, or isoquinoline *N*-oxide, and various 4-bromoquinolines. From amongst the multitude of products formed he was able to isolate a number of 3-bromo-4-quinolones. For example, he reports that 4-bromoquinoline with pyridine *N*-oxide in dioxan at 120 °C gives a mixture of pyridine (1.6%), 1-(2-pyridyl)-2-pyridone (16.1%), 3-bromo-4-quinolone (33%), 4-(3-pyridyloxy)quinoline (0.3%), 1-(2-pyridyl)-4-quinolone (0.6%), 4-quinolone (15.8%), and a low yield (1.4%) of an unidentified bromo-1-(2-pyridyl)-4-quinolone, m.p. 203 °C.

The mechanisms of these reactions are discussed and appear to involve a benzidine-type rearrangement via a Dewar-type π-complex.

Einhorn and Lauch[341] in their early work on 1-chloro-2-quinolone (**908**) observed that in the presence of acetic acid the 1-chloro-compound rearranges to give a chloro-2-quinolone, m.p. 206 °C, of unknown constitution. The reaction has been reinvestigated[342] and the product identified as 6-chloro-2-quinolone. Presumably an



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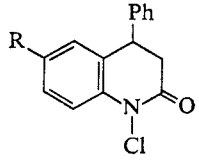

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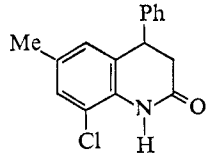


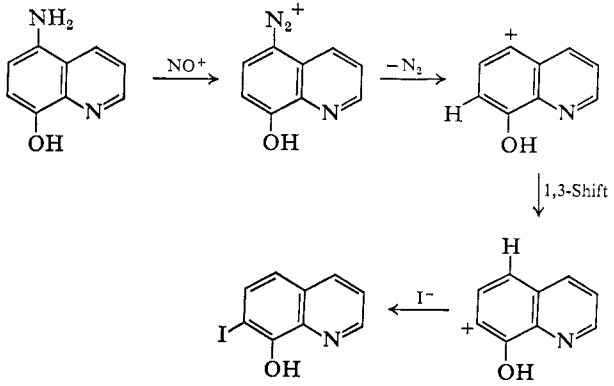
910

Orton-type rearrangement[1688] is taking place. It was also found that 1-chloro-1,2,3,4-tetrahydro-2-oxo-4-phenylquinoline (**909**; R = H) behaves similarly, while the corresponding 6-methyl compound (**909**; R = Me) yields the 8-chloro-derivative (**910**).[342] However, on photolysis in carbon tetrachloride solution with a medium-pressure mercury lamp, the 1-chlorotetrahydro-2-oxoquinolines undergo loss of halogen, accompanied by dehydrogenation, to give the corresponding 4-phenyl-2-quinolones.

The authors suggest that under photolytic conditions rearrangement of the 1-chloro-compound to either the 3- or 4-chloro-compound first occurs. Subsequent dehydrochlorination yields the observed 2-quinolone. Evidence for this reaction

pathway was forthcoming when it was found that 1,2,3,4-tetrahydro-2-oxo-4-phenylquinoline with *N*-bromosuccinimide gives a bromo-derivative which, on irradiation, loses hydrogen bromide to yield 4-phenyl-2-quinolone.

Gershon and McNeil[727] have reported the formation of 8-hydroxy-7-iodoquinoline as the major product (56%) from a Gattermann reaction on diazotized 5-amino-8-hydroxyquinoline. Along with this unexpected 7-iodo-compound are formed 8-hydroxyquinoline (37%), 8-hydroxy-5-iodoquinoline (3%), and 8-hydroxy-5,7-di-iodoquinoline (4%). The authors found that 7-amino-8-hydroxyquinoline under similar conditions undergoes extensive de-iodination, as does 8-hydroxy-5-iodo-quinoline. 8-Hydroxy-7-iodoquinoline, however, is virtually unaffected (1% de-iodination). On the basis of their results the authors propose that the 7-iodo-derivative is formed by heterolytic loss of nitrogen from the diazonium compound, giving the aryl cation, which then undergoes a 1,3-hydride ion shift, followed by nucleophilic attack of iodide ion at the cationic 7-position as outlined in Scheme 79.



SCHEME 79

K. Pharmaceutical, Chemotherapeutic, and Related Uses of Haloquinolines

The success of aminochloroquinolines as antimalarials has been referred to in several previous Sections of this Chapter, and the presence of chlorine at the 7-position of the quinoline nucleus appears to be of paramount importance in promoting the efficacy of these compounds.[122, 982, 1342, 1689] Also of great importance is the anti-amoebicidal action of halogenated 8-hydroxyquinolines, and several are well-known commercial compounds, e.g. "Yatren" and "Vioform". A vast amount of research has gone into elucidating the pharmacological effects and mode of action of these compounds, the details of which lie beyond the scope of this review. However, it may be mentioned that the relative merits of the various mono- and di-halogenated 8-hydroxyquinolines have been investigated, and it has been shown that the toxicity of the 8-hydroxyquinoline increases as the number of halogen substituents increases.[1690] It was found also that the relative positions of the halogen, or halogens, is important in defining activity; for example, 5-chloro-8-hydroxy-7-iodoquinoline is more active than the isomeric 7-chloro-5-iodo-derivative.[74] 5,7-Dichloro-8-hydroxy-2-methylquinoline and 8-hydroxy-5,7-di-iodoquinoline are effective against harmful intestinal organisms, and the analogous 5,7-difluoro-compound possesses similar activity to the 5,7-dichloro-derivative. Replacement of chlorine by fluorine in 5-chloro-8-hydroxy-7-iodoquinoline ("Vioform"), however, causes a reduction in

activity.[1691] The antifungal activity of halogen-substituted 8-hydroxyquinolines has recently been discussed.[1692] A comprehensive review covering the literature up to 1956, on the preparation and properties of the mono-, di-, and tri-halo-derivatives of 8-hydroxyquinoline, is available.[66]

2-Chloroquinoline has proved to be effective in the control of human body lice,[1693] while several 2-, 4-, and 8-haloquinolines have been used in the control of aphids.[1694] 4-Fluoro-2-methylquinoline is useful against the spider infestation of bean plants,[656] while halonitroquinolines are claimed[1695] to be 100% effective as fruit-fly repellants. 4-Chloro-3-nitroquinoline, as a 100 ppm aqueous suspension, is said[1696] to inhibit the germination of cucumber and wheat seeds, and also appears to have some herbicidal properties. 2- and 6-Chloroquinoline are used to prevent early sprouting of seed potatoes.[1697] Plant-growth inhibitory action is also shown by 2-chloro-4-methylquinoline.[1698] *

A large number of quaternary salts of halogenated quinolines have been screened for antitumour activity in mice.[1699, 1700]

III. Quinoline–Halogen Molecular Complexes

A. Introduction

Quinoline reacts with the halogens and interhalogens to form a whole series of halogen and interhalogen molecular complexes. Several of these complexes, particularly the quinolinium perbromides (Quinoline.HBr.Br_2)†, have proved to be of synthetic value since, as discussed in Section II.1.B.c(i) – they undergo decomposition on thermolysis, to yield mainly 3-bromoquinolines. Recent evidence[3, 13, 14] suggests that quinoline–bromine complexes are initially formed during the bromination of quinoline under mild neutral conditions.

Quinoline–halogen complexes appear to be of varying thermal stability, but all are sensitive to moisture. Many have been isolated as stable, generally red, crystalline solids, which when heated tend to decompose to give halogen and quinolinium halide.

The use of pyridinium perbromide as a brominating agent is well documented,[1701] and quinolinium perbromide ($C_9H_7N.HBr.Br_2$) appears to behave in a similar manner.[1702]

Various attempts to determine the structure of halogen–quinoline molecular complexes have been made. Many of the compounds appear to be charge-transfer complexes, and the charge-complex transfer theory, developed by Mulliken and reviewed by McGlynn,[1703] explains satisfactorily the structure of several quinoline–iodine, quinoline–iodine monochloride, and quinoline–iodine trichloride complexes. In many cases, however, the structure of the complex remains unknown. Of interest is a review by Andrews and Keefer[1704] which deals with molecular complexes of halogens and a whole range of organic compounds.‡

B. Quinoline–Bromine Complexes

Several, seemingly different, quinoline–bromine complexes have been reported. Lubavin[11] isolated a quinoline dibromide, $C_9H_7NBr_2$, m.p. 92–100 °C, from the reaction of quinoline hydrobromide with bromine, whereas Grimaux[12] isolated a

* A number of 4-halo-2-quinolones have found use in the control of rice blast.[2039]

† See footnote to Table 5, p. 375.

‡ For more recent reviews on this topic see refs. 2106–2108.

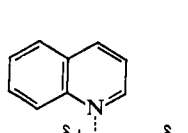
quinoline tetrabromide ($C_9H_7NBr_4$) from the reaction of an aqueous suspension of quinoline with bromine. The latter product is reported to be unstable in air and rapidly loses bromine and hydrogen bromide, while in boiling chloroform the complex deposits red–brown crystals of the "hydrobromide tetrabromide" ($C_9H_7NHBr.Br_4$). More recently Eisch[13, 14] has obtained a quinoline dibromide ($C_9H_7NBr_2$), m.p. 80–84 °C (decomp.) from the reaction of quinoline with bromine in dry carbon tetrachloride. He reinvestigated the early work of Grimaux and obtained a product similar to that previously reported, but which gave on analysis a bromine content indicative of a pentabromide ($C_9H_7NHBr.Br_4$) rather than a tetrabromide. The complex was easily reduced to quinoline with sulphurous acid, thus demonstrating the absence of nuclear bromination products. From infrared and ultraviolet spectra it was concluded that the complex is best represented as the quinolinium pentabromide (**911**) which in dilute solution dissociates as indicated:

$$[C_9H_7NH]^+Br_5^- \rightleftharpoons [C_9H_7NH]^+Br_3^- + Br_2.$$

911

The dibromide obtained by Lubavin is considered by Eisch[13] to be a perbromide of quinoline hydrobromide.

Eisch and Jaselskis[14] have carried out detailed ultraviolet studies on solutions of bromine and quinoline in carbon tetrachloride. They have also studied the dissociation constants of the bromine complexes of quinoline, 3-bromoquinoline, 8-bromoquinoline, and 8-methylquinoline. From their results they conclude that the principal species present in each case is a 1 : 1 quinoline–bromine adduct whose structure is best represented as an *n*-donor type complex (**912**) rather than a π-complex (**913**).



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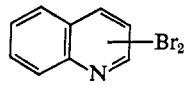

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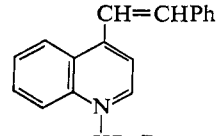


914

The former type is favoured on two main counts, namely (*a*) the observed dissociation constants of the quinoline–bromine complexes are of a size more compatible with an *n*-donor rather than a π-donor complex; and (*b*) the stability constants of the complexes vary remarkably with the nature and position of the substituent, a decrease in stability being particularly noticed with 8-substituted quinolines. The authors argue that π-donor complexes should be little affected by substituents, whereas *n*-donor complexes suffer serious steric effects as a result of substituents at the 8-position. Experiment shows that the quinoline–bromine complex is some one hundred times more stable than either the corresponding 8-methyl- or 8-bromoquinoline complex.

Gorenbein and his co-workers[1705] have shown that quinoline and bromine in nitrobenzene solution form a 1 : 1 molecular complex, $C_9H_7N.Br_2$.

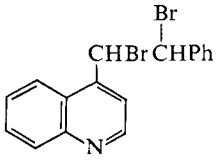
1-Benzoyl-1,2-dihydro-2,6-dimethylquinoline reacts with both bromine and chlorine in carbon tetrachloride solution,[89] but whereas in the latter case 3,4-chlorine addition takes place, the dibromo-compound, when boiled with dilute sulphuric acid, yields only bromine-free products, suggesting formation of a bromine–quinoline complex rather than an addition compound.

Buchmann and Schmuck[170] have brominated a series of 8-(alkylthio)quinolines in acetic acid. Bromination occurs as expected at the 5-position, and the products are isolated as the $HBr.Br_2$ derivatives. The free 5-bromo-8-thioethers are readily liberated on treatment with boiling acetone.

Smith and his co-workers[293] found that 4-styryl-quinoline with bromine in boiling chloroform or carbon tetrachloride solution gives mainly the complex (**914**) rather than, as expected, the α,β-dibromo-addition compound (**915**).

The corresponding styrylquinoline hydrochloride, however, undergoes successful addition of bromine with little halogen-complex formation.

Buchmann and Kirstein[810] found that 2-styrylquinoline with chlorine in acetic acid, iodine in acetic acid, and with bromine in either acetic acid, hydrobromic acid, or carbon disulphide, gives respectively the *N,N*-dichloro-, *N,N*-di-iodo-, and *N,N*-dibromo-complexes, whose structures were confirmed by infrared studies. The *N,N*-dibromo-compound (**916**; X = Br_2) is reported to yield the *N*-oxide (**916**; X = O) on treatment with sodium ethoxide.



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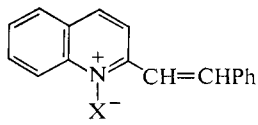

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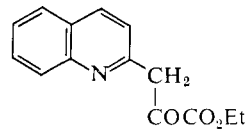


917

C. Quinoline–Iodine Complexes

Kleinberg and his co-workers[1706] have studied the behaviour of a solution of iodine in pyridine and in quinoline. In both cases polymeric products were formed which tempted the authors to suggest that nuclear iodination, to give possibly 2- and 4-iodoquinoline, which then undergo self-condensation, was taking place. Ultraviolet data indicate that quinoline and iodine react rapidly with the formation of the tri-iodide ion (I_3^-), and indeed suggest the formation of iodo- or polyiodo-quinolines. However, no substituted quinolines could be isolated.

Freezing-point determinations on the quinoline–nitrobenzene–iodine system have revealed the existence of a quinoline–iodine complex,$C_9H_7N.I_2$.[1707] Conductivity data also indicate the presence in the system of a 1 : 2 complex of type $C_9H_7N.2I_2$.

A detailed study[1708] has been carried out on the charge-transfer complexes formed by iodine with various *N*-heterocycles including quinoline, 6-methyl- and 6-chloroquinoline. Various thermodynamic and spectroscopic measurements are reported, and qualitatively the results are as predicted by the Mulliken theory.

A dark-green quinoline–iodine complex ($C_9H_7N.I_2$), m.p. 90 °C, has been isolated from the reaction of iodine with quinoline in carbon disulphide solution.[92] Ethyl (2-quinolyl)pyruvate (**917**) with ethanolic iodine is reported[1709] to yield a complex, the analysis of which indicates a 2 : 3 ester–iodine content. A similar complex consisting of a 1 : 3 ester–bromine ratio is formed on treating the pyruvate with bromine.

D. Quinoline–Interhalogen Complexes

Dittmar[323] reports that quinoline with iodine monochloride yields a 1 : 1 quinoline–iodine monochloride complex, m.p. 151 °C. Pictet and Krafft[1710] isolated the same compound from the reaction of quinoline and iodine trichloride in aqueous solution.

This iodine monochloride complex has since been prepared by several workers.[316, 1711, 1712]

Mouneyrat[1713] has reported preparation of the quinoline–iodine monobromide complex ($C_9H_7N.IBr$) on reaction of an aqueous suspension of quinoline with ethanolic iodine monobromide. Viscosity, density, conductivity, and freezing-point measurements indicate that, in nitrobenzene solution, quinoline forms a 1 : 1 and a 1 : 2 complex with iodine monobromide.[1714]

The iodine trichloride complex of quinoline ($C_9H_7N.ICl_3$) has been reported by Whitaker and his co-workers,[1712] who report a melting point of 134-139 °C, as opposed to the earlier reported[1715] value of 152–160 °C. Rogers and Meyer,[1716] who report a quinoline–iodine trichloride complex of m.p. 132 °C, have also prepared a 1 : 1 quinoline–iodine pentafluoride complex, $C_9H_7N.IF_5$ (m.p. ca. 100 °C) which when heated yields unidentified white crystals, m.p. 170 °C.

A list of quinoline complexes is given in Table 35.

TABLE 35. Quinoline–Halogen and –Interhalogen Complexes

Complex	M.p. (°C)	References
Quinoline.Br_2	81–84 d	3, 13, 1705
Quinoline.I_2	90	92, 1707
Quinoline.ICl	152, 159	316, 323, 1710, 1711, 1712, 1715, 1716
Quinoline IBr	129, 140	1713, 1714, 1716
Quinoline.2IBr		1714
Quinoline.ICl_3	139, 160	1712, 1715, 1716
Quinoline.IF_5	100	1716
3-Bromoquinoline.Br_2		14
8-Bromoquinoline.Br_2		14
8-Methylquinoline.Br_2		14
5-Aminoquinoline.ICl	198	316
6-Hydroxyquinoline.ICl	252	316
4,7-Dichloroquinoline.Br_5	136	1717
2-Styrylquinoline.Cl_2	110	810
2-Styrylquinoline.Br_2	178	810
2-Styrylquinoline.I_2	167	810
5-Bromo-6-methoxy-8-nitroquinoline.Br_2	157 d	136
5-Bromo-8-(methylthio)quinoline.Br_3	122	170
5-Bromo-8-(ethylthio)quinoline.Br_3	108	170
5-Bromo-8-(*n*-propylthio)quinoline.Br_3	97	170
5-Bromo-8-(isopropylthio)quinoline.Br_3	133	170
5-Bromo-8-(*n*-butylthio)quinoline.Br_3	75	170
5-Bromo-7-(isobutylthio)quinoline.Br_3	96	170
1-Benzoyl-1,2-dihydro-2,6-dimethylquinoline.Br_2	135	89
1-Benzoyl-1,2-dihydro-2,6,8-trimethylquinoline.Br_2	135	89

E. Halogen Acid Salts of Quinoline–Halogen and –Interhalogen Complexes

Early studies on the reaction of quinoline with halogens in halogen acid solution were carried out by Trowbridge.[322] He found that quinoline in hydrobromic acid solution reacts with bromine to give a "hydrobromide tetrabromide" ($C_9H_7N.HBr.Br_4$), m.p. 39 °C, which on exposure to air gradually changes to a red crystalline solid,

m.p. 88 °C, which he considered to be a mixture of lower perbromides of quinoline. On the basis of a series of reactions involving various quinolinium halides with different halogens Trowbridge came to the following conclusions:

(*a*) "Hydrochloride dichlorides," i.e. Q.HCl.Cl_2, are never formed.

(*b*) Chlorine always displaces bromide and iodide from the halide salt; and, with iodides, iodine monochloride is formed which subsequently yields the hydrochloride–iodine monochloride complex (Q.HCl.ICl).

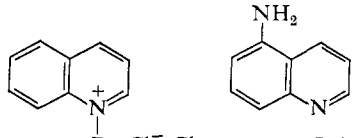
(*c*) Bromine displaces chloride and iodide to give perbromides (Q.HBr.Br_2),* and bromo-iodides (Q.HBr.BrI), respectively.

(*d*) Iodine will displace both chloride and bromide to give periodides (Q.HI.I_2).

It was also found that quinoline methohalides behave similarly, and a whole series of *N*-(*n*-propyl)quinolinium halide–halogen complexes, e.g. (**918**), have been described by Claus and Collischon.[280]

In boiling dilute nitric acid solution quinoline reacts with iodine to give, after addition of concentrated hydrochloric acid, quinoline hydrochloride iodine monochloride (C_9H_7N.HCl.ICl).[1711]

The reaction of iodine monochloride with various quinolines in hydrochloric acid solution has been investigated in some detail.[316] Quinoline itself gives a hydrochloride–iodine monochloride identical with that previously reported.[1710, 1711] 8-Hydroxyquinoline, not unexpectedly, undergoes di-iodination at the 5- and the 7-position, as does 8-aminoquinoline;[316] surprisingly, however, 5-aminoquinoline, when treated with iodine monochloride in a mixture of hydrochloric acid and acetic acid, yields the iodine monochloride (**919**).



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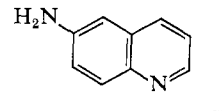
919



920

A similar complex is formed with 6-hydroxyquinoline, while 6-aminoquinoline yields the hydrochloride–iodine monochloride adduct (**920**). Iodoquinoline hydrochloride–iodine monochloride complexes have been isolated during the iodination of 8-hydroxyquinoline with iodine trichloride.[324]

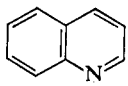
The reaction of quinoline with iodine trichloride (ICl_3) in aqueous solution was first investigated by Pictet and Krafft[1710] who obtained the complex, C_9H_7N.HCl.ICl, the formation of which was explained on the basis of initial hydrolysis of the iodine trichloride to iodine monochloride as follows:

$$2ICl_3 + 3H_2O \longrightarrow ICl + 5HCl + HIO_3$$

Later work by Chattaway and Garton,[1718] however, showed that quinoline in concentrated hydrochloric acid containing an equivalent of powdered iodine reacts with chlorine to give the quinoline hydrochloride–iodine trichloride complex (**921**). The corresponding hydrochloride–iodine trichloride adducts of several substituted quinolines were similarly prepared. Quinoline in sulphuric acid reacts with potassium tri-iodide to give a complex, m.p. 67 °C, for which structure (**922**) is proposed.[1719] This structure, however, must be considered suspect since, under identical conditions,

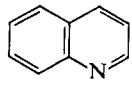
* See footnote to Table 5, p. 375.

Tinkler[1720] reports the formation of quinoline tri-iodide. The structure of the latter was confirmed by ultraviolet spectral measurements, which indicate, for solutions in both chloroform and ethanol, the presence of tri-iodide ion (I_3^-). Trowbridge,[322] however, reports formation of the hydriodide-tetraiodide (**922**) (m.p. 76 °C) on reaction of quinoline hydriodide with iodine in ethanol.



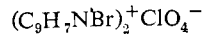
$HCl.ICl_3$

921



$HI.I_4$

922



923

Several halogen and interhalogen complexes of 4,7-dichloroquinoline have been prepared.[1717] The bromoquinolinium perchlorate (**923**) has been prepared by treating a perchloric acid solution of quinoline with hypobromous acid.[24] This salt behaves as a stabilized bromonium cation, somewhat similar to the more familiar nitronium salts, and slowly decomposes in aqueous solution to give a low yield (*ca.* 15%) of a mixture of bromoquinolines.

Quinoline *N*-oxide hydrohalide dihalide complexes of unknown composition have been described by Ochiai and Okamoto.[1721] Quinoline *N*-oxide hydrobromide on treatment with bromine in chloroform yields a halogen complex of molecular formula $(C_9H_7NO.HBr)_2Br$, while quinoline *N*-oxide hydriodide reacts with iodine to give dark purple needles of composition $(C_9H_7NO.HI)_2I_3$. 4-Bromo- and 3-bromoquinoline *N*-oxides with bromine in chloroform yield perbromides of unknown composition.

Many quinoline $HBr.Br_2$ complexes are known and have been obtained as stable crystalline compounds. Others have been isolated as intermediates in the bromination of quinoline and its derivatives under dilute acid or neutral conditions, as discussed in Section II.1.A.b. A list of these complexes and other quinolinium halide–halogen, and interhalogen complexes is given in Table 36.

TABLE 36. Quinolinium Halide–Halogen and –Interhalogen Complexes

Complex	M.p. (°C)	References
Quinoline.$HCl.Br_2$	105	10, 322
Quinoline.$HBr.Br_2$	99	10, 295, 322, 1702
Quinoline.HCl.ICl	112, 118	316, 322, 323, 1710, 1711
Quinoline.HBr.IBr	109	322
Quinoline.$HCl.ICl_3$	195 d	1718
Quinoline.$HBr.Br_4$	39, 86 ?	12, 322
Quinoline.$HI.I_4$	67, 76	322, 1719, 1720
Quinoline.MeCl.ICl		322
Quinoline.$MeCl.Br_2$	112	322
Quinoline.MeBr.IBr	108	322
Quinoline.$MeBr.Br_2$	108	322
Quinoline.$MeI.I_4$	70	322

TABLE 36 (*cont.*)

Complex	M.p. (°C)	References
Quinoline.*n*-PrCl.Cl_2		280
Quinoline.*n*-PrCl.Br_2	85	280
Quinoline-*n*-PrCl.I_2	62	280
Quinoline.*n*-PrBr.Cl_2	60	280
Quinoline.*n*-PrBr.Br_2	93	10, 280
Quinoline.*n*-PrBr.I_2	60	280
Quinoline.*n*-PrBr.I_4	49	280
Quinoline.*n*-PrI.Cl_2	81	280
Quinoline.*n*-PrI.Br_2	77	280
Quinoline.*n*-PrI.I_2	62	280
Quinoline.*n*-PrI.Cl_4	145	280
Quinoline.*n*-PrI.Br_4	48–58	280
Quinoline.*n*-PrI.I_4	50	280
2-Chloroquinoline.HCl.ICl_3	143 d	1718
6-Chloroquinoline.HCl.ICl_3	131 d	1718
6-Chloroquinoline.HBr.Br_2	129 d	171, 281
3-Bromoquinoline.HBr.Br_2	76	287
5-Bromoquinoline.HBr.Br_2	107 d	287
6-Bromoquinoline.HBr.Br_2	70	94, 287
7-Bromoquinoline.HBr.Br_2	107	94, 287
8-Bromoquinoline.HBr.Br_2	ca. 70 d	95, 287
4,7-Dichloroquinoline.HCl.ICl	133	1717
4,7-Dichloroquinoline.HCl.BrCl	127	1717
4,7-Dichloroquinoline.HCl.Br_2	114	1717
4,7-Dichloroquinoline.HCl.I_2	150	1717
4,7-Dichloroquinoline.HBr.Br_2	138	1717
5,6-Dibromoquinoline.HBr.Br_2		298
5,7-Dibromoquinoline.HBr.Br_2	215	283
5,8-Dibromoquinoline.HBr.Br_2		296, 297
6,7-Dibromoquinoline.HBr.Br_2		298
6,8-Dibromoquinoline.HBr.Br_2		297
2-Methylquinoline.HCl.ICl_3	149 d	1718
6-Methylquinoline.HBr.Br_2		290
8-Methylquinoline.HCl.ICl_3	152 d	1718
8-Methylquinoline.HBr.Br_2	124	291
6-Nitroquinoline.HCl.ICl_3	131 d	1718
6-Nitroquinoline.HBr.Br_2		177, 289
8-Nitroquinoline.HBr.Br_2		95
5,7-Dinitroquinoline.HBr.Br_2		288
5,8-Dinitroquinoline.HBr.Br_2		288
6,8-Dinitroquinoline.HBr.Br_2		288, 289
5-Chloro-8-hydroxyquinoline.HCl.ICl	149	324
5-Chloro-8-hydroxy-2-methylquinoline.HCl.ICl	146	324
5-Bromo-6-hydroxyquinoline.HBr.Br_2		131
8-Hydroxy-5-iodoquinoline.HCl.ICl	172	324
8-Hydroxy-5-iodo-2-methylquinoline.HCl.ICl	142	324
6-Methoxy-8-methylquinoline.HBr.Br_2		107
7-Bromo-5-(ethoxymethyl)-8-hydroxyquinoline.HBr.Br_2	133	153
6-Aminoquinoline.HCl.ICl	206	316
(Quinoline *N*-oxide hydrobromide)$_2$.Br	141	1721
(Quinoline *N*-oxide hydriodide)$_2$.I_3	134	1721
(4-Bromoquinoline *N*-oxide hydrobromide)$_2$.Br	158	1721
(3-Bromoquinoline *N*-oxide hydrobromide)$_2$.Br	185	1721

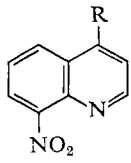
IV. Side-chain Halogen Derivatives

1. Preparation*

A. Direct Halogenation

Side-chain halogenation of alkylquinolines is not as predictable as that of alkylbenzenes, where mono-, di-, and tri-haloalkyl derivatives may be prepared by judicious choice of reaction conditions. It appears that halogenation of alkylquinolines is dependent on the reactivity of the alkyl group, which in turn depends on its position in the quinoline nucleus. Most of the direct-halogenation studies have been carried out on methylquinolines, and, as expected, methyl groups at the 2- and the 4-positions have been most thoroughly examined. The preparation of (halomethyl)pyridines and (halomethyl)quinolines is the subject of a short review.[1722]

Methyl groups at the 2- and 4-position of the quinoline nucleus are "activated" by the adjacent ring-nitrogen and, as such, should readily undergo halogenation. Koenigs[1723] first observed that 8-nitro-4-methylquinoline with bromine (2 equivalents) in boiling acetic acid containing anhydrous sodium acetate gives 4-(dibromomethyl)-8-nitroquinoline (**924**; R = $CHBr_2$). Under the same conditions but with 4 equivalents of bromine the 4-(tribromomethyl) derivative (**924**; R = CBr_3) was formed.



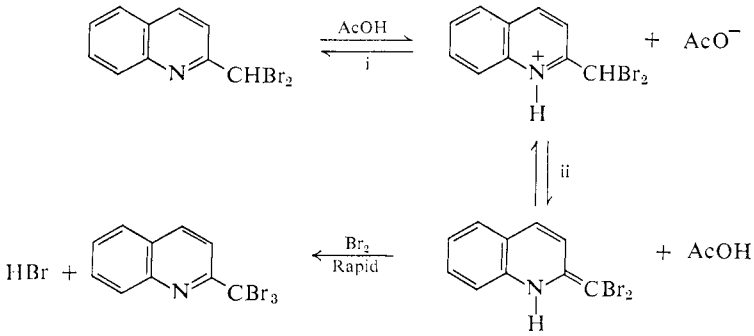
924

Hammick,[1724] found subsequently that quantitative yields of 2-(tribromomethyl)quinoline are available by treating 2-methylquinoline with an excess of bromine in a mixture of hot acetic acid and sodium acetate. In later work[1725] 2-(tribromomethyl)-8-nitroquinoline was prepared in a like manner in 100% yield, whereas 2-methyl-5-nitroquinoline proved to be more troublesome and even after an hour at 100 °C with bromine in acetic acid, afforded only a 17% yield of 5-nitro-2-(tribromomethyl)quinoline.

Hammick and his co-workers[1726] have investigated the mechanism of halogenation of 2-methylquinoline in an acetic acid–sodium acetate mixture. They found that the rate of bromination of 2-(dibromomethyl)quinoline under these conditions is independent of the concentration of both bromine and acetate ions. From their results they conclude that the rate-determining step does not involve a base (i.e. acetate ion)-catalysed process as was first thought,[1727] but rather "an acid-catalysed prototropic change followed by rapid bromination of the intermediate methylene base" as shown in Scheme 80. The authors liken the process to that prevailing in the acid-catalysed bromination of ketones.

According to Scheme 80, the acetic acid serves as a protonating agent, while acetate ion, as suggested previously,[1727] serves to buffer the hydrobromic acid formed in the reaction, which otherwise would decrease the rate of bromination by causing precipitation of the (dibromomethyl)quinoline as the insoluble hydrobromide. Step (ii) is considered to be rate-determining since the rate of substitution increases as the

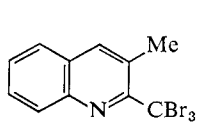
* See also Addenda, p. 696.



SCHEME 80

number of bromine substituents increases.[1726] It follows that under these reaction conditions the mono- and di-bromo-derivatives are rarely isolated.[1725] Progressive halogen-substitution decreases the basicity of the quinoline and hence stage (i) is unlikely to be rate-determining. The 2-(dibromomethyl) derivatives of 5-nitro and 8-nitro-quinoline undergo further bromination at rates in agreement with the predicted order of proton release from the α-carbon atom, i.e. the 8-nitro-isomer is brominated faster than the 5-nitro-isomer.[1726] The measured rate constants at 30 °C are found to be 2-(dibromomethyl)quinoline 1.70×10^{-4} s^{-1}, 2-(dibromomethyl)-8-nitroquinoline 8.0×10^{-4} s^{-1}, and for 2-(dibromomethyl)-5-nitroquinoline 0.40×10^{-4} s^{-1}.

This method of bromination has been used for the preparation of a number of substituted 2-(tribromomethyl)quinolines, including the 6-chloro-,[925] 7-chloro-,[768] 5-chloro-,[768] 6-nitro-,[1456] 8-nitro-,[1725, 1728] 4,7-dichloro-,[1123] 5-bromo-8-methoxy-,[169] 4-chloro-,[1349] 6-methyl-,[1729] and 5,8-dibromo-derivatives.[1349] The methyl group at the 2-position appears to be more reactive than methyl groups situated at other positions in the quinoline ring. For example, 2,3-dimethylquinoline on treatment with bromine in acetic acid–sodium acetate gives 3-methyl-2-(tribromomethyl)quinoline (**925**) in 86% yield,[1730] and 2,4-dimethylquinoline under similar conditions yields only the



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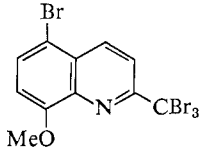
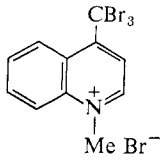


926

2-(tribromomethyl) derivative (78%).[1727] 8-Methoxy-2-methylquinoline reacts with bromine in acetic acid–sodium acetate solution to give the 5-bromo-2-(tribromomethyl) derivative (**926**).[169]

As expected, quaternization of the quinoline-nitrogen enhances the reactivity of the 2- and 4-methyl groups towards bromination, as illustrated by the fact that 4-methylquinoline does not undergo direct bromination, whereas 1,4-dimethylquinolinium iodide with bromine in acetic acid–sodium acetate yields the tribromomethyl derivative (61%) as the methobromide (**927**).[1727]

In contrast, 2-methylquinoline methiodide is reported[1731] to react with bromine in acetic acid at 100 °C to give the 2-(dibromomethyl)quinolinium iodide (**928**) in 75% yield.



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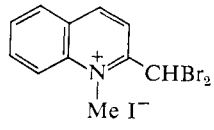

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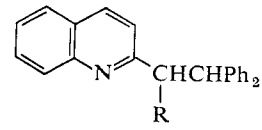
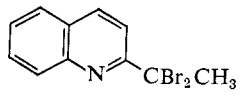


929

2-(2,2-Diphenylethyl)quinoline (**929**; R = H) with bromine in acetic acid gives the α-bromo-derivative (**929**; R = Br),[1732] whereas 2-ethylquinoline under similar conditions is dibrominated at the α-position to give the dibromo-derivative (**930**), which was not isolated but was hydrolysed directly to 2-acetylquinoline in good yield.[1730]



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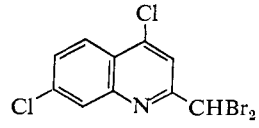
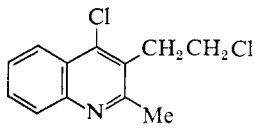


931

4,7-Dichloro-2-methylquinoline is reported[1123] to yield the 2-(dibromomethyl) derivative (**931**) on treatment with 2 equivalents of bromine.

As mentioned above, the rate of bromination of alkyl side chains in acetic acid–sodium acetate solution increases as the number of halogen substituents on the alkyl group increases. Thus, in general, bromination under these conditions yields no mono- or dibromo-methyl derivative,[1725] although Hammick and his co-workers[1726] report the preparation of 2-(dibromomethyl)-5-nitroquinoline by the action of bromine on 2-methyl-5-nitroquinoline in acetic acid–sodium acetate at temperatures less than 70 °C. (Mono- and di-halomethyl)quinolines are available, however, by other procedures; for example, bromination of 2-methylquinoline in acetic acid in the presence of boron trifluoride is reported[1733] to yield a mixture of 2-(bromomethyl)-quinoline (0.5%), 2-(dibromomethyl)quinoline (25.5%), and 2-(tribromomethyl)-quinoline (0.13%). Bromine in acetic acid brings about dibromination at the 2-methyl group of the dialkyl-dichloroquinoline (**932**), while with bromine in carbon tetrachloride solution the dibromo-compound (**933**; R = Me) gives the tetrabromo-derivatives (**933**; R = $CHBr_2$).[1452]



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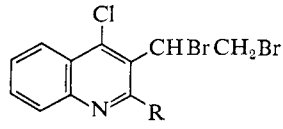
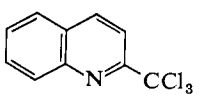


933

Examples of direct side-chain chlorination of alkylquinolines are less numerous, despite the fact that Hammick[1724] showed that they undergo chlorination in a manner analogous to the bromination reactions already discussed. Thus, 2-methylquinoline in acetic acid–sodium acetate mixture gives the (2-trichloromethyl) derivative (**934**) in high yield. In a similar manner the following substituted 2-(trichloromethyl)-quinolines have been prepared; 6-nitro-[1456] 8-chloro-6-nitro-,[1456] 8-methyl-6-nitro-,[1456] 4-carboxy-6-nitro-,[1456] and 4-chloro-.[1349]

Mathes and Schüly[1722] have reported a detailed procedure for the preparation of 2-(chloromethyl)quinoline, which is adaptable for the monochlorination of a number of 2-methylquinolines. The method involves treating 2-methylquinoline with chlorine (4 equivalents) in carbon tetrachloride solution in the presence of anhydrous sodium carbonate at temperatures around 60 °C. Under these conditions an 86% yield of the monochloro-derivative is claimed. 2-(Dichloromethyl)quinoline (4%) is formed as a by-product. Other solvents such as chloroform and trichloroethylene have also been used.[1734, 1735] A South African patent[1736] describes this method for the preparation of 6-methyl-2-(chloromethyl)quinoline (**935**).



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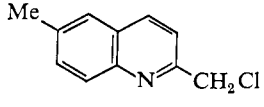

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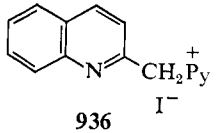
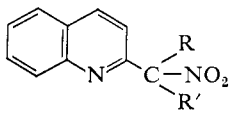


936

2-Methylquinoline is reported[1737] to react with iodine in the presence of pyridine at 100 °C to give the pyridinium iodide (**936**) in quantitative yield. A similar reaction is also observed with 3-picoline, isoquinoline, 3-methylisoquinoline, and 4-methylquinoline. Presumably the reaction requires prior formation of the 2-(iodomethyl)-quinoline which immediately quaternizes with the heteroaromatic base present.

As expected, alkylquinolines that bear strongly electron-withdrawing substituents on the alkyl group readily undergo halogenation. Thus, 2-(nitromethyl)quinoline with bromine in acetic acid, containing a little sulphuric acid, yields the bromo-derivative (**937**; R = H, R′ = Br), and with chlorine in acetic acid the corresponding α-chloro compound (**937**; R = H, R′ = Cl).[1738] With an excess of chlorine the dichloronitro-derivative (**937**; R = R′ = Cl) is obtained in 55% yield.

Diethyl (4-quinolyl)malonate (**938**; R = H) with bromine in chloroform gives the α-bromo-derivative (**938**; R = Br), whereas under similar conditions diethyl (2-quinolyl)malonate yields an unidentified product, m.p. 169 °C, the analysis of which indicates the presence of five bromine atoms.[1739]



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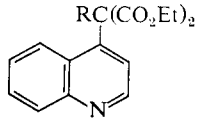

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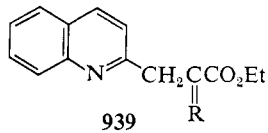
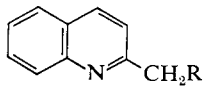


939

Bromination of ethyl (2-quinolyl)pyruvate (**939**; R = O) is complex (see Section III.B) whereas the nitrile (**940**; R = CN), the ester (**940**; R = CO_2Et), and the oxime (**939**; R = NOH) are brominated with little difficulty to give their α-bromo-derivatives in good yield.[1709]



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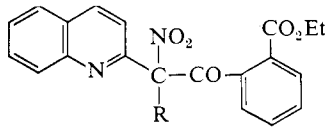
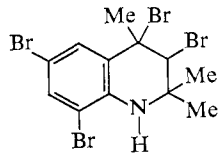


941

The bromination of α-nitro-α-(2-quinolyl)acetophenones has been investigated by Zalukaev and his co-workers. They find[1740] that the ketone (**941**; R = H), as its sodium salt, reacts with aqueous bromine over a period of 10 days to yield the α-bromo-derivative (**941**; R = Br) (61.5%). When the bromo-derivative is heated under reflux in carbon tetrachloride solution with bromine for 10 minutes and then kept at room temperature for 12 hours, loss of the acyl group and formation of the dibromonitro-compound (**937**; R = R′ = Br) are observed. A similar reaction occurs with the corresponding 4-quinolyl-substituted acetophenone.

The authors claim this to be the first example of the direct replacement of an acyl group by bromine (see, however, Section II.1.H.c). In a later publication[1741] chlorination of the ketone (**941**; R = H) in 0.1N-sodium hydroxide solution to give the α-chloro-derivative (**941**; R = Cl) is described. In the same paper the preparation of 2-(bromochloronitromethyl)quinoline (**937**; R = Br, R′ = Cl), by bromination (bromine in acetic acid) of 2-(chloronitromethyl)quinoline (**937**; R = Cl, R′ = H). is described.

The bromination of 1,2-dihydro-2,2,4-trimethylquinoline (**942**) has been investigated in some detail[203, 204, 1742] and has been discussed at length in Section II.1.A.e(iv). Further bromination studies of this 1,2-dihydroquinoline have been carried out[1501] and the product previously isolated by Cliffe[202] from the bromination of (**942**) in methanol has been shown to have the tetrabromo-structure (**943**) rather than, as thought, the structure (**944**). A minor product, also reported but unidentified by Cliffe, has been shown to be the pentabromo-derivative (**945**).



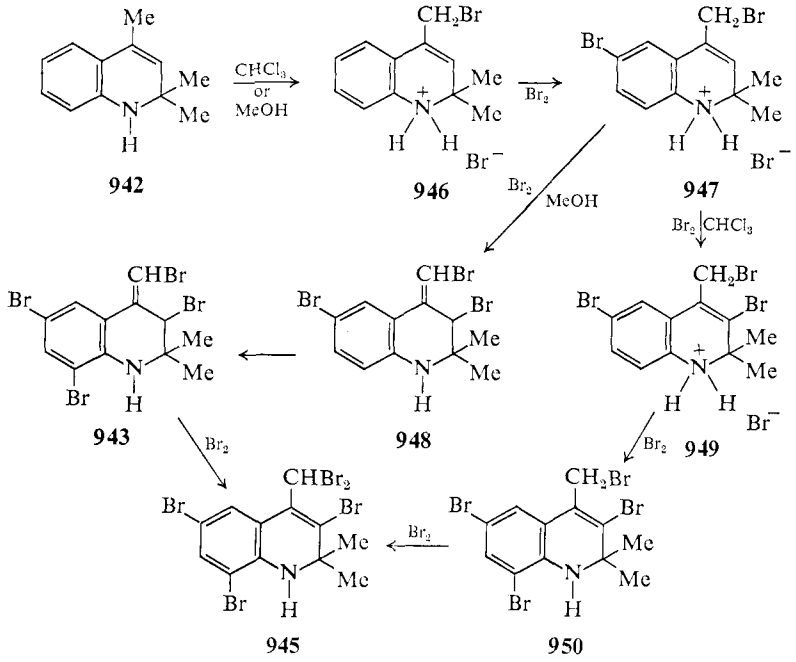
944

It appears that bromination of 1,2-dihydro-2,2,4-trimethylquinoline either in chloroform or in methanol solution proceeds by initial bromination of the 4-methyl group to give the 4-bromomethyl derivative (**946**), and then at the 6-position to give the dibromo-compound (**947**). Thereafter, the reaction pathways diverge as indicated in the reaction Scheme 81, and isomeric tribromo-compounds (**948** and **949**) can be obtained. Further treatment of the tetrabromo-compound (**943**) with bromine in chloroform yields the pentabromo-derivative (**945**) together with a high-melting yellow solid, for which dimeric structure (**951**) is proposed. The dimer becomes the major product when the dihydroquinoline (**942**) is brominated in concentrated sulphuric acid

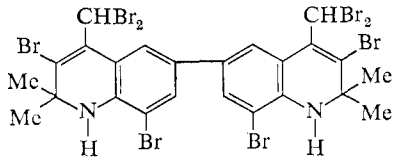
Chlorination of 1-acetyl-1,2-dihydro-2,2,4-trimethylquinoline (**952**; R = Ac) in carbon tetrachloride solution with either chlorine or sulphuryl chloride is a much less complicated affair than the brominations discussed above. In each case a monochloro-derivative, presumed to be the 4-(chloromethyl) compound, is formed.[203, 204] A large excess of chlorine results in formation of a mixture of a hexachloro-1,2-dihydroquinoline hexachloride and the analogous tetrachloride, while with a slight excess of sulphuryl chloride a low yield of a dichloro-compound is formed. None of these polychlorinated products has as yet been identified.

A few instances of side-chain bromination resulting from the decomposition of alkylquinolinium perbromides* have been recorded. Howitz and Schwenk[291] report

* See footnote to Table 5, p. 375.

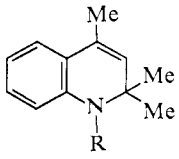


SCHEME 81



951

that 8-methylquinolinium perbromide in warm hydrochloric acid yields 3-bromo-8-(bromomethyl)quinoline (**953**; R = Br) in 35% yield. Later work,[292] however, indicated that halogen exchange had taken place during the reaction and that the product was in fact the chloromethyl compound (**953**; R = Cl).



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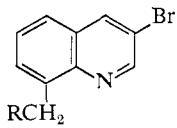

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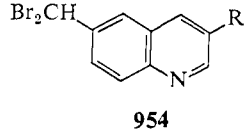
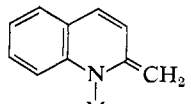


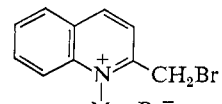
954

The dibromo-compound (**953**; R = Br) can be successfully prepared by using sulphuric acid in the reaction in place of hydrochloric acid.[292] Heating the $HBr.Br_2$ complex of 6-methylquinoline at 180 °C leads to the formation of a mixture of 6-(dibromomethyl)quinoline (**954**; R = H) and its 3-bromo-derivative (**954**; R = Br).[290]

8-Methylquinoline forms an addition compound with bromine in chloroform which at 160 °C yields 8-(bromomethyl)quinoline.[107, 1743] 1-Methyl-2-methylene-1,2-dihydroquinoline (**955**) with bromine in ether gives a halogen-addition compound,



955



956

m.p. 152 °C ($C_{11}H_{11}NBr_3$), which on dissolving in warm acetone decomposes to give bromoacetone and 2-(bromomethyl)quinoline methobromide (**956**).[1744]

Table 37 lists compounds whose preparation is covered by this section.

TABLE 37. (Haloalkyl)quinolines Prepared by Direct Halogenation

(Haloalkyl)quinoline	Method of preparation (yield)	References
BROMOMETHYL COMPOUNDS		
2-(Bromocyanomethyl)-	2-($NCCH_2$)-Q; Br_2/AcOH	1709
2-(Bromonitromethyl)-	2-(NO_2CH_2)-Q; Br_2/H_2SO_4/AcOH	1738
2-(1-Bromo-2,2-diphenylethyl)-	2-(Ph_2CHCH_2)-Q; Br_2/AcOH	1732
4-(Bromomethyl)-1,2-dihydro-2,2-dimethyl-	(i) 1-Ac-1,2-diH-2,2,4-triMe-Q; $Br_2/CHCl_3$ for 4 h at 0–10 °C; (ii) 1,2-diH-2,2,4-triMe-Q.HBr; $Br_2/CHCl_3$ stand for 2 days; (iii) 1,2-diH-2,2,4-triMe-Q; as above	203, 204, 1742
8-(Bromomethyl)-	(i) 8-Me-Q.HBr.Br_2; heat at 160 °C; (ii) 8-Me-Q.HBr; $Br_2/CHCl_3$ (39%)	107, 292, 1743
3-Bromo-8-(bromomethyl)-	8-Me-Q.HBr.Br_2; H_2SO_4 warm	292
CHLOROMETHYL COMPOUNDS		
2-(Chloromethyl)-	2-Me-Q; Cl_2/inert solvent/Na_2CO_3 for 6 h at 65 °C (60%)	1722, 1734, 1735
2-(Chloromethyl)-6-methyl-	2,6-diMe-Q; $Cl_2/CCl_4/Na_2CO_3$ 5.5 h at 60 °C	1736
2-(Chloronitromethyl)-	2-(NO_2CH_2)-Q; Cl_2/AcOH	1738
3-Bromo-8-(chloromethyl-	8-Me-Q.HBr.Br_2; HCl warm (35%)	291, 292
DIBROMOETHYL COMPOUNDS		
2-(1,1-Dibromoethyl)-	2-Et-Q; Br_2/AcOH at 90 °C for 30 min	1730
4-Chloro-3-(1,2-dibromoethyl)-2-(dibromomethyl)-	2-Me-4-Cl-3-[$BrCH_2$(Br)CH]-Q; Br_2/CCl_4	1452
4-Chloro-3-(1,2-dibromoethyl)-2-(dibromomethyl)-6-methoxy-	2-Me-4-Cl-3-[$BrCH_2$(Br)CH]-6-MeO-Q; as above	1452
DIBROMOMETHYL COMPOUNDS		
2-(Dibromomethyl)-, methiodide	1,2-diMe-Q'ium I^-; Br_2/AcOH at 100 °C for 30 min (75%)	1731

TABLE 37 (*cont.*)

(Haloalkyl)quinoline	Method of preparation (yield)	References
4-Chloro-3-(2-chloroethyl)-2-(dibromomethyl)-	2-Me-4-Cl-3-($ClCH_2CH_2$)-Q; Br_2/AcOH	1452
4-Chloro-3-(2-chloroethyl)-2-(dibromomethyl)-6-methoxy-	2-Me-4-Cl-3-($ClCH_2CH_2$)-6-MeO-Q; as above	1452
4,7-Dichloro-2-(dibromomethyl)-	2-Me-4,7-diCl-Q; Br_2/AcOH/AcONa for 1 h at 75–95 °C	1123
2-(Dibromomethyl)-5-nitro-	5-NO_2-2-Me-Q; Br_2/AcOH/AcONa at 70 °C	1726
2-(Dibromonitromethyl)-	2-[Br(NO_2)(*o*-$EtO_2C.C_6H_4CO$)CH]-Q; Br_2/CCl_4 boil 10 min then stand at room temp. for 12 h	1740
2-(Dibromonitromethyl)-4-methyl-	2-(NO_2CH_2)-4-Me-Q; Br_2/AcOH	1740
3,6,8-Tribromo-4-(dibromomethyl)-1,2-dihydro-2,2-dimethyl-	1-Ac-1,2-diH-2,2,4-triMe-Q; Br_2/$CHCl_3$; or from 4-($BrCH_2$)-1,2-diH-2,2-diMe-3,6,8-triBr-Q; Br_2/$CHCl_3$	203, 204, 1501, 1742
4-(Dibromomethyl)-8-nitro-	8-NO_2-4-Me-Q; Br_2/AcOH/NaOAc	1723
6-(Dibromomethyl)-	6-Br-Q.HBr.Br_2; heat at 180 °C for 2 h with Br_2	290
3-Bromo-6-(dibromomethyl)-	By product from above	290
DICHLOROMETHYL COMPOUNDS		
2-(Dichloromethyl)-	2-Me-Q; Cl_2 in inert solvent for 6 h at 65 °C	1734
2-(Dichloronitromethyl)-	(i) 2-(NO_2CH_2)-Q; Cl_2/AcOH for 15 min (55%); (ii) 2-[Br(NO_2)CH]-Q; Cl_2/AcOH	1738
TRIBROMOMETHYL COMPOUNDS		
2-(Tribromomethyl)-	2-Me-Q; Br_2/AcONa/AcOH few min under reflux then 30 min at 100 °C (100%)	942, 1724
5-Bromo-8-methoxy-2-(tribromo-methyl)-	8-MeO-2-Me-Q; Br_2/AcOH/AcONa at 80 °C (45%); (ii) 5-Br-8-MeO-2-Me-Q; Br_2/AcOH/AcONa at 100 °C for 30 min (94%)	169
4-Chloro-2-(tribromomethyl)-	2-Me-4-Cl-Q; Br_2/AcOH/AcONa (65%)	1349
5-Chloro-2-(tribromomethyl)-	2-Me-5-Cl-Q; Br_2/AcOH/AcONa for 30 min at 100 °C (91%)	769
6-Chloro-2-(tribromomethyl)-	2-Me-6-Cl-Q; Br_2/AcOH for 2 h at 80–95 °C then 24 h at room temp. (67%)	925
7-Chloro-2-(tribromomethyl)-	2-Me-7-Cl-Q; Br_2/AcOH for 30 min at 100 °C (84%)	769
4,7-Dichloro-2-(tribromomethyl)-	2-Me-4,7-diCl-Q; Br_2/AcOH/AcONa for 30 min at 100 °C (89%)	1123
3-Methyl-2-(tribromomethyl)-	2,3-diMe-Q; Br_2/AcOH/AcONa as above	1730
4-Methyl-2-(tribromomethyl)-	2,4-diMe-Q; Br_2/AcOH/AcONa (78%)	1727
6-Methyl-2-(tribromomethyl)-	2,6-diMe-Q; Br_2/AcOH/AcONa	1729

TABLE 37 (*cont.*)

(Haloalkyl)quinoline	Method of preparation (yield)	References
5-Nitro-2-(tribromomethyl)-	2-Me-5-NO_2-Q; Br_2/AcOH/AcONa for 1 h at 100 °C (17%)	1725
6-Nitro-2-(tribromomethyl)-	2-Me-6-NO_2-Q; Br_2/AcOH/AcONa	1456
8-Nitro-2-(tribromomethyl)-	2-Me-8-NO_2-Q; Br_2/AcOH/AcONa for 20 min at 100 °C (100%)	1725, 1728
4-(Tribromomethyl)-, methobromide	1,4-diMe-Q'ium I^-; Br_2/AcONa/H_2O stir for 30 min (61%)	1727
5,8-Dibromo-4-(tribromomethyl)-	4-Me-5,8-diBr-Q; Br_2/AcOH/AcONa under reflux for 8 h (34%)	1349
8-Nitro-4-(tribromomethyl)-	4-Me-8-NO_2-Q; Br_2/AcOH/AcONa	1723
TRICHLOROMETHYL COMPOUNDS		
2-(Trichloromethyl)-	2-Me-Q; Cl_2/AcOH/AcONa few min under reflux, then 30 min at 100 °C	1724
4-Chloro-2-(trichloromethyl)-	2-Me-4-Cl-Q; Cl_2/AcOH/AcONa (50%)	1349
4-Chloro-6-nitro-2-(trichloro-methyl)-	2-Me-4-Cl-6-NO_2-Q; Cl_2/AcOH/AcONa under reflux for 30 min	1456
8-Chloro-6-nitro-2-(trichloromethyl)-	2-Me-8-Cl-6-NO_2-Q; Cl_2/AcOH/AcONa under reflux for 30 min	1456
8-Methyl-6-nitro-2-(trichloromethyl)-	2,8-diMe-6-NO_2-Q; Cl_2/AcOH/AcONa; as above	1456
6-Nitro-2-(trichloromethyl)-	2-Me-6-NO_2-Q; Cl_2/AcOH/AcONa; as above	1456
6-Nitro-2-(trichloromethyl)-4-carboxylic acid	2-Me-6-NO_2-Q-4-CO_2H; Cl_2/AcOH/AcONa; as above	1456

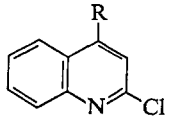
B. Use of N-*Halosuccinimides*

Campbell and his co-workers[1745, 1746] treated 4-methylquinoline with *N*-bromosuccinimide in boiling carbon tetrachloride and obtained an unstable product, m.p. 91 °C, which they asssumed to be 4-(bromomethyl)quinoline. Hasegawa,[1747] however, has carried out a similar reaction in the presence of benzoyl peroxide and found that, with a large excess of solvent, a good yield (70%) of 4-(bromomethyl)-quinoline, m.p. 66 °C, may be obtained. The large excess of solvent appears to be necessary in order to minimize self-quaternization of the 4-(bromomethyl)quinoline. Hasegawa has brominated 2-chloro-4-methylquinoline under similar conditions and obtained a mixture of 4-(bromomethyl)-2-chloroquinoline (**957**; R = CH_2Br) (45%), starting material (13%), 2-chloro-4-(hydroxymethyl)quinoline (**957**; R = CH_2OH) (13%), and 2-chloro-4-(dibromomethyl)quinoline (**957**; R = $CHBr_2$) (10%).

The bromomethyl compound (**957**; R = CH_2Br) appears to be less prone to self-condensation than the chlorine-free bromomethyl compound, and the authors suggest that this is due to the chloro-substituent decreasing the basicity of the ring-nitrogen atom.

1-Benzoyl-1,2-dihydro-2,2,4-trimethylquinoline (**952**; R = Bz) is reported[1748] to react with one equivalent of *N*-bromosuccinimide in carbon tetrachloride to give the

monobromo-derivative (**958**; R = CH_2Br) (85%). The dibromo-derivative (**958**; R = $CHBr_2$) (45%) may be prepared by using 2 molar equivalents of brominating agent. The 1-acetyl compound (**952**; R = Ac) behaves similarly.[203, 204]



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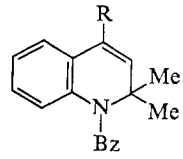

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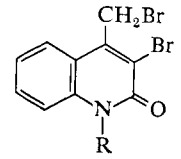
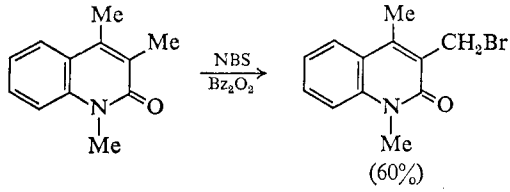
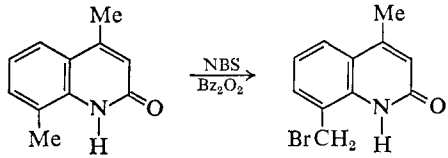


959

Daniels and his co-workers[115] found that 4-methyl- and 1,4-dimethyl-2-quinolone yield the respective 3-bromo-derivatives when treated with *N*-bromosuccinimide in the presence of benzoyl peroxide. If, however, the 3-position is blocked then side-chain bromination occurs in good yield. For example, 3-bromo-1,4-dimethyl-2-quinolone yields 3-bromo-4-(bromomethyl)-1-methyl-2-quinolone (**959**; R = Me) (54%). These authors also found that, in the presence of *N*-bromosuccinimide and benzoyl peroxide, methyl groups at positions 3, 7, and 8 are brominated in preference to the 4-methyl substituent, as exemplified in the annexed formulae.



(60%)

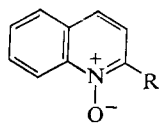


960 (50%)

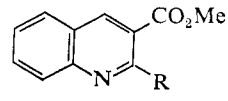
In order to account for the absence of bromination at the 4-methyl group the authors suggest that the attacking succinimido-radical, being electropositive, tends to avoid the 4-methyl group since it is located at an electron-deficient site of the quinoline nucleus. They argue that such an effect will allow precedence to the competing heterolytic breakdown of the *N*-bromosuccinimide and hence substitution at the 3-position. Significantly, 4,8-dimethyl-2-quinolone (**960**) in the presence of aluminium chloride, rather than benzoyl peroxide, undergoes halogenation exclusively at the 3-position (79%) (heterolytic reaction) in contrast to side-chain reaction. It appears that methyl groups at the 3-position, or located on the carbocyclic ring, are sufficiently electronegative to allow homolytic bromination to occur. Subsequently, however, a report has appeared, indicating that 4-methyl-2-quinolone, on treatment with *N*-bromo-succinimide in boiling chloroform, undergoes both nuclear and side-chain halogenation to give the dibromo-derivative (**959**; R = H).[114]

Lyle and his co-workers[1749] have reported on the bromination of a series of 2-substituted 3-methylquinolines by *N*-bromosuccinimide in boiling carbon tetrachloride. In each case the 3-(bromomethyl)quinoline was obtained in high yield.

The action of *N*-bromosuccinimide on 2-methylquinoline, under a wide variety of conditions, has been carefully studied by Hasegawa.[1750] He found that mixtures of the mono-, di-, and tri-bromo-derivatives of varying composition are obtained depending on the reaction conditions. With an excess of *N*-bromosuccinimide in boiling chloroform, 2-(dibromomethyl)quinoline (76%), together with 2-(tribromomethyl)-quinoline (4%), is obtained. Under the same conditions but with molar equivalents of reactants, a mixture of 2-(bromomethyl)- (22%), and (2-dibromomethyl)-quinoline (24%) is produced. In ether solution the dibromomethyl derivative appears to be the main product, whereas in carbon tetrachloride or benzene solution a high yield (55%) of the 2-(bromomethyl) derivative is achieved. Further studies by Hasegawa[1751] have shown that 2-methylquinoline *N*-oxide is brominated far more rapidly with *N*-bromosuccinimide than is 2-methylquinoline. With an equivalent of *N*-bromo-succinimide at room temperature for 1 hour, a mixture of 2-(dibromomethyl)-quinoline *N*-oxide (**961**; R = $CHBr_2$) (22%), 2-(bromomethyl)quinoline *N*-oxide (**961**; R = CH_2Br) (14%), and starting material (35%), is obtained.



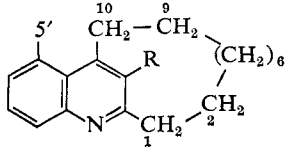
961



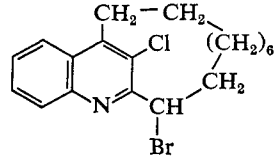
962

Methyl 2-methylquinoline-3-carboxylate (**962**; R = Me) reacts with *N*-bromo-succinimide to give the 2-(bromomethyl) derivative (**962**; R = CH_2Br),[1752] while 8-methylquinoline with *N*-bromosuccinimide in boiling carbon tetrachloride in the presence of benzoyl peroxide yields 8-(bromomethyl)quinoline (60–75%).[1753–1755] In the presence of ultraviolet light, however, a mixture of the monobromomethyl (63%) and dibromomethyl derivatives is obtained.[1754]

An interesting study on the bromination of the 2,4-quinolinophanes of type (**963**) has been carried out by Parham and his co-workers.[1164] Reaction of the chloro-compound (**963**; R = Cl) with an equivalent of *N*-bromosuccinimide yields the



963



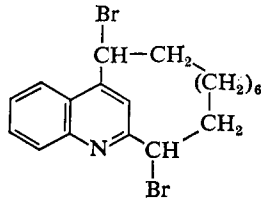
964

monobromo-derivative (**964**) (23%) which, on the basis of steric considerations, is assigned the *syn*-configuration.*

The failure of the chloro-compound (**963**; R = Cl) to undergo 1,10-dibromination (see diagram **963** for numbering) even in the presence of an excess of *N*-bromo-succinimide, or on further treatment of the monobromo-derivative (**964**) with *N*-bromosuccinimide, is thought to be due to crowding of the 10-methylene group by the *peri*(i.e. 5′)-hydrogen on the quinoline ring, and the 3-chlorine atom. The

* More recent work[2058] shows that the *anti*-1-chloro- and *anti*-1-bromo-derivatives of (**963**; R = Cl) may be prepared in high yield by treating the *anti*-hydroxy-compound with thionyl chloride and thionyl bromide, respectively, in benzene solution.

syn-configuration of bromo-compound (**964**) is also favoured on steric grounds, since the alternative *anti*-form is sterically crowded by the bridging methylene group and again by the 3-chloro-substituent. Some support for these claims is forthcoming from the results of bromination studies on the dechlorinated derivative (**963**; R = H). In this case the steric restraints mentioned above are removed, and dibromination should be possible. Experimentally this is found to be the case, and with 2 equivalents of *N*-bromosuccinimide the 1,10-dibromo-derivative (**965**) is obtained in 47% yield.



965

Table 38 deals with compounds concerned in this Section.

TABLE 38. (Bromoalkyl)quinolines Prepared by the Action of *N*-Bromosuccinimide (NBS) on Alkylquinolines

(Bromoalkyl)quinoline*	Reaction conditions (yield)	References
2-(Bromomethyl)-	2-Me-Q; NBS/CCl_4/Bz_2O_2 for 4.5 h at room temp. (55%)	1750
2-(Bromomethyl) *N*-oxide	2-Me-Q *N*-oxide; NBS/$CHCl_3$ for 1 h at room temp. (14%)	1751
Me 2-(bromomethyl)-3-carboxylate	2-Me-Q-3-CO_2Me; NBS/CCl_4	1752
2-Bromo-3-(bromomethyl)-	3-Me-2-Br-Q; NBS/CCl_4 (93%)	1749
3-(Bromomethyl)-2-chloro-	3-Me-2-Cl-Q; NBS/CCl_4 (95%)	1749
3-(Bromomethyl)-1,4-dimethyl-2-quinolone	1,3,4-triMe-2-Q'one; NBS/CCl_4/Bz_2O_2 under reflux (60%)	115
3-(Bromomethyl)-4-methyl-2-quinolone	3,4-diMe-2-Q'one; NBS/CCl_4/Bz_2O_2 under reflux (53%)	115
3-(Bromomethyl)-2-iodo-	3-Me-2-I-Q; NBS/CCl_4 (45%)	1749
3-(Bromomethyl)-2-quinolone	3-Me-2-Q'one; NBS/CCl_4 (72%)	1749
4-(Bromomethyl)-	4-Me-Q; NBS/CCl_4 at 60 °C for 30 min; or with NBS/CCl_4/Bz_2O_2 at 90 °C for 1 h (70%)	1745, 1746, 1747
3-Bromo-4-(bromomethyl)-2-quinolone	4-Me-2-Q'one; NBS/$CHCl_3$ under reflux for 8 h	114
3-Bromo-4-(bromomethyl)-1-methyl-2-quinolone	1,4-diMe-3-Br-2-Q'one; NBS/CCl_4/Bz_2O_2 under reflux (54%)	115
4-(Bromomethyl)-2-chloro-	4-Me-2-Cl-Q; NBS/CCl_4/Bz_2O_2 u.v. for 1 h (45%)	1747

* See footnote to Table 1, p. 340.

TABLE 38 (*cont.*)

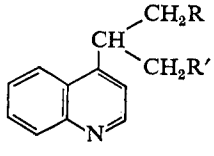
(Bromoalkyl)quinoline*	Reaction conditions (yield)	References
1-Benzoyl-4-(bromomethyl)-1,2-dihydro-2,2-dimethyl-	1-Bz-1,2-diH-2,2,4-triMe-Q; NBS/CCl_4 under reflux for 10–15 min (85%)	1748
7-(Bromomethyl)-1,4-dimethyl-2-quinolone	1,4,7-triMe-2-Q'one; NBS/CCl_4/Bz_2O_2 under reflux (61%)	115
8-(Bromomethyl)-	8-Me-Q; NBS/CCl_4 under reflux for 12 h (75%); (ii) or in the presence of u.v. (63%)	1753, 1754, 1755
8-(Bromomethyl)-4-methyl-2-quinolone	4,8-diMe-2-Q'one;NBS/CCl_4/Bz_2O_2 under reflux (50%)	115
2-(Dibromomethyl)-	2-Me-Q; NBS/$CHCl_3$/Bz_2O_2 for 1 h at room temp. (71%)	1750
2-(Dibromomethyl) *N*-oxide	2-Me-Q *N*-oxide; NBS/$CHCl_3$ for 1 h at room temp. (22%)	1751
1-Benzoyl-4-(dibromomethyl)-1,2-dihydro-2,2-dimethyl-	1-Bz-1,2-diH-2,2,4-triMe-Q; 2NBS/CCl_4 under reflux for 10–15 min (45%)	1748
2-Chloro-4-(dibromomethyl)-	4-Me-2-Cl-Q; NBS/CCl_4/Bz_2O_2 u.v. for 1 h (10%)	1747
8-(Dibromomethyl)-	8-Me-Q; NBS/CCl_4 u.v. at 70 °C	1754

* See footnote to Table 1, p. 340.

C. Replacement of Hydroxyl groups

a. USE OF HALOGEN ACIDS. Early work by Koenigs[1723] indicates that the propane-1,3-diol (**966**; R = R′ = OH) with hydriodic acid and red phosphorus yields a mixture of the monoiodo- (**966**; R = I, R′ = OH) and the di-iodo-derivative (**966**; R = R′ = I).

In a similar manner Meisenheimer and his co-workers[1756] prepared 1,2,3,4-tetrahydro-4-(2-iodoethyl)quinoline (**967**) and 4-(2-iodoethyl)quinoline (**968**) from



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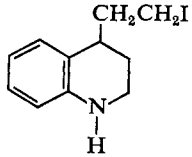

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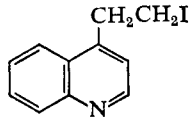
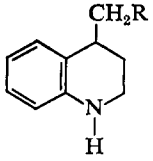


968

the respective alcohols. 4-(Bromomethyl)-1,2,3,4-tetrahydroquinoline (**969**; R = Br) has been obtained[1757] by heating 1,2,3,4-tetrahydro-4-(hydroxymethyl)quinoline (**969**; R = OH) with hydrobromic acid at 100 °C.



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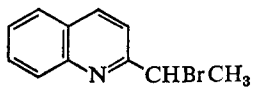
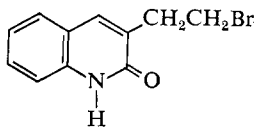


970

Other reactions of this type include preparation of 2-(1-bromoethyl)quinoline (**970**) from 2-(1-hydroxyethyl)quinoline,[1758] of 6-(chloromethyl)-[1759, 1760] and 6-(bromoethyl)-quinoline[1759] from 6-(hydroxymethyl)quinoline, and of 3-(2-bromoethyl)-2-quinolone (**971**) from 3-(2-hydroxyethyl)-2-quinolone.[831]



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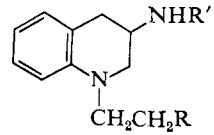
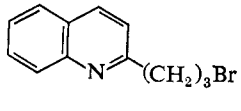


972

Kaslow and Schlatter[1761] have described a general method for the synthesis of 5-, 6-, and 7-(bromomethyl)quinoline, which involves heating the (hydroxymethyl)-quinoline with a solution of hydrogen bromide in glacial acetic acid. The 3-amino-tetrahydro-1-(2-hydroxyethyl)quinolines (**972**; R = OH, R′ = H or $PhCH_2$) are reported[1762, 1763] to react with hydrobromic acid or phosphorus tribromide at 100 °C to yield the corresponding bromo-derivatives (**972**; R = Br, R′ = H or $PhCH_2$). 2-(3-Ethoxypropyl)quinoline, heated under reflux with fuming hydrobromic acid (66%), undergoes replacement of the ethoxy-group to give the bromo-compound (**973**), as the hydrobromide, in 85% yield, together with the tricyclic material (**974**) (ca. 10%).[1764]



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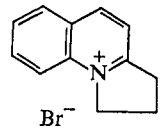
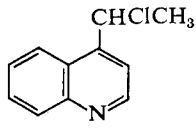


974

b. Use of Thionyl Chloride. 4-(1-Hydroxyethyl)quinoline reacts with thionyl chloride in ether to give the chloroethyl compound (**975**) in 70% yield.[401] Similarly 4-(hydroxymethyl)-1-methyl-2-quinolone (**976**; R = OH) yields 4-chloromethyl)-1-methyl-2-quinolone (**976**; R = Cl) (72%) when heated with thionyl chloride in benzene for several hours.[1765]



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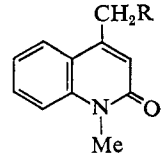


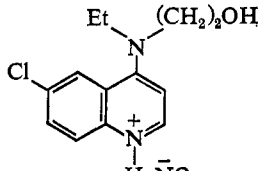
976

Kaslow and Schlatter[1761] in their investigations into the preparation of (halomethyl)quinolines describe a general method for the synthesis of (chloromethyl)-quinolines that involves heating the (hydroxymethyl)quinoline, as the preformed hydrochloride, with thionyl chloride. Yields of 65–85% are reported. By this method 4-chloro- and 4,6-dichloro-3-(chloromethyl)-7-(trifluoromethyl)quinoline have been prepared in high yield (90–95%).[460]

Thionyl chloride in boiling toluene converts 2-(hydroxymethyl)quinoline into 2-(chloromethyl)quinoline (93%),[1766] while thionyl chloride in boiling chloroform has

been used to prepare 6-(chloromethyl)quinoline (78%)[1767] and 4-(chloromethyl)-2-quinolone (90%)[1768] from the respective hydroxymethyl compounds.

Both side-chain and nuclear chlorination are observed[1769] when the nitrate salt (**977**) is treated with thionyl chloride. The resulting 3-chloro-4-(2-chloroethylamino)-derivative (**978**) is thought to arise by replacement of the hydroxy-group, and then



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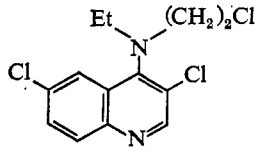


978

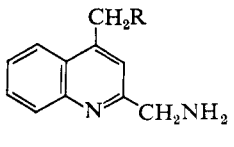
electrophilic chlorination at the 3-position by chloronium ion generated, presumably, by the nitrate present acting as an oxidizing agent on thionyl chloride.

c. Use of Phosphorus Halides. 3- and 4-(Bromomethyl)quinoline have been prepared[1727] by treating the appropriate (hydroxymethyl)quinoline with phosphorus tribromide in cold benzene. The yield in both cases is high (72% and 75%, respectively). This method has been reported[1761] as being unsuitable for the preparation of 6-(bromomethyl)quinoline, although no reasons were given.

2-(Chloromethyl)quinoline and 4-(bromomethyl)quinoline have been prepared[1770] from the (hydroxymethyl) compounds by using phosphorus trichloride and phosphorus tribromide, respectively. Phosphorus pentachloride in boiling chloroform converts 3-(hydroxymethyl)quinoline into 3-(chloromethyl)quinoline hydrochloride in high yield (70%).[1771]

4-(Hydroxymethyl)-1-methyl-2-quinolone undergoes replacement of the hydroxy-group, to yield the (bromoalkyl)quinolone (**976**; R = Br), when heated with phosphorus tribromide at 110–120 °C for 3 hours;[115] apparently no 2-bromo-derivative is formed.

Phosphorus oxychloride has been used for the preparation of 2-(aminomethyl)-4-(chloromethyl)quinoline (**979**; R = Cl) (46.9%) from the 4-(hydroxymethyl) derivative (**979**; R = OH),[1772] and for the preparation of the 2-chloroethyl derivative



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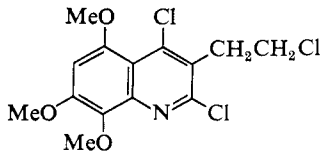


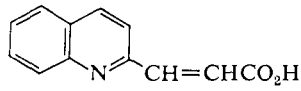
980

(**980**).[569] In the latter case the starting material is the corresponding 4-hydroxy-3-(2-hydroxyethyl)-2-quinolone, and side-chain chlorination, in contrast to the bromination procedure mentioned above, is accompanied by halogenation at the 2- and 4-positions.

The 1-(2-hydroxyethyl) derivative (**972**; R = OH, R′ = $PhCH_2CH_2$), when shaken with phosphorus tribromide in carbon tetrachloride, yields the 1-(2-bromoethyl) derivative (**972**; R = Br, R′ = $PhCH_2CH_2$).[300]

D. Addition of Halogen or Hydrogen Halide to Multiple Carbon—Carbon Bonds

Carlier and Einhorn[1773] report that 3-(2-quinolyl)acrylic acid (**981**) in acetic acid solution adds bromine to yield the dibromopropanoic acid (**982**), m.p. 181 °C, from which 2-ethynylquinoline may be obtained by decarboxylation and then debromination.



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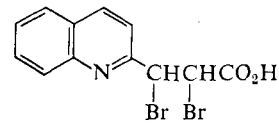
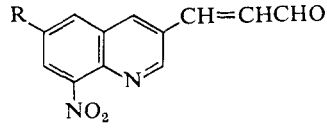


982

Alberts and Bachman,[1774] however, have reinvestigated this reaction and obtained a dibromide (96%), m.p. 228–230 °C, which on dehalogenation gave, not the acetylene, but the acrylic acid (**981**). This dibromide, which was shown conclusively to be the addition product (**982**), was obtained by treating the acid (**981**) with an equivalent of bromine in acetic acid, carbon disulphide, carbon tetrachloride, or nitrobenzene solution. Treatment of the acid with a 2 : 1 molar excess of bromine yielded a dibromo-tribromide complex, m.p. 176 °C, which in boiling acetone again produced the dibromo-compound (**982**). When the dibromo-tribromide was left in air for 48 hours a solid, m.p. 179–180 °C, analysing for 3.5 bromine atoms per molecule, was formed, which the authors suggested was, in all probability, the product reported by Carlier and Einhorn.

3-(8-Nitro-3-quinolyl)- and 3-(6,8-dinitro-3-quinolyl)-acrolein (**983**; R = H and NO_2, respectively) with bromine in acetic acid at 100 °C yield the corresponding



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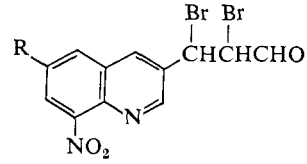
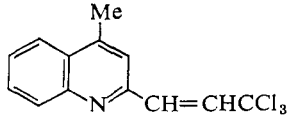


984

dibromopropionaldehydes (**984**; R = H and NO_2, respectively).[1775] The (trichloropropyl) derivative (**985**) is reported[1776] to react with bromine in carbon disulphide to yield the dibromo-derivative (**986**), while the nitro-compound (**987**) on treatment



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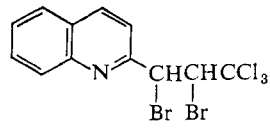

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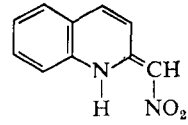
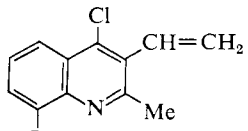


987

with bromine in acetic acid yields a dibromo-compound[1777] which later studies[1740] showed to be the 2-(dibromonitromethyl)quinoline (**937**; R = R′ = Br).

The 3-vinylquinoline (**988**; R = H) with bromine in carbon tetrachloride undergoes addition to give the dibromo-compound (**989**),[1452] whereas with bromine in acetic

acid or chloroform the 8-hydroxy-3-vinylquinoline (**988**; R = OH) suffers nuclear bromination at the 5- and 7-positions.[166]



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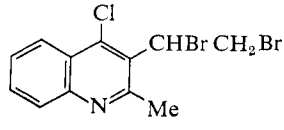
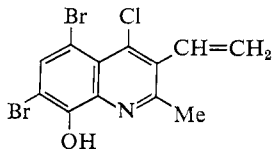


989

However, the 8-hydroxy-derivative (**990**) with bromine in boiling carbon tetrachloride yields the tetrabromo-compound (**991**; R = Me), which on further bromination, with bromine in chloroform, yields the 2-(dibromomethyl) derivative (**991**; R = $CHBr_2$).[166]



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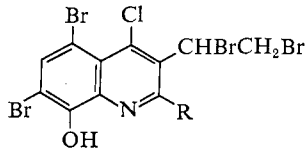
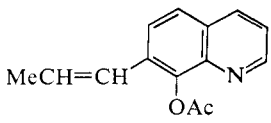


991

In contrast the 8-acetoxy-7-propenylquinoline (**992**), with bromine in boiling chloroform, undergoes only bromine addition.[160]



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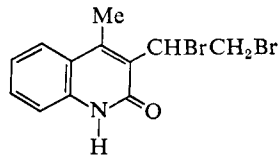
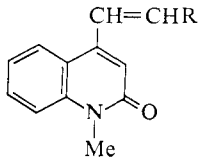


993

4-Methyl-3-vinyl-2-quinolone reacts smoothly with bromine in chloroform to give the dibromo-compound (**993**) in quantitative yield,[1778] as do the 2-quinolones (**994**; R = 2- and 4-quinolyl).[1765]



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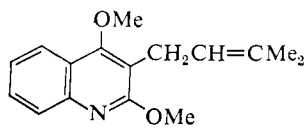
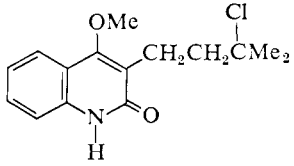


995

Grundon and his co-workers[1779] have shown that the 3-butenyl-dimethoxyquinoline (**995**) on prolonged treatment with hydrogen chloride in boiling di-isopropyl ether undergoes cleavage of the 2-alkoxy-group and hydrogen halide addition to the side chain to give the tertiary alkyl chloride (**996**); seemingly addition of hydrogen chloride is a much slower process than ether cleavage since on carrying out the reaction for 1.5 hours the 3-butenyl-2-quinolone is obtained in 92% yield.

1,2-Di-(2-quinolyl)ethylene (**997**; Ar = 2-C_9H_6N) reacts with bromine in carbon tetrachloride to give the corresponding 1,2-dibromoethane in 90% yield.[1780] The styrylquinoline (**997**; Ar = *p*-ClC_6H_4) behaves similarly.[1732]



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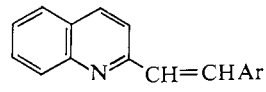
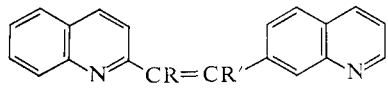


997

Di-(2-quinolyl)acetylene, prepared by copper-catalysed debromination of 2-(tribromomethyl)quinoline in pyridine (see p. 671), with bromine in carbon tetrachloride gives the so-called α-1,2-dibromo-1,2-di-(2-quinolyl)ethylene (**998**; R = R′ = Br). This product is different from β-1,2-dibromo-1,2-di-(2-quinolyl)-ethylene prepared by controlled copper-catalysed debromination of 2-(tribromomethyl)quinoline.[1781]



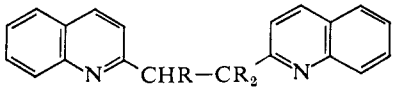
998

These α- and β-bromo-compounds were considered by the authors to be the *cis*- and *trans*-isomers, and in a later paper[1782] the α-isomer was in fact shown to be the *trans*-dibromo-compound, while the β-isomer was, surprisingly, the more stable *cis*-form. The greater stability of the *cis*-isomer probably arises from the fact that in the *trans*-configuration neither quinoline ring can be in the same plane as the ethylene bond owing to steric interactions with the bulky bromine atoms, whereas in the *cis*-isomer one quinoline ring can take up a position which is coplanar with the ethylenic bond. The *trans*-compound isomerizes to the *cis*-form in boiling methanolic potassium hydroxide, whereas *cis* → *trans*-isomerization is achieved on irradiation of the *cis*-isomer with ultraviolet light.[1781] The *cis*-dichloro-compound isomerizes under similar conditions.

Di-(2-quinolyl)acetylene reacts readily with 2N-hydrochloric acid to yield 1-chloro-1,2-di-(2-quinolyl)ethylene (**998**; R = Cl, R′ = H) and less readily with hydrobromic acid to give the corresponding 1-bromo-derivative (**998**; R = Br, R′ = H).[1782] Hydriodic acid yields the *trans*-1,2-di-(2-quinolyl)ethylene (**998**; R = R′ = H) together with an unstable, unidentified, iodine-containing compound, m.p. 102–103 °C.[1782]

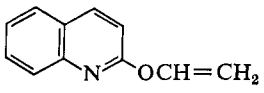
Hammick and his co-workers[1782] found that on going from the unsubstituted 1,2-diquinolylethylenes to the 1,2-dihalo-1,2-diquinolylethylenes, the order of stability of the geometric isomers changes from *trans* greater to *cis* greater. Thus hydrogen chloride and hydrogen bromide react with 1,2-di-(2-quinolyl)acetylene to give mainly *trans*-addition products, but, because of the greater steric requirements of the bromine atoms, more *cis*-isomer is obtained in the latter than in the former reaction. An order of decreasing stability for the *trans*-isomers of 1-2-di(2-quinolyl)- > 1-chloro-1,2-di-(2-quinolyl)- > 1-bromo-1,2-di-(2-quinolyl)- > 1,2-dichloro-1,2-di-(2-quinolyl)- ≏ 1,2-dibromo-1,2-di-(2-quinolyl)ethylene, is observed.

The monochloro- and monobromo-derivatives (**998**; R′ = H, R = Cl and Br, respectively) react with chlorine, and with bromine in carbon tetrachloride solution to give the appropriate 1,1,2-trihalo-1,2-di-(2-quinolyl)ethanes (**999**; R = Cl or Br, respectively).[1782]



999

2-Quinolyl vinyl ether (**1000**) with hydrogen chloride in carbon tetrachloride solution at 0 °C yields only the hydrochloride.[1783] However, with chlorine under the same conditions the dichloroethyl 2-quinolyl ether (**1001**) is obtained.



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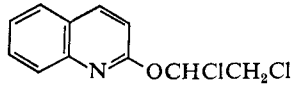

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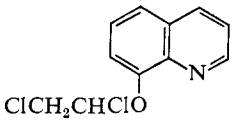
8-(Vinyloxy)quinoline under similar conditions yields a mixture of the dichloroethyl ether (**1002**) and the 2-chlorovinyl ether (**1003**).



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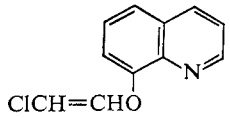
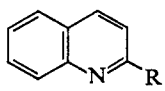


1003

E. Reductive Dehalogenation of (Di- and Tri-halomethyl)quinolines

Hammick and his co-workers have carried out a rigorous investigation into methods of synthesis of mono-, di-, and tri-halomethylquinolines. As pointed out by Hammick in an early paper,[1725] 2-methylquinoline cannot be selectively brominated to give the mono- or di-bromomethyl derivative since the rate of bromination of the alkyl side chain increases as the number of halogen substituents increases.[1726, 1727] Other routes for the synthesis of the mono- and di-bromomethyl compounds were, therefore, sought. It was observed[1725] that tribromomethyl derivatives of quinoline readily undergo controlled reductive dehalogenation to give the required mono- and dibromomethyl derivatives. For example, 2-(tribromomethyl)quinoline on treatment with 2 molar equivalents of stannous chloride in acetone yields 2-(dibromomethyl)-quinoline (**1004**; R = $CHBr_2$) (60%).[1725] In the presence of 4 molar equivalents of stannous chloride, a product thought to be the monobromo-derivative (**1004**; R = CH_2Br) (50%) is obtained. However, further studies[1727] revealed that this



1004

compound is in fact the chloromethyl derivative (**1004**; R = CH_2Cl), halogen exchange having taken place during reduction. 2-(Bromomethyl)quinoline may be obtained[1727] from 2-(tribromomethyl)quinoline in 54% yield by using stannous bromide in acetone as the reducing agent, under strictly controlled conditions. Baxter and Richards[711] have prepared 2-(bromomethyl)-7-chloro-6-methylquinoline from the corresponding 2-(tribromomethyl) derivative under similar conditions. Titanous chloride, and sodium arsenite in aqueous ethanol, have also been used to effect reductive dehalogenations.[1725]

An improved method of reductive dehalogenation, which involves boiling an acetic acid solution of the (trihalomethyl)quinoline with a calculated quantity of tin and hydrochloric acid, has been developed by Hammick and his co-workers,[1727] and by this method 2-(dichloromethyl)- (**1004**; R = $CHCl_2$) and 2-(chloromethyl)-quinoline (**1004**; R = CH_2Cl) have been prepared, the former in 72% yield.

Brown and Hammick[1729] observed that 2-(tribromomethyl)quinoline (**1004**; R = CBr_3) in boiling tetralin readily loses halogen to yield the 2-(dibromomethyl) derivative; and 6-methyl-2-(tribromomethyl)quinoline behaves similarly. Under more harsh conditions (tetralin at 100 °C for 6 hours, then at 150 °C for 2 hours), the (tribromomethyl)quinoline is reduced to 2-(bromomethyl)quinoline in 74% yield.[1781] These results are discussed in more detail in a later Section (IV.2.A.).

Dirstine and Bergstrom[1784] report that 2-(tribromomethyl)quinoline, when heated in a mixture of ethanol and sulphuric acid at 105 °C, is reduced to the dibromomethyl compound (98%). Seemingly the dehalogenation fails in methanol, and proceeds, with much charring, in *n*- and iso-propyl alcohol only at higher temperatures (130 °C). Sharp[1785] has carried out the same reaction in boiling 20% sulphuric acid–ethanol mixture.

These results have been partly substantiated by Astell–Burt and Hammick[1786] who, in a study on the effects of acidity on the rate of acid–alcohol-induced reductive dehalogenation of 2-(tribromomethyl)quinoline, found that reduction fails in methanol and *tert*-butyl alcohol, whereas reduction is very rapid in propan-2-ol, and also in ethanol, even in the absence of acid. In accord with these observations it has been reported[1349] that 4-chloro-2-(tribromomethyl)quinoline in boiling propan-2-ol reduces to the 2-(dibromomethyl) derivative in 77% yield. 2-(Tribromomethyl)-quinoline and 4-chloro-2-(trichloromethyl)quinoline, however, appear to be inert under these conditions.

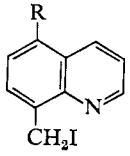
A mixture of sodium hydrogen sulphide and an excess of ethanethiol in boiling diethyl ether is reported[1787] to reduce 2-(tribromomethyl)quinoline to 2-(dibromomethyl)quinoline in 82.5% yield. 2-(Dibromonitromethyl)quinoline (**1004**; R = CBr_2NO_2) with ethanolic ammonia undergoes debromination to give the 2-(bromonitromethyl)quinoline (**1004**; R = $CHBrNO_2$).[1738]

F. Halogen Exchange Reactions

Early work by Howitz showed that 8-(bromomethyl)quinoline[1788] and 8-(chloromethyl)-5-nitroquinoline[292] with methyl iodide at 80 °C give the 8-(iodomethyl) derivatives (**1005**; R = H and NO_2, respectively), in quantitative yield.

Further work by Howitz and Nöther[292] showed that the product obtained from the decomposition of 8-methylquinolinium perbromide* in the presence of hydrochloric acid is not the 3-bromo-8-(bromomethyl) compound (**1006**; R = Br) as originally thought,[291] but is rather the 3-bromo-8-(chloromethyl)quinoline (**1006**; R = Cl), halogen exchange having taken place during the reaction.

* See footnote to Table 5, p. 375.



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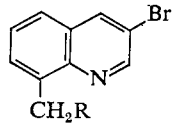

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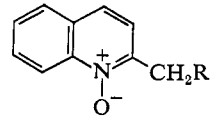
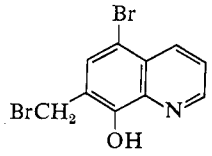


1007

2-(Bromomethyl)quinoline in boiling 10% hydrochloric acid undergoes during 1 hour bromine–chlorine exchange to yield 2-(chloromethyl)quinoline (92%).[1750] Similarly 4-(bromomethyl)quinoline and 4-(bromomethyl-2-chloroquinoline with boiling 15% hydrochloric acid give the corresponding 4-(chloromethyl)quinolines in 80% and 85% yield, respectively.[1747] 2-(Chloromethyl)quinoline *N*-oxide (**1007**; R = Cl) can be obtained by boiling 2-(bromomethyl)quinoline *N*-oxide (**1007**; R = Br) with hydrochloric acid.[1751]

6-(Chloromethyl)quinoline reacts with sodium iodide in acetone to give 6-(iodomethyl)quinoline in 21.5% yield.[1759] (Bromonitromethyl)quinoline (**1004**; R = $CHBrNO_2$) does not undergo bromine–iodine exchange if heated with potassium iodide and ethanol, but rather loses halogen to give the 2-(nitromethyl)quinoline (**1004**; R = CH_2NO_2).[1741] With chlorine in acetic acid, however, the (bromonitromethyl) compound undergoes both chlorination and halogen exchange to give the (dichloronitromethyl) derivative (**1004**; R = CCl_2NO_2) (55%).[1738]

7-(Chloromethyl)-8-hydroxyquinoline hydrochloride when stirred with aqueous bromine suffers nuclear bromination and chlorine–bromine exchange to give what is thought to be the dibromo-compound. (**1008**).[1789] However, in light of later



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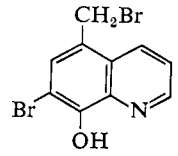


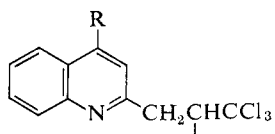
1009

studies[157, 162] (p. 643) this product is more likely to be the isomeric 7-bromo-5-(bromomethyl)-8-hydroxyquinoline (**1009**).

2-(Tribromomethyl)- and 2-(trichloromethyl)-quinoline with antimony trifluoride (Swarts reaction) give 2-(trifluoromethyl)quinoline.[1790, 1791]

G. Miscellaneous Methods

a. Aldol Condensation and Chloromethylation Reactions. Several 3-trichloropropyl derivatives of quinoline have been prepared by aldol condensations between 2-methylquinolines and chloral. At 110 °C these reagents are reported[1792, 1793] to give the 2-(3,3,3-trichloro-2-hydroxy) derivative (**1010**; R = H). The same



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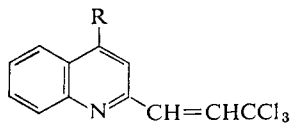
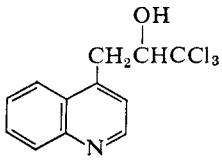


1011

product is obtained[1794] when the condensation is carried out in the presence of zinc chloride at 100 °C, whereas in pyridine solution at the same temperature dehydration to the propene derivative (**1011**; R = H) (95%) is observed.[1774]

2,4-Dimethylquinoline condenses with chloral in pentyl acetate at 140 °C to give the hydroxy-compound (**1010**; R = Me).[1795] In the presence of zinc chloride, however, the major product is the trichloropropene (**1011**; R = Me).[1776] 4-Methylquinoline has also been condensed to give the corresponding trichlorohydroxypropyl compound (**1012**).[1793, 1796]



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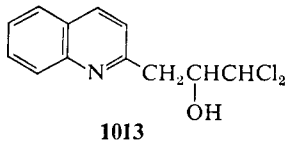

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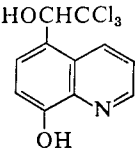


1014

2-Methylquinoline condenses with dichloroacetaldehyde in the presence of zinc chloride to give the dichlorohydroxypropyl derivative (**1013**), albeit in low yield (5%), whereas with chloroacetaldehyde condensation is unsuccessful under a wide range of reaction conditions.[1797]

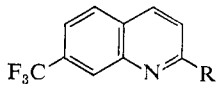
8-Hydroxyquinoline reacts slowly with chloral hydrate in 95% sulphuric acid at room temperature to give the 5-(2,2,2-trichloro-1-hydroxyethyl) derivative (**1014**).[155]

The chloromethylation of 8-hydroxyquinoline and its derivatives has been investigated in some detail[157, 162, 1798] and the main product appears to be in each case the 5-chloromethyl derivative, although early workers[1789] assumed that chloromethylation had occurred at the 7-position.

b. Skraup and Related Reactions. Gilman and Blume[868] were the first to prepare (trifluoromethyl)quinolines by means of the Skraup reaction. In their hands *m*-(trifluoromethyl)aniline under normal Skraup conditions yielded a mixture (56.5%) of 5- and 7-(trifluoromethyl)quinoline, which on fractional distillation yielded pure 7-(trifluoromethyl)quinoline (**1015**; R = H) (31.8%) as a low-melting solid. Purification of the 5-(trifluoromethyl) isomer was achieved by fractional crystallization of its oxalate, which eventually yielded the product, as an oil, in 5.7% yield. Pouterman and Girardet[869] carried out similar reactions and obtained the 5-(trifluoromethyl) isomer in 33.6% yield. The 6- and 8-(trifluoromethyl)quinolines have also been prepared from *p*-amino- and *o*-amino-benzotrifluoride, respectively.[1799]

2-Methyl-7-(trifluoromethyl)quinoline (**1015**; R = Me) is obtained[1790, 1791] by treating *m*-(trifluoromethyl)aniline with crotonaldehyde under Skraup conditions, while under similar conditions *m*-methoxyaniline is reported[1791] to react with 3,3,3-trifluorocrotonaldehyde ($CF_3CH{=}CH.CHO$) to yield 7-methoxy-2-(trifluoromethyl)quinoline. Skraup reactions on 3-amino-4-hydroxy- and 3-amino-4-methoxybenzotrifluoride yield 8-hydroxy- and 8-methoxy-5-(trifluoromethyl)quinoline (**1016**; R = OH and OMe, respectively).[1800]

6-Nitro-7-(trifluoromethyl)quinoline (**1017**) is obtained in 56% yield by means of a Skraup reaction on 5-amino-2-nitrobenzotrifluoride,[1801] and 8-nitro-7-(trifluoromethyl)-, 8-nitro-5-(trifluoromethyl)-, and 5-nitro-7-(trifluoromethyl)quinoline have likewise been prepared[726] from the appropriate nitro(trifluoromethyl)anilines. A Skraup reaction on 3,5-bis(trifluoromethyl)aniline (**1018**) yields 5,7-bis(trifluoromethyl)quinoline (33%).[1802]



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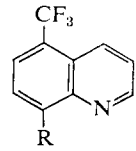

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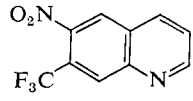
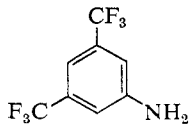


1017

ω-Haloacetoacetanilides may be prepared by direct halogenation of acetoacetanilides, and on treatment with concentrated sulphuric acid undergo Knorr cyclization to the 4-(halomethyl)-2-quinolones.[114, 115, 355] Some confusion regarding this reaction arose on account of an early report by Knorr[111] that bromination of acetoacetanilide yields the α-bromo-derivative, which on cyclization gives 3-bromo-4-methyl-2-quinolone. However, later workers[112, 114] showed that the primary bromination product is in fact the ω-bromo-compound (**1019**; R = Br), which on cyclization



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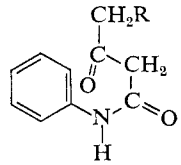

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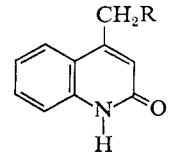
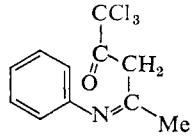


1020

yields 4-(bromomethyl)-2-quinolone (**1020**; R = Br) (97%).[355] Reaction of ω-bromoacetoacetanilide with sodium iodide in acetone or methanol yields the ω-iodo-compound (**1019**; R = I) which cyclizes in concentrated sulphuric acid at room temperature to give 4-(iodomethyl)-2-quinolone (**1020**; R = I).[1803]

Ethyl (trifluoroaceto)acetate ($CF_3COCH_2CO_2Et$) reacts with arylamines under Conrad–Limpach conditions to yield 2-(trifluoromethyl)-4-quinolones;[390, 453, 627] likewise, ethyl (trichloroaceto)acetate has been used for the synthesis of 2-(trichloromethyl)-4-quinolones.[955]

The (trichloroacetyl)acetone anil (**1021**) in concentrated sulphuric acid at 100 °C cyclizes to give 4-(trichloromethyl)-2-methylquinoline (**1022**) (72%).[1804]



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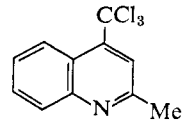
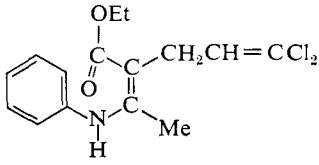


1022

Gyul'budagyan and his co-workers[592, 1805, 1806] have prepared a series of 3-(3-chloroalkyl) derivatives of 4-quinolone by Conrad–Limpach-type cyclization of the appropriate anilinocrotonates. For example, the 3-anilino-2-(dichloroallyl)crotonate (**1023**) cyclizes in hot paraffin oil to give the quinolone (**1024**) in 69% yield.[1805] Several (trifluoromethyl)-4-quinolones have been prepared by heating esters of type (**1025**) in diphenyl ether.[1368, 1421]



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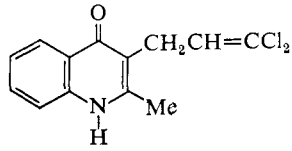

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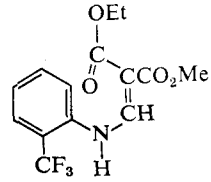
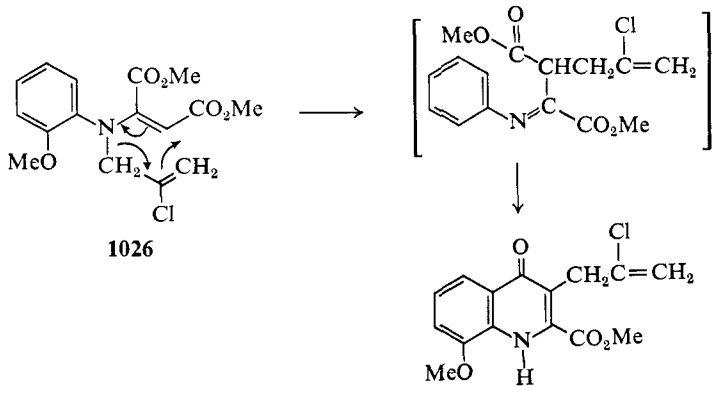


1025

Winterfeldt and his co-workers[1807] were able to prepare the *N*-allyl-*N*-vinylarylamine (**1026**) by treating *N*-(2-chloroallyl)-*o*-methoxyaniline with dimethyl acetylenedicarboxylate. When heated at 210 °C for 12 hours the product undergoes a [3,3]-sigmatropic shift (a hetero-Cope rearrangement), followed by cyclization to give the 3-(2-chloroallyl)-4-quinolone (**1027**) in 90% yield, as outlined in Scheme 82.



1026

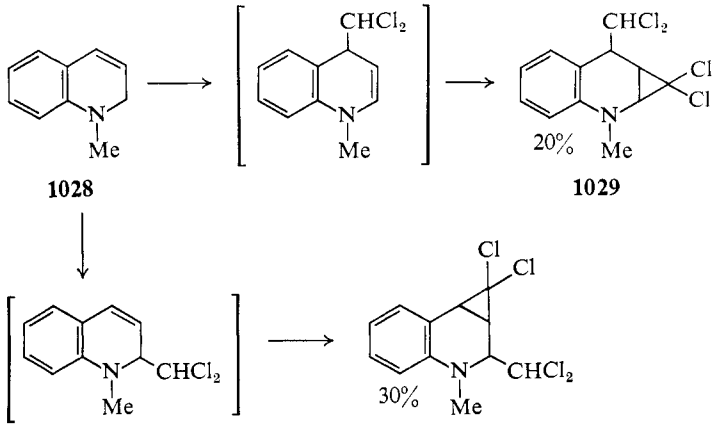
1027

SCHEME 82

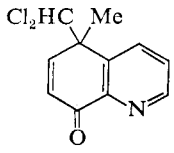
Phosphorus pentachloride is reported[599, 1208-1211] to react with ω-chloroacetanilide to give 4-anilino-2-(chloromethyl)-3-chloroquinoline. The reaction appears to proceed by initial formation of an imidoyl chloride and is discussed in more detail in Section II.1.S.k.

c. REACTIONS INVOLVING DIHALOCARBENES. The reactions of 1,2-dihydroquinolines with halocarbenes have been investigated.[1808] 1,2-Dihydro-1-methyl-2-phenylquinoline failed to react with dibromocarbene, generated by pyrolysis of phenyl(tribromomethyl)mercury, or with dichlorocarbene. 1,2-Dihydro-1-methylquinoline (**1028**) also failed to react with dibromocarbene, and with dichlorocarbene generated from ethyl trichloroacetate. However, with dichlorocarbene, prepared by the action of 50% sodium hydroxide on chloroform, reaction takes place to give a mixture of two products for which structures (**1029**) and (**1030**), have been proposed. These insertion products are thought to arise by addition of the dichlorocarbene to the initially formed dichloromethyl intermediates as indicated in Scheme 83.

Hamada and his co-workers,[1809] conducting a Reimer–Tiemann reaction (chloroform and potassium hydroxide) on 8-hydroxy-5-methylquinoline, unexpectedly obtained the 5-(dichloromethyl)-8-oxoquinoline (**1031**).



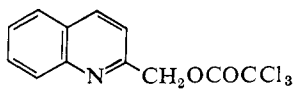
SCHEME 83



1031

d. PREPARATION FROM CARBOXYLIC ACIDS. 2-(Trifluoromethyl)quinoline has been prepared[1810] in 72% yield by heating quinoline-2-carboxylic acid with sulphur tetrafluoride at 120 °C for 8 hours in a stainless-steel vessel. In a similar manner quinoline-3- and -4-carboxylic acid, in the presence of sulphur tetrafluoride and hydrogen fluoride at 150–170 °C, yield 3- and 4-(trifluoromethyl)quinoline in 42% and 69% yield, respectively.[395]*

e. REACTION OF *N*-OXIDES WITH ACYLATING AGENTS. 4-Methylquinoline *N*-oxide reacts with *p*-toluenesulphonyl chloride in dimethylformamide solution in the presence of the boron trifluoride–diethyl ether complex at 100 °C to yield 4-(chloromethyl)-quinoline (34%);[787, 1811] at 150 °C only tar formation is observed. 2-(Chloromethyl)-quinoline can be obtained in a similar manner from 2-methylquinoline *N*-oxide. 2-Methylquinoline *N*-oxide also reacts with trichloroacetyl chloride in either chloroform or acetonitrile solution to give a mixture of 2-(hydroxymethyl)quinoline, 2-(chloromethyl)quinoline, and the trichloroacetyl ester (**1032**).[1812]

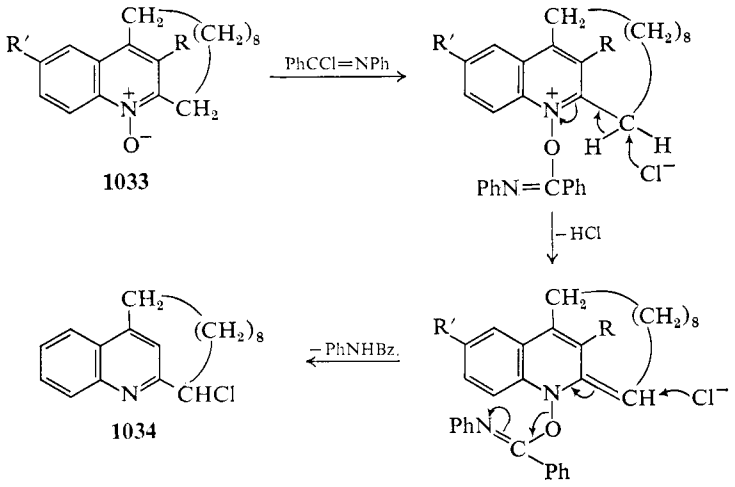


1032

Parham and Sloan[793] found that the [2,4]quinolinophane *N*-oxide (**1033**; R = Cl, R′ = H) on treatment with benzimidoyl chloride yields the dichloro-derivative (**1033**;

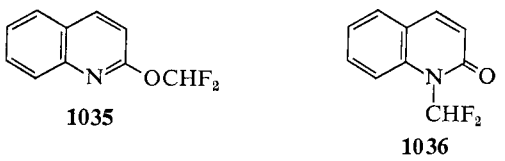
* Fluorinations by sulphur tetrafluoride have been reviewed recently.[2036]

R = R′ = Cl) (see Section II.1.G.c). However, in the absence of the 3-chloro-substituent (i.e. **1033**; R = R′ = H) the reaction follows a different course to yield the α-chloro-derivative (**1034**) as indicated in the following Scheme.



It is suggested in explanation of these results that removal of the 3-chloro-substituent allows the benzylic methylene of the bridging methylene chain to adopt an sp^2-hybridization state, whereas inspection of molecular models indicates that with a 3-chloro-substituent sufficient constraint is placed on the methylene chain to prevent sp^2-hybridization and hence chlorination.

f. Direct Introduction of Haloalkyl Groups. The sodium salt of 2-quinolone is reported[1813] to react with chlorodifluoromethane in the presence of sodium *tert*-butoxide to give a mixture of 2-(difluoromethoxy)quinoline (**1035**) (18–35%) and



1-(difluoromethyl)-2-quinolone (**1036**) (10–18%), together with two unidentified crystalline products of molecular formula $C_{19}H_{13}FN_2O_2$, m.p. 148 °C, and $C_{28}H_{19}N_3O_3$, m.p. 216 °C. The two identified products are thought to arise via a reaction involving difluorocarbene, while the unknown products appear to be di- and tri-substituted methylene derivatives. The authors suggest that they are formed via the the carbanionic species, Q-OCF_2^- and Q-NCF_2^- derived from (**1035**) and (**1036**), respectively. The reaction has since appeared in the patent literature with modified reaction conditions.[1814] In place of *tert*-butoxide a 50% sodium hydride dispersion in mineral oil is used as the base, and the solvent is 1,2-dimethoxyethane.

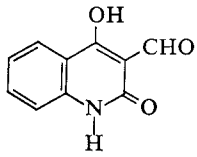
Quinoline is reported[1815] to undergo perfluoro-octylation in 11% yield when irradiated in a quartz vessel at 60 °C with ultraviolet light in the presence of perfluoro-octanesulphonyl chloride ($C_8F_{17}SO_2Cl$). 8-Hydroxyquinoline has been treated similarly.

Perfluoroquinoline undergoes perfluoroalkylation when treated with hexafluoropropene in the presence of fluoride ion.[1250] The reactions are somewhat complex and have been discussed in some detail in Section II.2.C.g.

Kobayashi and his co-workers[1816, 1817] have reported a useful method of introducing trifluoromethyl groups onto the quinoline nucleus. The process, which is basically an Ullmann reaction, involves treating a haloquinoline with trifluoroiodomethane (CF_3I) in an aprotic solvent in the presence of copper powder. 2-Chloroquinoline, kept in dimethylformamide at 130 °C for 24 hours, gives a 10% yield of 2-(trifluoromethyl)quinoline, whereas 2-iodoquinoline, under the same conditions, gives the 2-(trifluoromethyl) derivative in 60% yield. 3-Bromoquinoline yields only a trace of trifluoromethyl compound, whereas 3-iodoquinoline, in acetonitrile, gives 3-(trifluoromethyl)quinoline in 30% yield. The authors find that by changing the solvent high yields of the 3-(trifluoromethyl) derivative can be obtained from the readily accessible 3-bromoquinoline; for example, in pyridine solution a 63% yield is reported, while in hexamethylphosphoramide yields of 74% are achieved. 4-Chloro- and 6-bromo-quinoline, in dimethylformamide at 140 °C, give the 4- and 6-(trifluoromethyl) derivatives in 11% and 28% yield, respectively.

g. Preparation from Carbonyl Compounds. The reaction of aldehydes and ketones with phosphorus halides to give *gem*-dihalo-compounds is a well-known preparative procedure but appears to have been little used for the preparation of (dichloroalkyl)quinolines.

Sato and Ohta[568] during their studies on the synthesis of nordictamnal found that the 4-hydroxy-2-quinolone-3-carbaldehyde (**1037**) reacts with boiling phosphorus oxychloride to give the tetrachloro-compound (**1038**).



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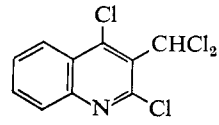
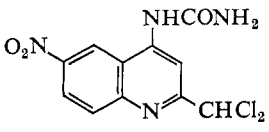


1038

The dichloromethyl derivative (**1039**) has been obtained by heating the corresponding aldehyde with phosphorus pentachloride in carbon tetrachloride.[1456]



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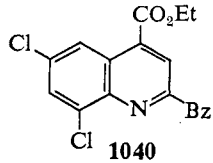

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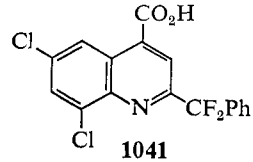
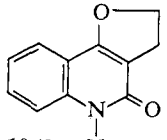


1041

Suggiomo and his co-workers[940] have shown that ethyl 2-benzoyl-6,8-dichloroquinoline-4-carboxylate (**1040**) with sulphur tetrafluoride in aqueous solution at 120 °C is converted into the (difluorobenzyl)quinoline carboxylic acid (**1041**).

h. Ring Opening of Cyclic Ethers. Various researchers[570–574] in connection with their work on the dictamnine-type alkaloids, have shown that dihydrofuroquinolines, e.g. (**1042**), on treatment with phosphorus halides suffer cleavage of the furan ring,

and good yields of 2,4-dichloro-3-(2-chloroethyl)quinolines, e.g. (**1043**), may be obtained (also see Section II.1.D.b(iii) and Table 11).



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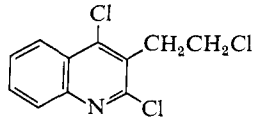
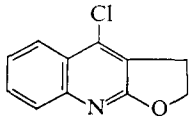


1043

The isomeric dihydrofuro[2,3-*b*]quinoline (**1044**), on treatment with boiling 48% hydrobromic acid, undergoes analogous cleavage of the furan ring to yield 3-(2-bromoethyl)-4-chloro-2-quinolone (**1045**).[572]



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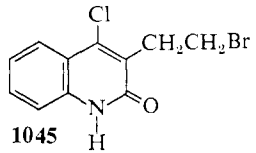
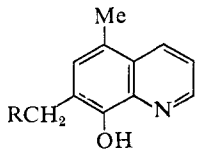


1045

i. Other Methods. 8-Hydroxyquinolines undergo chlorination at the 5- or 7-position on treatment with *tert*-butyl hypochlorite in boiling carbon tetrachloride.[157] However, the hydroxymethyl compound (**1046**; R = OH), in which both these positions are blocked, on treatment with *tert*-butyl hypochlorite for 2 days in a mixture of pyridine and carbon tetrachloride, yields the chloromethyl derivative (**1046**; R = Cl) (60%).



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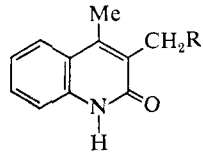
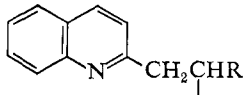


1047

The (3-quinolonyl)acetic acid (**1047**; R = CO_2H) as its silver salt undergoes the Hunsdiecker reaction (bromine in boiling carbon tetrachloride) to yield 3-(bromomethyl)-4-methyl-2-quinolone (**1047**; R = Br).[115]

2-(3,3,3-Trichloro-2-hydroxypropyl)quinoline (**1048**; R = CCl_3) reportedly[1818] undergoes dehydration when treated with phosphorus pentachloride in chloroform to give the (trichloropropenyl) derivative (**1049**; R = CCl_3).



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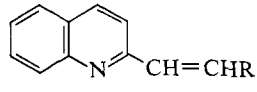
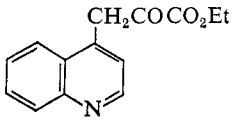


1049

Similarly thionyl chloride in ether[1819] or phosphorus pentachloride in chloroform[1797] brings about dehydration of the dichloro-hydroxy-compound (**1048**; R = $CHCl_2$) to the (dichloropropenyl) derivative (**1049**; R = $CHCl_2$).

Bromination of ethyl (4-quinolyl)pyruvate (**1050**) results, not only in hydrolysis of the ester, but also in decarbonylation and decarboxylation to give 4-(bromomethyl)-quinoline as the hydrobromide.[1820]

7-(Trifluoromethyl)quinoline may be obtained by reductive deiodination of 8-iodo-7-(trifluoromethyl)quinoline using ethanolic potassium hydroxide.[726]



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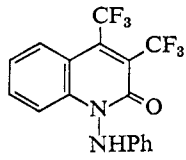

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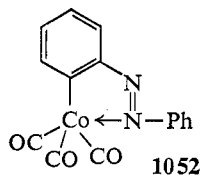


1052

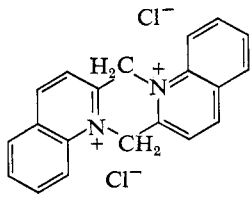
An interesting synthesis of 1-anilino-3,4-bis(trifluoromethyl)-2-quinolone (**1051**) has been reported by Bruce and his co-workers.[1821] They obtained the 2-quinolone by reaction of the azobenzene–cobalt carbonyl complex (**1052**) with hexafluorobut-2-yne ($CF_3C \equiv CCF_3$). An organocobalt complex is also formed. The authors were able to show that the yield of 2-quinolone increases from 30% to 65% as the reaction time is increased from 12 to 18 hours, whereas the yield of the complex decreases from 60% to 25%.

2. Properties and Reactions

A. Introduction

Of the known (haloalkyl)quinolines by far the most investigated are the (halomethyl) derivatives. It appears that the stability of these compounds decreases in the order trihalomethyl > dihalomethyl > monohalomethyl, and fluoro > chloro > bromo > iodo.[1722] In fact, few monoiodo-derivatives have been prepared and as far as the author is aware di- and tri-iodomethyl derivatives are unknown.

As expected, the (trihalomethyl)quinolines are weak bases and do not form isolable hydrochlorides, in contrast to the mono- and di-halo-derivatives, which are more basic and form stable hydrohalides. In fact the (monohalomethyl)quinolines are most conveniently stored as their hydrochloride salts, since the free bases are unstable and can decompose exothermally on storage. Purification of the free bases by distillation is not recommended for the monohalo-derivatives,[1722] and it has been suggested[1722] that (monohalomethyl)quinolines, like their methylpyridine counterparts, undergo self-condensation to yield structures of type (**1053**).



1053

In direct contrast to the order of stability of the free bases, the resistance towards acid-hydrolysis decreases in the order monohalomethyl > dihalomethyl > trihalomethyl. Under basic conditions the mono- and di-halo-derivatives yield red–brown resinous products of unknown composition. The action of nucleophiles on the halo-compounds is discussed in Sections IV.2.c(a–e).

As with most benzylic halides, the halogen atom is very labile and the (monohalomethyl)quinolines are both lachrymatory and vigorous skin-irritants, and their handling warrants the utmost caution.

As mentioned on p. 641, 2-(tribromomethyl)quinoline in boiling tetralin gives 2-(dibromomethyl)quinoline in good yield.[1729] Robertson and Waters[1822] suggest that this reaction involves homolysis of the tribromomethyl group to yield bromine radicals. Hammick and his co-workers[1823] have confirmed this postulate and have shown that 2-(tribromomethyl)quinoline with xylene and mesitylene gives side-chain-brominated products by a free-radical process, as follows:

$$QCBr_3 \underset{}{\overset{\Delta}{\rightleftharpoons}} \dot{Q}CBr_2 + Br\cdot$$

$$ArCH_3 + Br\cdot \longrightarrow ArCH_2\cdot + HBr$$

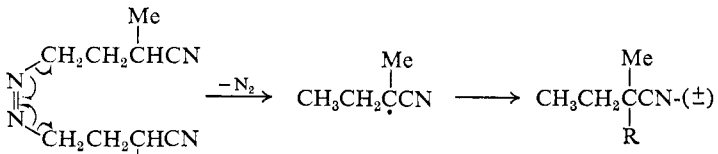
$$ArCH_2\cdot + QCBr_3 \longrightarrow ArCH_2Br + QCBr_2\cdot$$

$$ArCH_3 + QCBr_2\cdot \longrightarrow ArCH_2\cdot + QCHBr_2$$

The authors found that 70% of the bromine lost from the (tribromomethyl)quinoline appears in the methyl group of the aromatic substrate.

It was also shown that cyclohexene, heated under reflux with 2-(tribromomethyl)-quinoline for 3 hours, suffers allylic bromination to give 3-bromocyclohexene (61%) together with 2-(dibromomethyl)quinoline (78%). At higher temperatures 2-(dibromomethyl)quinoline undergoes similar reactions. For example, heating 2-methylquinoline with 2-(dibromomethyl)quinoline at 150 °C for 2 hours affords 2-(bromomethyl)quinoline in 50% yield.

Ford and Waters[1824] have found that the azo-compound (**1054**) undergoes thermally induced homolysis to yield the radical (**1055**) which abstracts halogen from



1054 **1055** **1056**

2-(tribromomethyl)quinoline to give a mixture of the nitrile (**1056**; R = H) and the bromonitrile (**1056**; R = Br) (32%), both as racemates, together with 2-(dibromomethyl)quinoline (15%).

Lists of known (haloalkyl)quinolines are given in Tables 58–63 at the end of this Chapter.

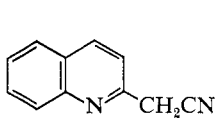
B. Spectra

An X-ray study on 2-(dichloromethyl)- and 2-(trichloromethyl)-quinoline has been carried out by Kaluski and Golankiewicz.[1825] The dichloro-compound was found to exist as colourless prisms, elongated along the *b*-axis, whereas the 2-(trichloromethyl) compound exists as colourless monoclinic plates.

*C. Nucleophilic Displacement of Halogen**

a. DISPLACEMENT BY NUCLEOPHILIC CARBON. 2-(Bromomethyl)quinoline[1826] and 2-(chloromethyl)quinoline[1766] react with potassium cyanide in boiling ethanol to yield the 2-(cyanomethyl) derivative (**1057**). 6-(Chloromethyl)quinoline[1759, 1761] and 8-(bromomethyl)quinoline[1754] react similarly.

1-Benzoyl-4-(bromomethyl)-1,2-dihydro-2,2-dimethylquinoline (**1058**; R = Br) with sodium cyanide in boiling ethanol gives the 4-(cyanomethyl)quinoline (**1058**; R = CN) in 20% yield.[1748]



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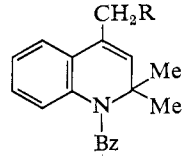

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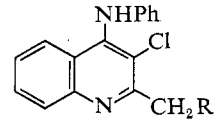
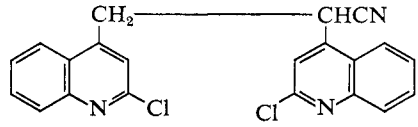


1059

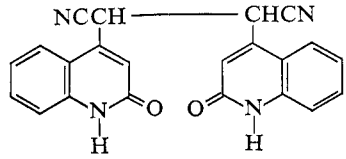
3-(Chloromethyl)quinoline hydrochloride in boiling 60% aqueous ethanol undergoes chlorine replacement, when treated with potassium cyanide in the presence of potassium iodide, to give 3-(cyanomethyl)quinoline (52%).[1771] von Braun and Heymons[599] obtained 4-anilino-3-chloro-2-(cyanomethyl)quinoline (**1059**; R = CN) by treating the corresponding chloromethyl compound (**1059**; R = Cl) with potassium cyanide in ethanol.

Chudgar and Trivedi[1827] reported that 2-chloro-4-(chloromethyl)quinoline with boiling ethanolic potassium cyanide gives, not the expected 2-chloro-4-(cyanomethyl) derivative, but 1-cyano-1,2-bis-(2-chloro-6-quinolyl)ethane (**1060**).



1060

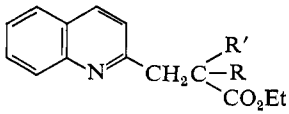
4-(Bromomethyl)-2-quinolone under similar conditions yields an analogous product, which on treatment with phosphorus oxychloride is converted into the dichloro-compound (**1060**). However, some confusion appears to exist concerning these reactions since an earlier report by Kametani and his co-workers,[1768] apparently overlooked by the Indian workers,[1827] records that 4-(bromomethyl)-2-quinolone with boiling aqueous potassium cyanide yields the dicyano-diquinolonylethane (**1061**). Apparently no 4-(cyanomethyl)-2-quinolone is formed in this reaction.



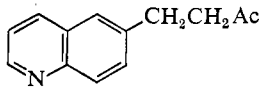
1061

* See also Addenda, p. 698.

2-(Bromomethyl)quinoline with ethyl acetoacetate, and with diethyl malonate, in the presence of sodium ethoxide yields the esters (**1062**; R = H, R′ = Ac and CO_2Et, respectively) in 91% and 90% yield.[1727] 2-(Chloromethyl)quinoline reacts



1062



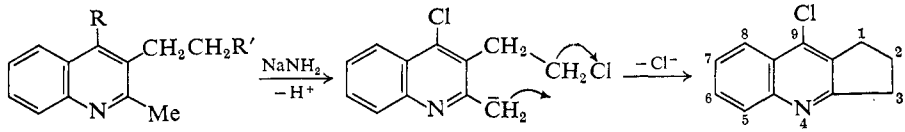
1063

similarly with diethyl malonate.[817] 6-(Chloromethyl)quinoline condenses with ethyl acetoacetate in the presence of sodium in absolute ethanol to give, after hydrolysis, 4-(6-quinolyl)butan-2-one (**1063**) (28%).[1761]

1-Benzoyl-4-(bromomethyl)-1,2-dihydro-2,2-dimethylquinoline (**1058**; R = Br) reacts with diethyl malonate carbanion to give, after basic hydrolysis, the stable *gem*-dicarboxylic acid [**1058**; R = $CH(CO_2H)_2$] (46.5%).[1748] Diethyl acetamidomalonate condenses with 2-(bromomethyl)quinoline in the presence of sodium ethoxide to give the acetamido-dicarboxylic ester (**1062**; R = CO_2Et, R′ = NHAc).[1828] 6-(Chloromethyl)- and 8-(bromomethyl)-quinoline undergo similar reactions.[1767]

2-(Bromomethyl)quinoline with ethyl α-acetamido-α-cyanoacetate gives the condensation product (**1062**; R = CN, R′ = NHAc), which on hydrolysis yields a substituted alanine derivative.[1829] 8-(Bromomethyl)quinoline and its 3-bromo- and 5-nitro-derivatives react similarly.

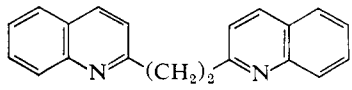
An interesting synthesis of the 9-chloro-2,3-dihydrocyclopenta[*b*]quinoline (**1066**) has been achieved[832] by reaction of 4-chloro-3-(2-chloroethyl)-2-methylquinoline (**1064**; R = R′ = Cl) with sodium amide in dry benzene at 100 °C for 5 hours.



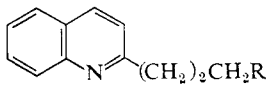
1064 **1065** (70%) **1066**

Presumably the base abstracts a proton from the "activated" 2-methyl group to yield the carbanion (**1065**), which then carries out an intramolecular displacement of chlorine from the alkyl side chain as illustrated.

2-(Bromomethyl)quinoline reacts with methylmagnesium iodide to give 2-ethylquinoline in 68% yield, while under Wurtz conditions (i.e. sodium wire in boiling dry xylene), 1,2-di-(2-quinolyl)ethane (**1067**) is obtained in 46% yield.[1727] In a similar manner the corresponding di-(4-quinolyl)ethane has been prepared from the 4-(bromomethyl) compound.



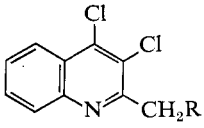
1067



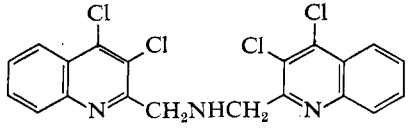
1068

2-(3-Bromopropyl)quinoline (**1068**; R = Br) with sodium acetylide in liquid ammonia gives the acetylene (**1068**; R = C≡CH) in 80% yield.[1764]

b. Displacement by Nucleophilic Nitrogen. von Braun found that 3,4-dichloro-2-(chloromethyl)quinoline (**1069**; R = Cl) with liquid ammonia yields a mixture of the primary amine (**1069**; R = NH_2) (72%) and the secondary base (**1070**) (22%).[1830]

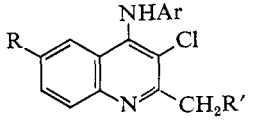


1069

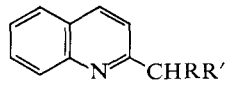


1070

The 4-anilino-compound (**1071**; R = H, R′ = Cl, Ar = Ph) under similar conditions yields a mixture of the primary base (**1071**; R′ = NH_2, R = H, Ar = Ph) (78%), and the corresponding secondary base (20%).[1830] 3-Chloro-2-(chloromethyl)-6-ethoxy-4-(*p*-ethoxyanilino)quinoline (**1071**; R = EtO, R′ = Cl, Ar = *p*-$EtOC_6H_4$) gives 65% and 28% yield of primary and secondary base, respectively, which in ethanolic ammonia decrease to 30% and 50% yield, respectively.



1071



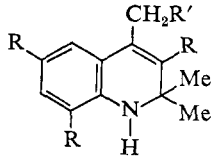
1072

6-(Chloromethyl)quinoline with concentrated ammonia solution at room temperature yields 6-(aminomethyl)quinoline (45%).[1831] However, 5-(chloromethyl)-8-hydroxyquinoline[162] and its 2- and 7-methyl derivatives,[157] when shaken with dilute ammonia solution, yield the 5-(hydroxymethyl) rather than the 5-(aminomethyl) derivatives.

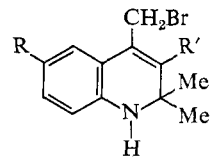
2-(Bromonitromethyl)quinoline (**1072**; R = Br, R′ = NO_2), on treatment with anhydrous ethanolic ammonia, undergoes loss of bromine to yield 2-(nitromethyl)-quinoline as its ammonium salt.[1738] 2-(1-Bromoethyl)quinoline (**1072**; R = Me, R′ = Br) reacts with ethanolic ammonia to yield the corresponding 2-(1-aminoethyl)-quinoline (**1072**; R = Me, R′ = NH_2).[1758] 3-(2-Chloroethyl)-2-methylquinoline (**1064**; R = H, R′ = Cl) under similar conditions yields 3-(2-aminoethyl)-2-methylquinoline (**1064**; R = H, R′ = NH_2).[833]

6-(Chloromethyl)quinoline condenses readily with aqueous dimethyl- or diethylamine at 60 °C to give the corresponding 6-(dialkylaminomethyl)quinoline.[1831] Similarly, 8-(bromomethyl)quinoline condenses with diethylamine[1832, 1833] or dimethylamine[1833] in toluene or benzene solution in the presence of potassium carbonate, or with ethylamine in ethanol,[1832] to yield the respective 8-(alkylaminomethyl)-quinolines. 2-(Isopropylaminomethyl)-6-methylquinoline has been prepared by condensing 2-(chloromethyl)-6-methylquinoline with isopropylamine.[1736] 4-(Chloromethyl)-1-methyl-[1765] and 4-(bromomethyl)-2-quinolone[1768] are reported to condense readily, and in high yield, with aliphatic amines.

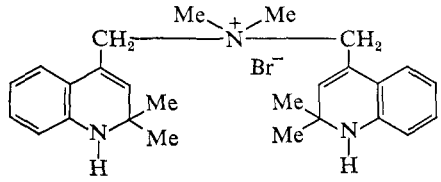
3,6,8-Tribromo-4-(bromomethyl)-1,2-dihydro-2,2-dimethylquinoline (**1073**; R = R′ = Br) reacts with aqueous-ethanolic dimethylamine to yield the dimethylaminomethyl compound (**1073**; R = Br, R′ = Me_2N).[204, 1742] The monobromo-compound (**1073**; R = H, R′ = Br), however, yields a mixture of the expected dimethylamino-derivative (**1073**; R = H, R′ = Me_2N) and the quaternary salt (**1074**). The latter product presumably is formed by attack of the base (**1073**; R = H, R′ = Me_2N) on unchanged 4-(bromomethyl) compound.



1073

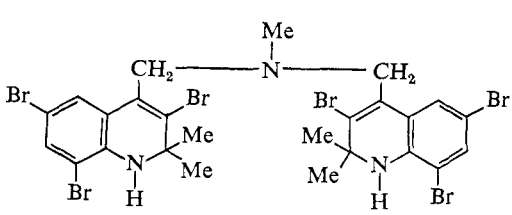


1075



1074

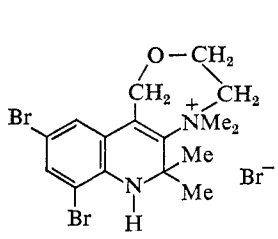
The 1-acetyl derivative of the monobromo-compound (**1073**; R = H, R′ = Br), however, reacts readily with aliphatic amines in either benzene or acetone solution to yield the corresponding 4-(alkylaminomethyl) derivatives.[1834] Also, successful condensation may be achieved by treating the dry powdered hydrobromide of the bromomethyl compound either with the alkylamine in hydrocarbon solution or with an excess of alkylamine. The dibromo- and tribromo-compounds (**1075**; R = Br, R′ = H, and R = R′ = Br, respectively) also react smoothly with alkylamines to give the 4-(alkylaminomethyl) derivatives.[1834] Methylamine reacts with the tetrabromo-compound (**1073**; R = R′ = Br) (2 mol) to yield the tertiary amine (**1076**).[1834]



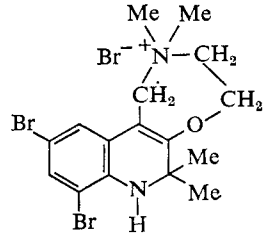
1076

The tetrabromo-compound is also reported to react with an excess of 2-(dimethylamino)ethanol at 95 °C to give what is thought to be either the oxazepinium salt (**1077**) or its isomer (**1078**).

Various heterocyclic amines including piperidine,[107, 162, 817, 1831-1833] morpholine,[1831, 1834] 1-methylpiperazine,[1834] 1,2,3,4-tetrahydroquinoline,[1760, 1835] and pyrrolidine[162] have been successfully condensed with 2-,[817] 5-,[162, 1835] 6-,[1760, 1831] and 8-(chloromethyl)[107, 1832, 1833] and/or -(bromomethyl)quinolines. 2-(Chloromethyl)-quinoline *N*-oxide in benzene solution at room temperature condenses readily with

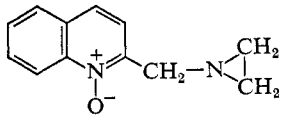


1077



1078

piperidine,[817] and in boiling acetonitrile reacts with aziridine to give the ethylenimine derivative (**1079**).[1836] 6-(Chloromethyl)quinoline with a calculated amount of piperazine gives *N*,*N*′-di(6-quinolylmethyl)piperazine (**1080**) in 85.4% yield.[1760]



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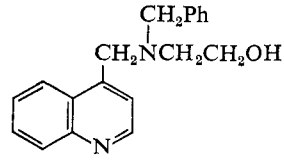
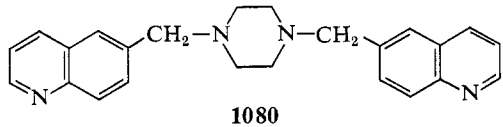


1081

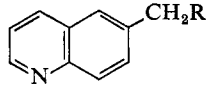


1080

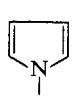
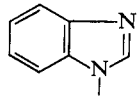
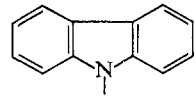
Aromatic amines have been condensed either neat, or in ethanol solution, with 8-(bromomethyl)quinoline,[1832] 6-(chloromethyl)quinoline,[1831] and with various substituted 2-(chloromethyl)quinolines.[599] 4-(Bromomethyl)-2-quinolone reacts with aniline, under reflux, and with *p*-anisidine in boiling *n*-pentyl alcohol to give the respective 4-(arylaminomethyl)-2-quinolones.[401] 4-(Bromomethyl)quinoline has been condensed[1745, 1746] with *N*-benzylethanolamine to give the tertiary base (**1081**) which is a precursor in the synthesis of heterocyclic analogues of dibenamine [$(PhCH_2)_2$-$NCH_2CH_2Cl.HCl$)], a successful sympatholytic drug.

Very few reports of the condensation of (haloalkyl)quinolines with hydrazines have appeared in the literature. However, 2-(bromomethyl)quinoline methobromide has been treated with several hydrazines (e.g. $PhNHNH_2$) to give the corresponding (quinolylmethyl)hydrazines.[1744]

6-(Chloromethyl)quinoline reacts with alkali–metal salts of pyrrole, benzimidazole, and carbazole in boiling acetonitrile to give the *N*-alkylated derivatives (**1082**; R = I, II, and III, respectively) in yields of 28.8%, 86.2%, and 76.9%.[1760]



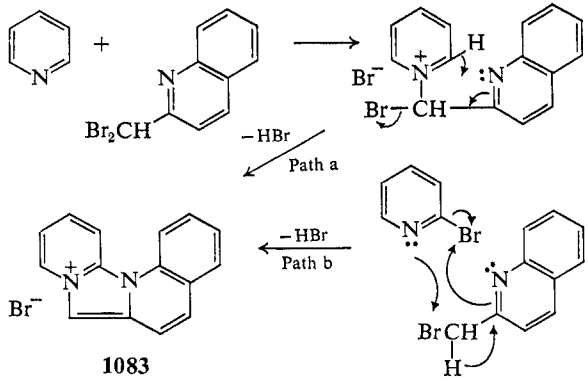
1082

R =  (I)  (II)  (III)

2-(Bromomethyl)- and 4-(bromomethyl)quinoline quaternize readily, and in high yield (93%), with pyridine in benzene solution.[1727]

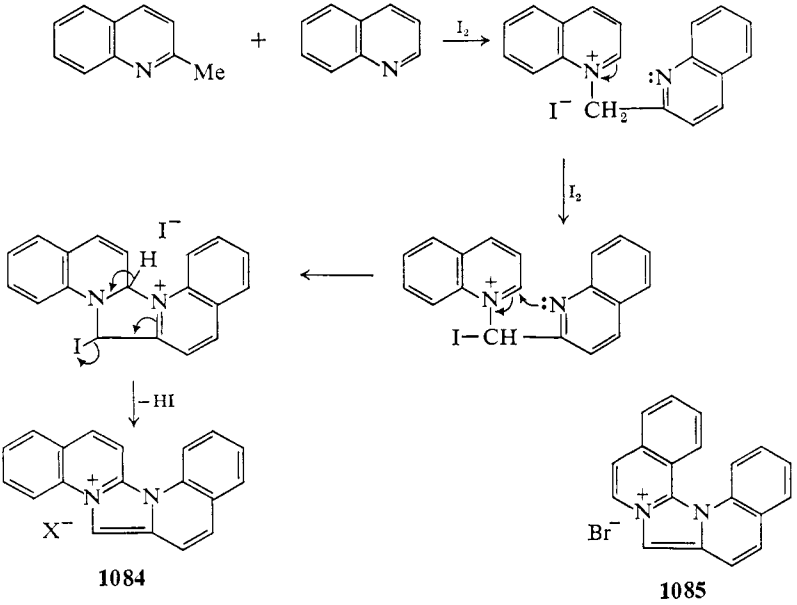
Attempts[1837] to synthesize compounds related to the light-sensitive pigment "Besthorn's Red" have led to the preparation of quinolinoglyoxalinium salts. These salts are readily obtained by reaction of 2-(bromomethyl)quinolines with tertiary bases. For example, 2-(dibromomethyl)quinoline in boiling pyridine yields the pyridoquinolinoglyoxalinium bromide (**1083**) as indicated in Scheme 84 (path a).

Alternatively the bromide (**1083**) may be prepared by heating 2-(bromomethyl)-quinoline and 2-bromopyridine under reflux in benzene (Scheme 84; path b).



SCHEME 84

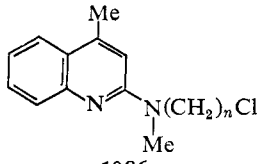
2-(Dibromomethyl)quinoline and quinoline react in a similar manner to yield the diquinolinoglyoxalinium compound (**1084**; X = Br), while with isoquinoline the isomeric system (**1085**) is obtained.



SCHEME 85

Systems similar to (**1084**) may be prepared[1838] by treating quinoline with 2-methylquinoline in the presence of iodine at 100 °C. The reaction is thought to proceed as indicated in Scheme 85.

2-(ω-Chloroalkyl)quinolines of type (**1086**), on treatment with base, undergo intramolecular cyclization to the quaternary salts (**1087**; n = 2 or 3).[1769]



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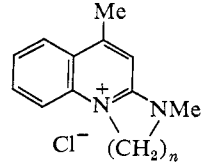
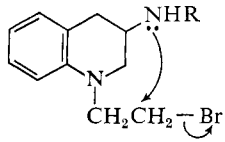
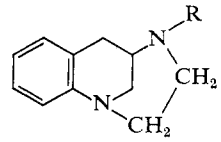


1087

The bridged benzo[*g*][1,4]diazocine (**1089**; R = H) has been prepared in 43% yield by treating 3-amino-1-(2-bromoethyl)-1,2,3,4-tetrahydroquinoline (**1088**; R = H) with potassium carbonate in boiling toluene.[1762, 1763] The *N*-benzyl derivative (**1089**; R = $PhCH_2$) (53%) is prepared in a similar manner.

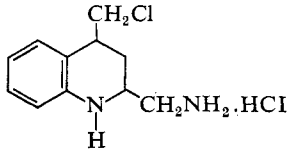


1088



1089

Kametani and his co-workers[1772] have prepared the hexahydrodiazocine (**1091**) (40%) by treating 2-(aminomethyl)-4-(chloromethyl)-1,2,3,4-tetrahydroquinoline hydrochloride (**1090**) with potassium carbonate in boiling xylene.



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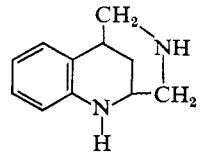
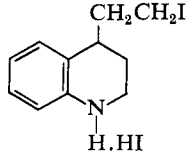
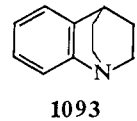


1091

Meisenheimer and his co-workers[1756] reported that 1,2,3,4-tetrahydro-4-(2-iodoethyl)quinoline hydriodide (**1092**), on treatment with N-sodium hydroxide at 60–70 °C, undergoes intramolecular nucleophilic displacement of iodine to give the benzoquinuclidine (**1093**).

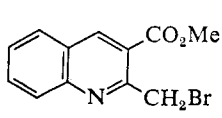


1092

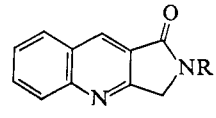


1093

Treatment of methyl 2-(bromomethyl)quinoline-3-carboxylate (**1094**) with ammonia or benzylamine yields the cyclic amides (**1095**; R = H and $PhCH_2$ respectively).[1752]

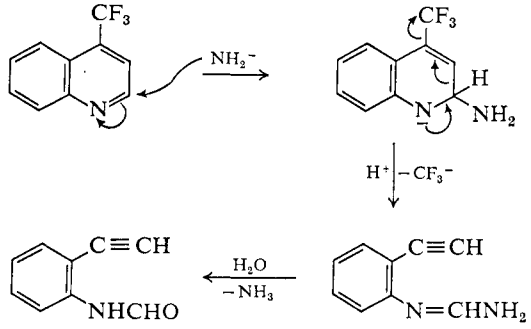


1094



1095

The reactions of 2-, 3-, and 4-(trifluoromethyl)quinoline with sodium amide have been reported;[1839] and it is found that the nature of the products varies with the position of the (trifluoromethyl) substituents.* 2-(Trifluoromethyl)quinoline suffers nucleophilic displacement of the (trifluoromethyl) group, to give 2-aminoquinoline in 69.5% yield, while 4-(trifluoromethyl)quinoline gives a mixture of the expected Chichibabin product, i.e. 2-amino-4-(trifluoromethyl)quinoline (4%), and the unexpected (*o*-formamidophenyl)acetylene (**1096**) (6%). The latter product is thought to arise as indicated in Scheme 86.



1096

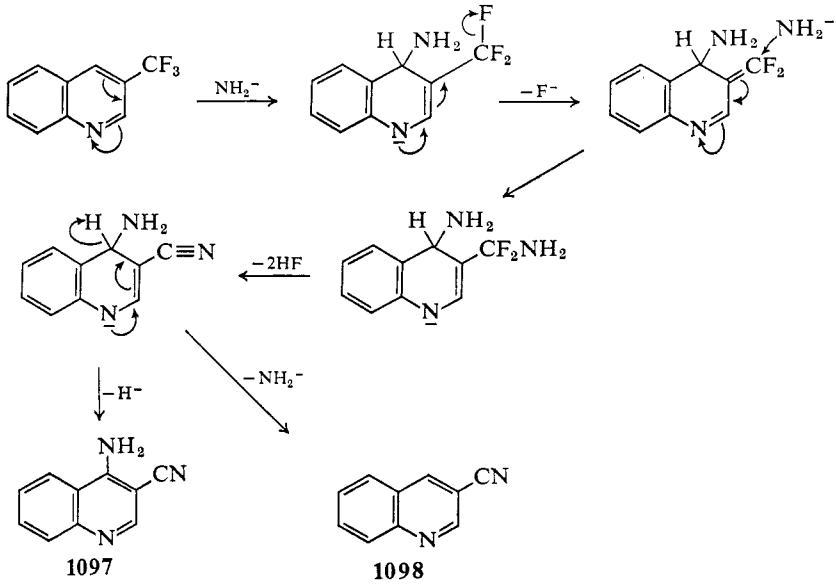
SCHEME 86

The reaction with 3-(trifluoromethyl)quinoline is somewhat more complicated in that nucleophilic attack by amide ion takes place at the 4-position, and at the (trifluoromethyl) group, to give 4-amino-3-cyanoquinoline (**1097**) (2.5%) and 3-cyanoquinoline (**1098**) (20%), as indicated in Scheme 87.

c. DISPLACEMENT BY NUCLEOPHILIC OXYGEN. (i) (*Monohaloalkyl)quinolines.* The (monohalomethyl)quinolines are highly resistant towards acid hydrolysis, whereas with alkali they yield "intensely reddish-brown, resinous products of unknown composition".[1722] However, hydrolysis of (monohalomethyl)quinolines has been accomplished under a wide variety of conditions.

Howitz and Schwenk[291] have shown that 3-bromo-8-(chloromethyl)quinoline is hydrolysed by ethanolic potassium hydroxide to the 8-(hydroxymethyl) compound, and similar hydrolyses have been performed on 4-anilino-3-chloro-2-(chloromethyl)-quinoline[599] and 4-(bromomethyl)-2-quinolone.[1768] Sodium acetate in methanol brings about hydrolysis of 4-(bromomethyl)-2-chloroquinoline to 2-chloro-4-(hydroxymethyl)quinoline (**1099**) in 93% yield, without effecting hydrolysis of the

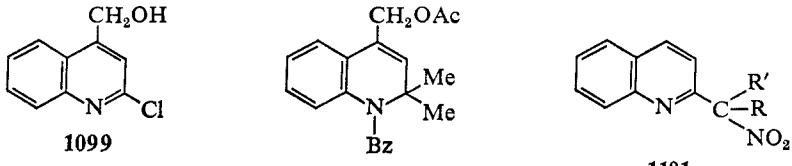
* For subsequent work see ref. 2097.



1097 1098

SCHEME 87

labile 2-chlorine atom.[1747] Sodium acetate in acetic acid has been used for the hydrolysis of 4-(bromomethyl)-2-quinolone,[355] and under the same conditions 1-benzoyl-4-(bromomethyl)-1,2-dihydro-2,2-dimethylquinoline yields the 4-(acetoxymethyl) derivative (**1100**) in 88% yield.[1748] 2-(Chloromethyl)quinoline is hydrolysed to the (hydroxymethyl) compound in high yield (84%) by boiling aqueous sodium acetate.[787]



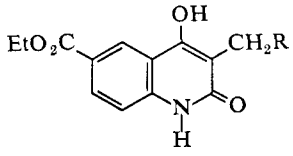
1099 **1100** **1101**

2-(Bromonitromethyl)quinoline (**1101**; R = Br, R′ = H) is recovered unchanged from boiling 20% potassium hydroxide solution.[1738] The dichloronitromethyl compound (**1101**; R = R′ = Cl) is also unaffected by aqueous alkali, but with ethanolic potassium hydroxide the monochloronitro-compound (**1101**; R = Cl, R′ = H) is obtained.

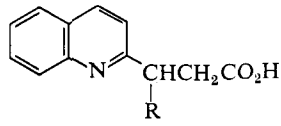
Despite the stated[1722] resistance of (halomethyl)quinolines towards acid hydrolysis, Kermack and Wight[107] report that 8-(bromomethyl)- and 8-(bromomethyl)-5-nitroquinoline are hydrolysed by hot, dilute sulphuric acid to the corresponding 8-(hydroxymethyl) derivatives.

The 3-chlorobut-2-enyl derivative (**1102**; R = CH=CMeCl) is hydrolysed by warm (50 °C) sulphuric acid to the methyl ketone (**1102**; R = CH_2COMe) (67.3%).[592]

Likewise, other methyl ketones have been prepared in high yields (70–81%) from a number of chloro- and bromo-substituted 3-(3-chlorobut-2-enyl)quinolines.[1840]

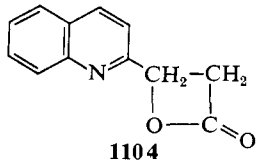


1102

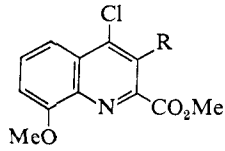


1103

The 3-bromo-3-(2-quinolyl)propanoic acid (**1103**; R = Br), formed by the addition of hydrogen bromide in acetic acid to 3-(2-quinolyl)acrylic acid, reacts with cold aqueous sodium carbonate to give the hydroxy-acid (**1103**; R = OH) together with the β-lactone (**1104**).[1818] With hot sodium carbonate solution elimination of bromine and decarboxylation occur to give 2-vinylquinoline, while with an excess of ammonia solution the amide of the hydroxy-acid (**1103**; R = OH) is formed.



1104



1105

The dichloro-ester [**1105**; R = $CH_2CCl{=}CH_2$], formed by the action of thionyl chloride in dimethylformamide on the corresponding 4-quinolone undergoes selective hydrolysis of the alkyl chloride in cold concentrated sulphuric acid, to give the methyl ketone (**1105**; R = CH_2COCH_3).[1807]

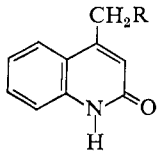
Kaslow and Schlatter[1761] have successfully prepared 6-(ethoxymethyl)quinoline by treating 6-(chloromethyl)quinoline with sodium ethoxide, while the methyl ether (**1106**; R = OMe) is obtained in high yield (78%) by heating the bromo-compound (**1106**; R = Br) with sodium methoxide in methanol.[401] The methyl and ethyl ethers are similarly prepared from 6-(chloromethyl)quinoline.[1759]

Burckhalter and Leib[162] report that 5-(chloromethyl)-8-hydroxyquinoline in the presence of dilute hydrochloric acid, or in dimethylformamide solution, yields the binuclear ether (**1107**). They also report the preparation of a series of ethers derived from 5-(chloromethyl)-8-hydroxyquinoline by treating the chloromethyl compound with the appropriate alcohol under reflux in the presence of sodium hydrogen carbonate.

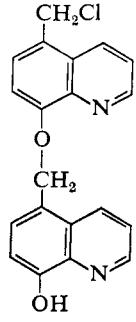
Using this method, Aristov and his co-workers[154, 1841] have prepared a whole series of alkyl, alkenyl, and alkynyl ethers from 5-(chloromethyl)-8-hydroxyquinoline. The allyl ether (**1108**) is obtained by heating the (chloromethyl) compound under reflux in ethyl acetate solution with allyl alcohol for 2 hours.[1842]

Kohl and Pracejus[1748] were able to obtain 1-benzoyl-1,2-dihydro-2,2-dimethylquinoline-4-carboxylic acid (**1109**) in 8% yield by treating a methanolic solution of 1-benzoyl-4-(bromomethyl)-1,2-dihydro-2,2-dimethylquinoline with carbon monoxide in the presence of nickel tetracarbonyl at room temperature.

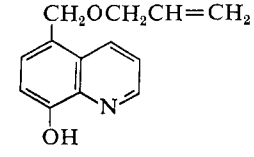
A German Patent[1843] reports oxidative hydrolysis of 4-(chloromethyl)- and 4-(bromomethyl)-quinoline to quinoline-4-carboxylic acid by sodium hydroxide and 30% hydrogen peroxide at 50 °C.



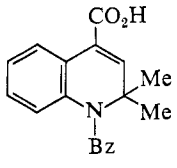
1106



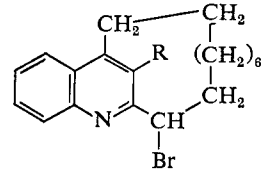
1107



1108



1109



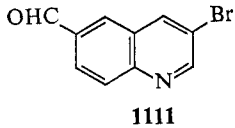
1110

The bromo-substituents in compounds (**1110**; R = H and Br) are reported[1164] to resist acid hydrolysis. The authors (Parham *et al.*), on the basis of preliminary studies, suggest that the bromine atoms resemble other bridgehead halides in that replacement by an S_N2 mechanism is inhibited by steric interference, while S_N1 processes are prohibited by the inability of the reacting carbon centre to form a planar sp^2-carbonium ion.

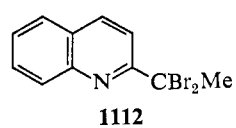
(ii) (*Dihaloalkyl)quinolines.* Hydrolysis of *gem*-(dihaloalkyl)quinolines provides a convenient method for the synthesis of quinoline aldehydes.

Howitz and Philipp[290] showed that 3-bromo-6-(dibromomethyl)quinoline, heated with aqueous potassium carbonate solution at 120 °C, yields 3-bromoquinoline-6-carbaldehyde (**1111**).

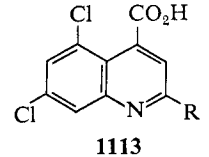
Quinoline-8-carbaldehyde is reported to be readily available by boiling 8-(dibromomethyl)quinoline in water for 20 minutes.[1754] However, the preferred method of hydrolysis appears to involve treating the (dibromomethyl)quinoline with silver nitrate in boiling aqueous ethanol, and by using this method high yields of a number of quinoline-2-[1123, 1725, 1731, 1785, 1844] and -4-carbaldehydes[1747] have been obtained.



1111



1112

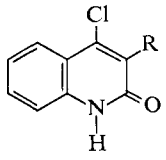


1113

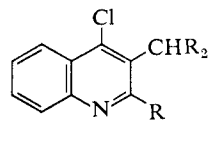
Koenigs, in an early publication,[1723] reported that hydrolysis of 4-(dibromomethyl)-8-nitroquinoline to 8-nitroquinoline-4-carbaldehyde can be accomplished by using lead acetate in glacial acetic acid or, better, silver acetate in 60% acetic acid. 2-(1,1-Dibromoethyl)quinoline (**1112**), on hydrolysis, yields 2-acetylquinoline,[1730] while the (dibromobenzyl)quinoline (**1113**; R = $PhCBr_2$) yields the 2-benzoylquinoline-4-carboxylic acid (**1113**; R = PhCO) (84%).[940] In the last two reactions the (dibromoalkyl)quinolines, which were prepared by dibrominating the corresponding alkylquinoline with bromine in acetic acid, were not isolated, but were hydrolysed *in situ* by dilute sulphuric acid.

Sato and Ohta[568] treated 4-chloro-3-(dichloromethyl)-2-quinolone (**1114**; R = $CHCl_2$) with sodium methoxide in boiling methanol to obtain the acetal [**1114**;

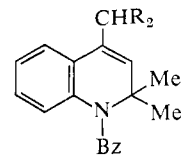
R = $CH(OMe)_2$], which, on acid hydrolysis, yielded the aldehyde (**1114**; R = CHO). The chloro-aldehyde was not isolated but was treated with an excess of sodium methoxide to yield the 4-methoxy-derivative.



1114



1115

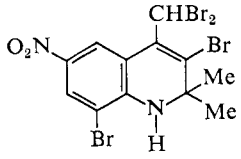


1116

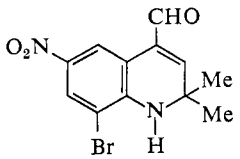
In the same paper it is reported that the tetrachloro-compound (**1115**; R = Cl) is resistant to hydrolysis and does not react with concentrated sulphuric acid, aniline, or hydroxide ion. However, with sodium methoxide in boiling methanol, methanolysis to give the 2-methoxy-acetal (**1115**; R = OMe) is observed. In contrast, with boiling methanolic potassium hydroxide 2,4-dimethoxyquinoline-3-carbaldehyde is obtained.[567]

Hammick[1725] reports that 2-(bromomethyl)- and 2-(dibromomethyl)quinoline remain unchanged after being warmed (50 °C) with oleum for 12 hours. The dibromo-compound, however, readily undergoes hydrolysis to the aldehyde (100%) in the presence of ethanolic silver nitrate. Acetal formation (**1116**; R = OEt) (74%) is observed on heating 1-benzoyl-4-(dibromomethyl)-1,2-dihydro-2,2-dimethylquinoline (**1116**; R = Br) with sodium ethoxide in ethanol in the presence of silver nitrate.[1748]

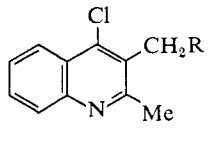
The tetrabromodihydronitroquinoline (**1117**), on hydrolysis with aqueous-ethanolic sodium hydroxide, suffers loss of the 3-bromo-substituent as well as the expected hydrolysis of the *gem*-dibromo-group, to yield the aldehyde (**1118**).[1501]



1117



1118



1119

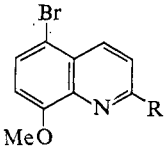
The 3-(3,3-dichloropropenyl)quinoline (**1119**; R = $CH{=}CCl_2$) with 96% sulphuric acid at 100 °C undergoes hydrolysis to the quinolylpropanoic acid (**1119**; R = CH_2-CO_2H) (61.5%).[1805] Other substituted 3-(3-quinolyl)propanoic acids have been prepared by this method.[1805]

(iii) *(Trihaloalkyl)quinolines.* Hydrolysis of trihalomethyl compounds is an effective method for the synthesis of carboxylic acids and much use has been made of this reaction for the preparation of quinolinecarboxylic acids. The most used technique involves heating the (trihalomethyl)quinoline under reflux with sulphuric acid of various strengths. Hammick,[1724] and Campbell and his co-workers[942] obtained quinoline-2-carboxylic acid in quantitative yield from 2-(tribromomethyl)- or 2-(trichloromethyl)-quinoline using a 1 : 10 water–sulphuric acid mixture, while 20% sulphuric acid is sufficient to bring about hydrolysis of 5-[1725] and 8-nitro-2-(tribromomethyl)quinoline[1725, 1728] to the respective nitroquinoline-2-carboxylic acid. Other quinolinecarboxylic acids have been prepared similarly.[169, 768, 1730]

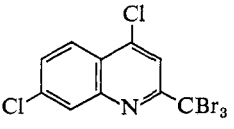
5- and 7-(Trifluoromethyl)quinoline, on being heated with either hydrobromic acid in a sealed tube[869] or with 80% sulphuric acid,[868] undergo hydrolysis to quinoline-5- and 7-carboxylic acid, respectively. However, 8-amino-7-(trifluoromethyl)-quinoline is inert towards concentrated sulphuric acid,[726] while with hot concentrated hydrochloric acid the amino-group is lost with formation of 8-hydroxy-7-(trifluoromethyl)quinoline, which, in contrast, is readily hydrolysed by concentrated sulphuric acid to 8-hydroxyquinoline-7-carboxylic acid.

Boiling 5-bromo-8-methoxy-2-(tribromomethyl)quinoline (**1120**; R = CBr_3) with a solution of silver nitrate in aqueous dioxan gives the quinoline-2-carboxylic acid (**1120**; R = CO_2H) in 85% yield.[169]

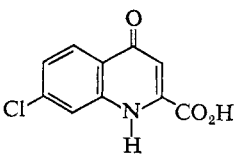
Boiling aqueous silver nitrate also brings about hydrolysis of 2-methyl-4-(trichloromethyl)quinoline to 2-methylquinoline-4-carboxylic acid,[1804] while under similar conditions the dichloro-(tribromomethyl)quinoline (**1121**) undergoes loss of nuclear



1120

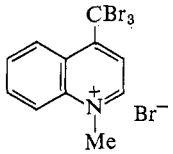


1121

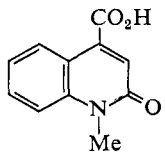


1122

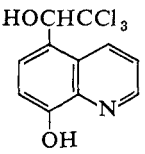
and side-chain halogen to yield 7-chloro-4-quinolone-2-carboxylic acid (**1122**).[1123] 6-Chloro-2-(tribromomethyl)quinoline in hot aqueous-ethanolic silver nitrate is hydrolysed to the 2-carboxylic acid which under the reaction conditions esterifies to yield ethyl 6-chloroquinoline-2-carboxylate (44%).[925] 1-Methyl-4-(tribromomethyl)-quinolinium bromide (**1123**) on treatment with silver nitrate in aqueous acetic acid at 100 °C for 2 hours yields 1-methyl-2-quinolone-4-carboxylic acid (**1124**) in 62% yield.[1727]



1123



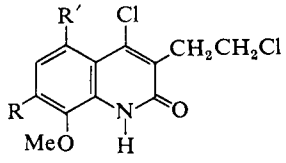
1124



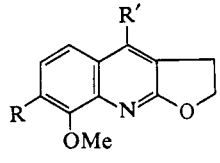
1125

The hydrolysis of (trihalomethyl)quinolines under basic conditions has been little investigated. 2-(Trichloromethyl)-4-quinolones, however, are reported[955] to be hydrolysed by 10% aqueous sodium hydroxide to the corresponding 4-quinolone-2-carboxylic acids in yields of 33–58%. 8-Hydroxy-5-(3,3,3-trichloro-1-hydroxyethyl)-quinoline (**1125**) on hydrolysis with methanolic potassium hydroxide yields a mixture of 8-hydroxyquinoline-5-carbaldehyde and -5-carboxylic acid.[155] 8-Methoxy-5-(trifluoromethyl)quinoline is unaffected by boiling aqueous-alcoholic alkali, whereas 8-hydroxy-5-(trifluoromethyl)quinoline is hydrolysed to the 5-carboxylic acid in cold dilute sodium hydroxide.[1800]

(iv) *Hydrolysis Accompanied by Intramolecular Cyclization.* Grundon and McCorkindale[570, 573] during their studies on the synthesis of dictamnine alkaloids found that 4-chloro-3-(2-chloroethyl)-8-methoxy-2-quinolone (**1126**; R = R′ = H) in boiling aqueous ethanol containing silver oxide, or with alumina in benzene, undergoes ring closure to give the dihydrofuro[2,3-*b*]quinoline (**1127**; R = H, R′ = Cl) in 95% yield.



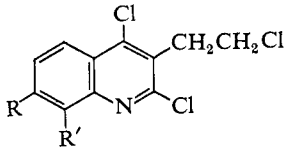
1126



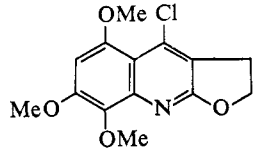
1127

Ohta and Mori[571, 574] similarly were able to cyclize the dichloro-compound (**1126**; R = MeO, R′ = H) in boiling 10% methanolic potassium hydroxide. However, under these conditions the 4-chlorine atom suffers nucleophilic displacement and the trimethoxy-compound (**1127**; R = R′ = MeO), identical with the alkaloid, dihydroskimmianine, is obtained. The 8-methoxy-compound (**1126**; R = R′ = H) under similar conditions yields the dimethoxy-derivative (**1127**; R = H, R′ = MeO), while the isomeric 7-methoxy-2-quinolone yields a mixture of the 4-chloro- and 4-methoxy-substituted dihydrofuro[2,3-*b*]quinolines.[574]

The dimethoxyquinoline (**1128**; R = R′ = MeO) in boiling glacial acetic acid yields a mixture of the 2-quinolone (**1126**; R = MeO, R′ = H) and the furo[2,3-*b*]-quinoline (**1127**; R = MeO, R′ = Cl).[574] The 7- and 8-methoxyquinolines (**1128**; R = MeO, R′ = H; and R = H, R′ = MeO, respectively), however, under similar conditions, yield only the 2-quinolones.



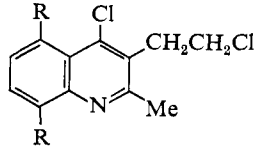
1128



1129

Govindachari and his co-workers[569] report that the dichloro-2-quinolone (**1126**; R = R′ = MeO) on treatment with silver oxide in boiling aqueous dioxan cyclizes to give the dihydrofuro[2,3-*b*]quinoline (**1129**).

4-Chloro-3-(2-chloroethyl)-2-methylquinoline (**1130**; R = H) in the presence of benzaldehyde and acetic anhydride undergoes an aldol condensation at the "activated" 2-methyl group, and also cyclizes, presumably by way of the 3-(2-hydroxyethyl) derivative, to yield the furo[3,2-*c*]quinoline (**1131**).[624]



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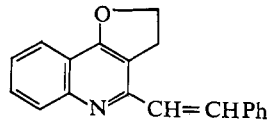
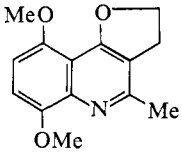


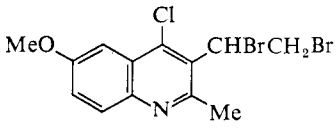
1131

In a similar manner the dimethoxy 3-(2-chloroethyl)-4-chloroquinaldine (**1130**; R = MeO) cyclizes to the dihydrofuro[3,2-*c*]quinoline (**1132**) in acetic acid at 160 °C.[828]

Nagaoka[1452] has studied in some detail the acid-promoted cyclization of the dibromoethyl derivative (**1133**). In a sealed tube which acetic acid–sodium acetate at

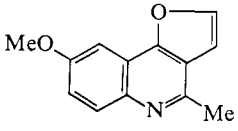


1132

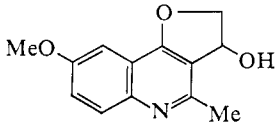


1133

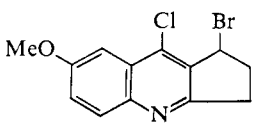
160 °C cyclization and debromination to give the furo[3,2-*c*]quinoline (**1134**) is observed, while in acetic acid at 100 °C the hydroxy-derivative (**1135**) is formed. Remarkably, however, when the dibromo-compound is heated with 50% sulphuric acid for 24 h at 130 °C, cyclization onto the 2-methyl group occurs, without loss of the 4-chlorine atom, to give the bromocyclopenta[*b*]quinoline (**1136**).



1134

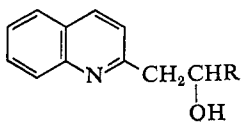


1135

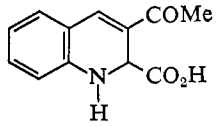


1136

(v) *Action of Base on* 2-(3,3,3-*Trichloro*-2-*hydroxypropyl*)*quinoline*. Einhorn[1794, 1845] treated this compound (**1137**; R = CCl_3) with alcoholic sodium hydroxide and obtained the expected 3-(2-quinolyl)acrylic acid together with a bright orange solid, $C_{12}H_{10}NO_2Na.3H_2O$, which he formulated as the trihydrated sodium salt of the hydroxy-acid (**1137**; R = CO_2H).

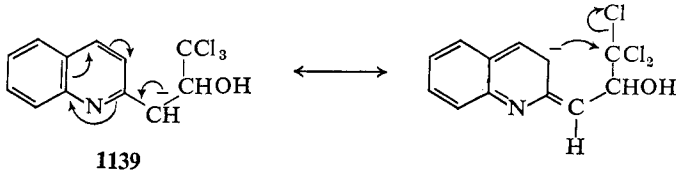


1137

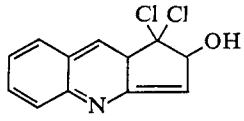


1138

The orange product, however, was later shown[1846] to be the sodium salt of 3-acetyl-1,2-dihydroquinoline-2-carboxylic acid (**1138**), and its mode of formation has since been the subject of several investigations. Woodward and Kornfeld[1846] suggested a mechanism which involves initial loss of an α-proton to give the mesomeric carbanion (**1139** ↔ **1140**), which ring closes with loss of chloride ion to give the



1139 1140

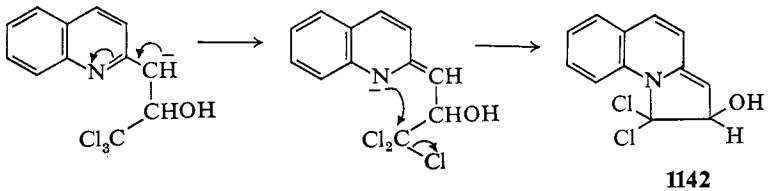


1141

SCHEME 88

dichlorocyclopentene derivative (**1141**) as outlined in Scheme 88. A further seven stages are then proposed before the acetyl compound (**1138**) is obtained.

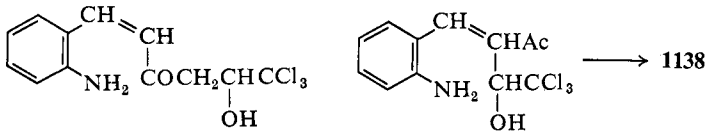
Brown, Hammick, and Robinson[1847] challenged this mechanism on the basis that the carbanion (**1139** ↔ **1140**), if formed, would be more likely to undergo cyclization to the pyrrolino-quinoline (**1142**) (Scheme 89) rather than the cyclopentene derivative



1142

SCHEME 89

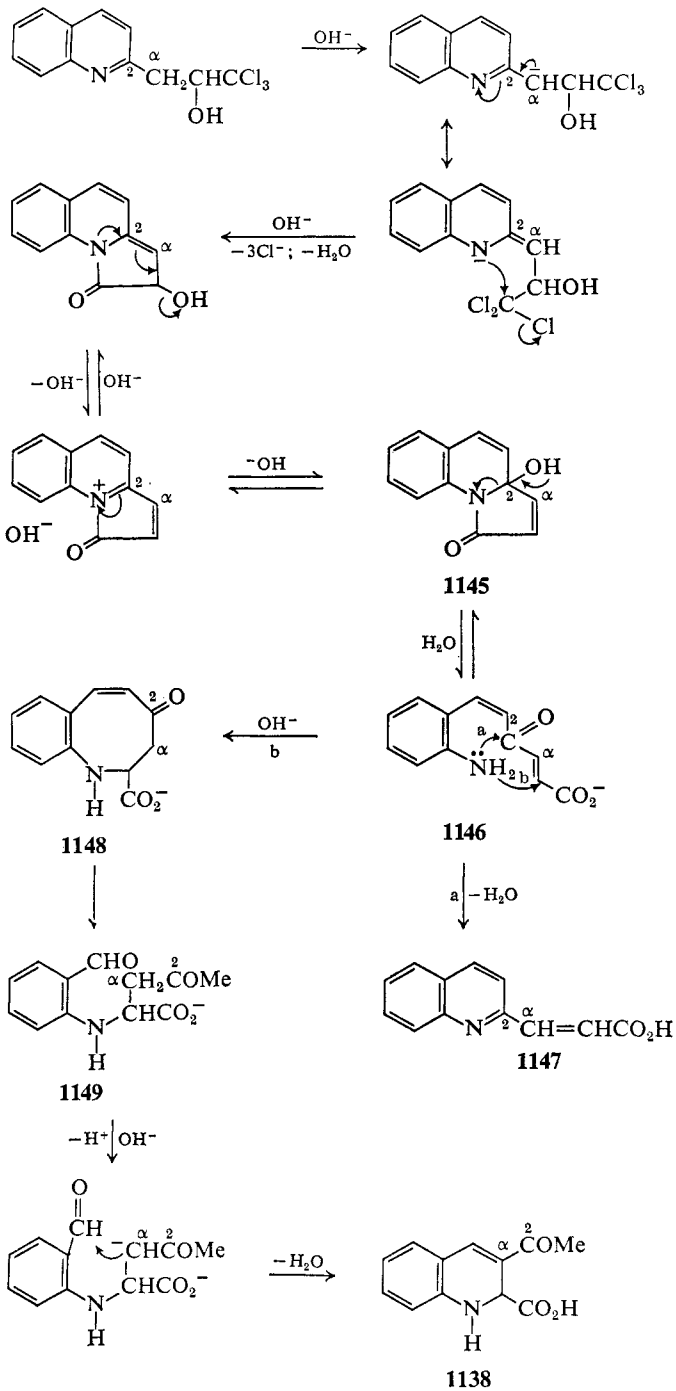
(**1141**). These authors speculated on the possible formation of the *o*-aminobenzylidene derivative (**1143**), which by a 1,3-transfer of the *o*-aminobenzylidene group (to give **1144**) followed by ring closure and hydrolysis would yield the observed product (**1138**).



1143 **1144**

Woodward and Kornfeld[1846] considered a similar reaction sequence but rejected it on the basis of experiments with model compounds, while Robinson and his co-workers[1847] suggested that differentiation between the various mechanisms might be possible by means of carbon-labelling experiments. However, it was left to Dauben and Vaughan,[1848] some three years later, to carry out the actual experiment. They synthesized the chloral condensation product (**1137**; R = CCl_3) labelled at the α-carbon atom with ^{14}C. On carrying out the base-catalysed rearrangement, an acetylquinoline-2-carboxylic acid was obtained, which, on mild oxidation at 0 °C, gave 3-acetylquinoline containing all the ^{14}C label. Hence the Woodward–Kornfeld mechanism, which predicts that the α-carbon centre in the starting material will be the carboxylic acid-carbon of the final product, is incorrect. Further degradative studies indicated that the labelled carbon, originally in the side chain, becomes incorporated in the pyridine ring of the final product. In order to resolve the problem the reactions were repeated with the trichloro-compound labelled at the 2-position of the quinoline nucleus. Subsequent investigation indicated that the labelled carbon appears in the final product as the carbonyl-carbon of the acetyl group. This distribution of ^{14}C is as expected on the basis of a mechanism of the type tentatively proposed by Robinson and his co-workers. Dauben and Vaughan, however, put forward a more definite reaction scheme to explain the formation of the reaction products, as indicated below (Scheme 90). (In the reaction scheme the ^{14}C carbon centres, as labelled by Dauben and Vaughan, are designated throughout as "2" and "α" for clarity.)

The key intermediate, namely the amino-carboxylic acid (**1146**), is arrived at by means of a series of prototropic shifts and finally by hydrolysis of the lactam (**1145**). Attack by the amino-group at the carbonyl function, as shown (**1146** → **1147**), results

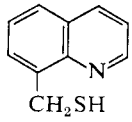


SCHEME 90

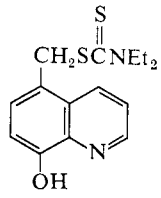
in the formation of the acrylic acid (**1147**), the major reaction product. Alternatively a Michael addition across the ethylenic bond (**1146** → **1148**) yields the eight-membered cyclic ketone (**1148**), which by a retro-aldol condensation gives the keto-aldehyde (**1149**). Base-catalysed ring closure of this dicarbonyl compound, as indicated (**1149** → **1138**), yields the product (**1138**), which, as can be seen, bears the ^{14}C labels at positions in agreement with those predicted on the basis of the degradative experiments.

In contrast to these results the isomeric 4-(3,3,3-trichloro-2-hydroxypropyl)-quinoline reacts normally with aqueous alkali to give 2-(4-quinolyl)acrylic acid,[1846, 1849] as does 4-methyl-2-(3,3,3-trichloro-2-hydroxypropyl)quinoline.[1795, 1846]

d. Displacement by Nucleophilic Sulphur. 8-(Bromomethyl)quinoline and warm ethanolic potassium hydrogen sulphide react to give the thiol (**1150**) in 96% yield.[1755] Under similar conditions 6-(chloromethyl)quinoline yields the 6-methanethiol.[1850] 6-(Chloromethyl)quinoline[1850] and 8-(bromomethyl)quinoline[1743] with hot ethanolic sodium or potassium sulphide yield the corresponding sulphides.



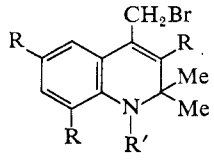
1150



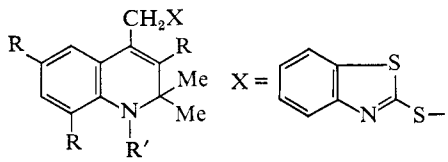
1151

A series of *N,N*-disubstituted dithiocarbamate esters, e.g. (**1151**), have been prepared[1851] by treating 5-(chloromethyl)-8-hydroxyquinoline with the sodium salts of *N,N*-disubstituted dithiocarbamic acids in dioxan solution containing sodium hydrogen carbonate. Yields are in the region of 45–60%.

1-Acetyl-4-(bromomethyl)-1,2-dihydro-2,2-dimethylquinoline (**1152**; R = H, R′ = Ac), and the tetrabromo-derivative (**1152**; R = Br, R′ = H), with sodium benzothiazole-2-thiolate in boiling acetone give the benzothiazolyl methyl thioethers



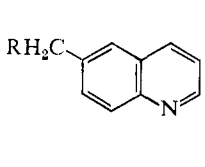
1152



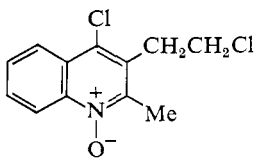
1153

(**1153**; R = H, R′ = Ac; and R = Br, R′ = H, respectively; X as shown).[1834] With potassium thiocyanate the corresponding 4-(thiocyanatomethyl) compounds (**1153**; X = SCN; R and R′ as before) are obtained in high yield. 6-(Chloromethyl)quinoline reacts with potassium thiocyanate in boiling methanol to yield 6-(thiocyanatomethyl)-quinoline (**1154**; R = SCN) in good yield.[1850]

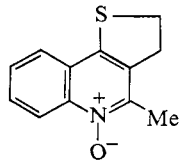
4-Chloro-3-(2-chloroethyl)-2-methylquinoline *N*-oxide (**1155**) undergoes ring closure to the 2,3-dihydrothieno[3,2-*c*]quinoline *N*-oxide (**1156**) on treatment with



1154

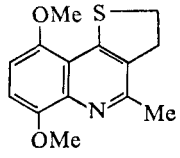


1155

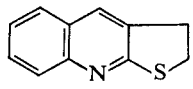


1156

ethanolic hydrogen sulphide in the presence of sodium ethoxide.[1852] Other thieno[3,2-*c*]quinolines, e.g. (**1157**), have been prepared[166, 828, 831] by treating 4-chloro-3-(2-chloroethyl)quinaldines with thiourea in boiling ethanol.



1157



1158

3-(2-Bromoethyl)-2-chloroquinoline with thiourea under similar conditions gives 2,3-dihydrothieno[2,3-*b*]quinoline (**1158**) in good yield.[831]

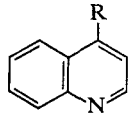
e. Miscellaneous Displacement Reactions. 6-(Chloromethyl)quinoline with potassium selenocyanate in boiling methanol undergoes chlorine displacement to yield 6-(selenocyanatomethyl)quinoline (**1154**; R = SeCN).[1850]

Lugovkin[1853] has been able to prepare a series of quinolylphosphonate esters of type [**1154**; R = $PO(OR')_2$] by treating 6-(chloromethyl)quinoline with sodium dialkyl phosphites, $(R'O)_2PO^-Na^+$. The yields range from 21% (R′ = Me) to 73.5% (R′ = Et). With triethyl phosphite at 135 °C a vigorous reaction takes place and the phosphonate ester [**1154**; R = $PO(OEt)_2$] is formed, presumably by way of an Arbuzov rearrangement.

Of interest also is the reaction of 8-methoxy-5-(trifluoromethyl)quinoline with boiling hydriodic acid, as reported by Pettit and Tatlow.[1800] The expected cleavage of the methyl ether is observed, together with hydrolysis of the (trifluoromethyl) group. However, the product actually isolated proved to be 8-hydroxyquinoline, decarboxylation having occurred during hydrolysis.

D. Dehalogenation and Dehydrohalogenation

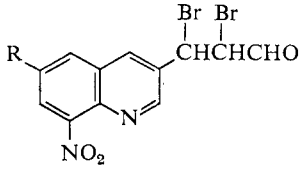
a. Base-catalysed Reactions. 4-(2-Iodoethyl)quinoline (**1159**; R = CH_2CH_2I) with sodium hydroxide in aqueous acetone undergoes dehydroiodination to give 4-vinylquinoline.[1756] In contrast, Johnson and Hamilton[401] report that 4-(1-chloroethyl)quinoline (**1159**; R = $CHClCH_3$) is very resistant to both hydrolysis and dehydrochlorination.



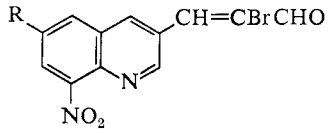
1159

1160

Alberts and Bachman[1774] have studied the dehalogenation of 1,2-dibromo-2-(2-quinolyl)propanoic acid (**1160**) under a variety of conditions. They found that debromination to 3-(2-quinolyl)acrylic acid goes readily and in high yield (90%) with a variety of bases (sodium carbonate, sodium ethoxide, pyridine, sodium hydrogen carbonate). In contrast 1,2-dibromo-2-(8-nitro-3-quinolyl)propionaldehyde (**1161**;



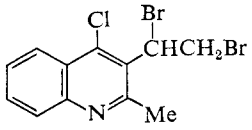
1161



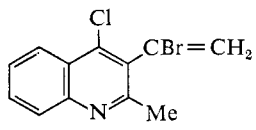
1162

R = H), when shaken with sodium carbonate or heated under reflux with acetic acid, undergoes dehydrobromination to give the 2-bromoacrolein (**1162**; R = H).[1775] The 6,8-dinitro-derivative (**1161**; R = NO_2) behaves similarly.

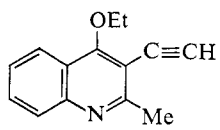
Ozawa and Nagaoka[833] have prepared 2-methyl-3-vinylquinoline by heating 3-(2-chloroethyl)-2-methylquinoline with 50% ethanolic sodium hydroxide, and other substituted 4-chloro-3-vinylquinolines have since been prepared by this method.[827, 1498] The dibromo-compound (**1163**) with potassium carbonate in boiling ethanol suffers dehydrobromination to the 3-(1-bromovinyl) derivative (**1164**).[1452]



1163



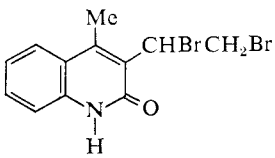
1164



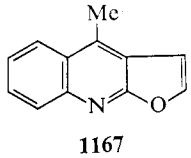
1165

In contrast, when ethanolic sodium hydroxide is used, debromination is accompanied by replacement of the 4-chlorine atom to yield the acetylene (**1165**).

When 3-(1,2-dibromoethyl)-4-methyl-2-quinolone (**1166**) is heated with triethylamine in chloroform solution, cyclization and dehydrobromination occurs to give the furo[2,3-*b*]quinoline (**1167**) in 95% yield.[1778]



1166



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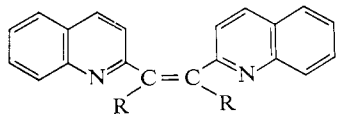
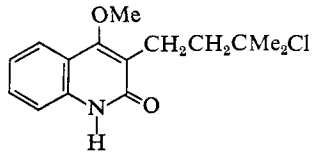


1168

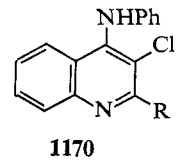
At room temperature 2-(tribromomethyl)quinoline reacts with copper bronze and pyridine to give *cis*-1,2-dibromo-1,2-di-(2-quinolyl)ethylene (**1168**; R = Br) (36%).[1781, 1782] Under similar conditions 2-(dibromomethyl)quinoline yields the corresponding *trans*-diquinolylethylene. In boiling pyridine, however, 2-(tribromomethyl)quinoline undergoes coupling and complete dehalogenation to give 1,2-di-(2-quinolyl)acetylene in 25% yield.

The acetylene was also obtained by treating the *cis*-dibromoethylene (**1168**; R = Br) with copper bronze in boiling pyridine.[1781] However, 2-(trichloromethyl)-quinoline under these conditions failed to yield the acetylene but rather gave the *cis*-dichloroethylene (**1168**; R = Cl) (22%), which defied all attempts at dechlorination. However, irradiation of the *cis*-dichloro-compound with ultraviolet light brought about isomerization to the *trans*-isomer, which with copper bronze in pyridine readily underwent *trans*-elimination of chlorine to give the required (diquinolyl)acetylene.[1781] 1,2-Di-(2-quinolyl)acetylene has been prepared in high yield (74%) by boiling the dibromoethylene derivative (**1168**; R = Br) with ethanolic potassium hydroxide.[1780] *trans*-1,2-Di-(2-quinolyl)ethylene (69%) may be prepared by heating 1,2-dibromo-1,2-di-(2-quinolyl)ethane with copper bronze powder in pyridine.[1782]

Potassium *tert*-butoxide in dimethyl sulphoxide effects dehydrochlorination of the 3-(3-chlorobutyl)-2-quinolone (**1169**) to the corresponding but-2-enyl derivative in high yield (86%).[1779]



1169

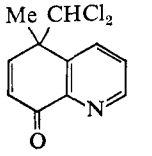


1170

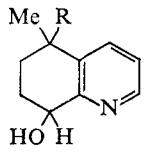
b. Reductive Dehalogenation. Presumably the reductive dehalogenation of (haloalkyl)quinolines can be carried out by any of the methods described in Section II.2.H. In practice, however, few examples of side-chain dehalogenation, under reducing conditions, appear to have been reported.

von Braun and Heymons[599] found that the dichloro-compound (**1170**; R = CH_2Cl), treated with either tin and hydrochloric acid or zinc and acetic acid, suffers reductive loss of the alkyl rather than the heteroaryl chloride, to yield the 2-methylquinoline (**1170**; R = Me).

4-(Bromomethyl)-2-quinolone is reduced by zinc in boiling acetic acid to 4-methyl-2-quinolone.[114] Isogai[1854] found that the (dichloromethyl)oxoquinoline (**1171**) in ethanol solution is reduced by hydrogen and either platinum oxide or palladium–charcoal to the tetrahydro-hydroxy-derivative (**1172**; R = $CHCl_2$), which resists further reduction. However, with palladium charcoal in the presence of potassium hydroxide reduction to the dechlorinated derivative (**1172**; R = Me) can be achieved.



1171



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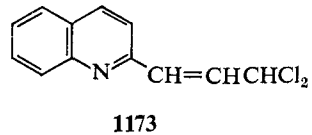
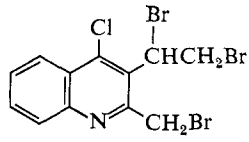


1173

The (dichloropropenyl)quinoline (**1173**) with palladium charcoal in glacial acetic acid suffers reduction of the olefinic double bond in preference to dechlorination,[1819] while with tin and hydrochloric acid reduction of the pyridine ring and formation of the 1,2,3,4-tetrahydro-derivative of (**1173**) is observed.

The tribromo-chloroquinoline (**1174**) on reduction with hydrogen in the presence of palladium–charcoal undergoes complete dehalogenation to give 3-ethyl-2-methylquinoline.[1452] 4-Chloro-2-(dibromomethyl)-3-vinylquinoline behaves similarly.

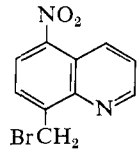


1174

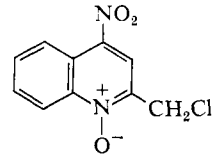
E. Electrophilic Substitution

Few examples of the electrophilic substitution of (haloalkyl)quinolines have appeared in the chemical literature. Halogenation has been covered in Sections II.1.A–B; the few reports on the nitration of (monohalomethyl)quinolines are recorded below.

Early work by Howitz and his co-workers[1788] indicates that 8-(iodomethyl)-quinoline, on treatment with hot nitric acid, undergoes oxidation to the 8-carbaldehyde. However, 8-(bromomethyl)quinoline with mixed acids yields the 5-nitro-derivative (**1175**).[107, 292]



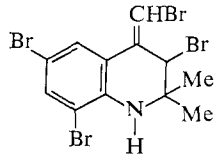
1175



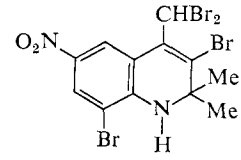
1176

2-(Chloromethyl)quinoline *N*-oxide on treatment with potassium nitrate in 86% sulphuric acid at 50 °C yields a mixture of the 4-nitro-derivative (**1176**) and an unidentified nitro-compound, m.p. 139 °C.[1836]

Nitration of the tetrabromohydroquinoline (**1177**) yields the nitro-tetrabromo-derivative (**1178**).[1501] Seemingly the 6-bromo-substituent is displaced by the incoming



1177



1178

nitro-group and the hydrogen bromide formed adds to the exocyclic double bond to give (**1178**) as the major product. A dinitro-tribromo-derivative appears also to have been formed but it was not identified.

F. Miscellaneous

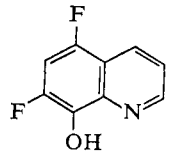
8-(Bromomethyl)quinoline is reported[1855] not to yield a Grignard reagent when treated with magnesium in dry diethyl ether.

V. Addenda

This section deals mainly with those references concerning haloquinolines that appeared during final preparation of this manuscript, i.e. the period January 1973–December 1975. Included are a few references that were overlooked in the initial literature survey.

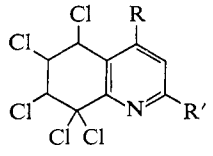
Addenda to II.1.A. Direct Halogenation

c. Fluorination. Direct fluorination of the quinoline nucleus has been achieved by Gershon and his co-workers[1856] who were able to obtain 5,7-difluoro-8-hydroxyquinoline (**1179**) by reaction of 5-fluoro-8-hydroxyquinoline with trifluoromethyl hypofluorite (CF_3OF) in trichlorofluoromethane at −70 °C.

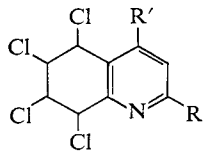


1179

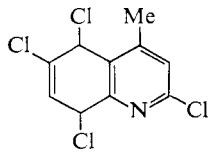
d. Chlorination. 4-Methylquinoline with chlorine in carbon tetrachloride gives the pentachloro-tetrahydroquinoline (**1180**; R = Me, R′ = H) in 20% yield.[1857] 4-Chloro-2-methylquinoline similarly gives the hexachloro-derivative (**1180**; R = Cl, R′ = Me) (17%) along with 4,5,8-trichloro-2-methylquinoline (6%), 4,6,8-trichloro-2-methylquinoline (17%), and an unidentified trichlorinated 4-chloro-2-methylquinoline (2%).



1180



1181



1182

In contrast, 2-chloro-4-methylquinoline yields the pentachlorotetrahydro-derivative (**1181**; R = Cl, R′ = Me) (42%), which on heating undergoes stepwise loss of hydrogen chloride to give initially 2,5,6,8-tetrachloro-5,8-dihydro-4-methylquinoline (**1182**), and finally 2,6,8-trichloro-4-methylquinoline. 2-Ethoxy-4-methylquinoline with chlorine in carbon tetrachloride yields the tetrachloro-derivative (**1181**; R = OEt, R′ = Me) (which readily loses hydrogen chloride to give 6,8-dichloro-2-ethoxy-4-methylquinoline), along with 3,6-dichloro-4-methyl-2-quinolone (40%). Under the same conditions 4-chloroquinoline yields 3,4,6,8-tetrachloroquinoline (40%), while 2-chloroquinoline gives a mixture of 2,5,6,7,8-pentachloro-5,6,7,8-tetrahydroquinoline (**1181**; R = Cl, R′ = H) (15%) and an unidentified tetrachloroquinoline, m.p. 199.5 °C (14%).

Gershon and his co-workers,[1858] following their studies[80, 81, 146, 277] on the halogenation of 8-hydroxyquinoline, have looked at the halogenation of 8-methoxyquinoline in some detail; the various factors influencing the ease of halogenation, and the orientation of the halogen substituents in the two systems, are compared and

contrasted. Briefly, chlorination of the methyl ether with 1 mol of chlorine in 93% sulphuric acid, glacial acetic acid, or pyridine at ambient temperatures results in the formation of 5-chloro-8-methoxyquinoline (97–100%), and only in pyridine solution is any of the 7-chloro-isomer formed (3%). In acetic acid solution the 5-chloro-derivative is still the only product even when an excess of halogen is used, whereas in the other solvent systems the 5,7-dichloro-derivative becomes the major product (73–100%). In chloroform solution only poor yields (25–35%) of the 5-chloro-derivative are obtained, while attempts to chlorinate the ether in either diethylamine or 10% sodium hydroxide solution failed.

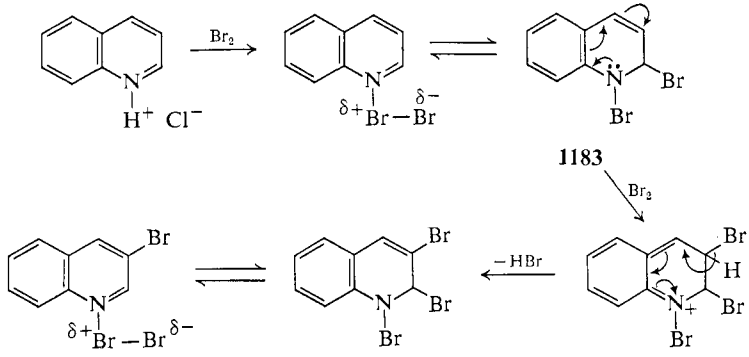
8-Hydroxyquinoline and its 2-methyl derivative are reported[1859] to undergo monochlorination at the 5-position on treatment with chlorine in dilute hydrochloric acid.

e. Bromination. A continuous gas-phase bromination of quinoline has been described.[2027]

Bromination of 8-methoxyquinoline in sulphuric acid, acetic acid, chloroform, or pyridine solution results in exclusive formation of the 5-bromo-derivative regardless of the amount of halogen employed.[1858] As with chlorination, the reaction fails in diethylamine and 10% aqueous sodium hydroxide.

1,2,3,4-Tetrahydro-6-hydroxy-1-methylquinoline hydrochloride in acetic acid is brominated at the 7-position,[1860] as is 5-fluoro-8-hydroxyquinoline.[1856]

3-Bromoquinoline has been obtained in high yield (81%) by treating a slurry of quinoline hydrochloride in nitrobenzene at 180 °C with bromine.[1861, 2028] The reaction is thought to proceed through 1,2-addition product (**1183**) as outlined in Scheme 91.



SCHEME 91

A number of substituted 3-bromo-4-methyl-2-quinolones have been prepared[1862, 1863] by treating 4-methyl-2-quinolones with bromine in acetic acid in the presence of a small amount of iodine. 5,6,7-Tribromo-8-hydroxyquinoline may be prepared in 92% yield by treating 6-bromo-8-hydroxyquinoline with bromine in acetic acid at room temperature.[1858]

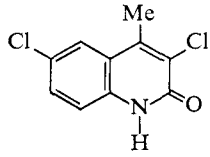
f. Iodination. 8-Hydroxy-2-methylquinoline[1864] and 7-bromo-8-hydroxyquinoline[1856] react with iodine, in potassium iodide solution and in ethanol, respectively, to give in each case the 5-iodo-derivative. In the latter reaction the 7-bromo-8-hydroxy-5-iodoquinoline formed has m.p. 204 °C (decomp.) as opposed to the previously reported[64] value of 146 °C. 5-Bromo-8-hydroxyquinoline yields the 7-iodo-derivative.[1856]

Surprisingly, iodination of 8-methoxyquinoline failed under all the conditions employed (see above) for its chlorination and bromination.[1858]

A number of substituted 3-iodo-4-methyl-2-quinolones have been prepared[1863] by treating the corresponding 4-methyl-2-quinolones with ethanolic iodine in the presence of hydriodic acid. However, attempts to iodinate several 4-hydroxy-2-quinolones under similar conditions failed.

Addenda to II.1B. Indirect Halogenation

6-Chloro-1,2,3,4-tetrahydro-4-methyl-2-oxoquinoline reacts with thionyl chloride to give 3,6-dichloro-4-methyl-2-quinolone (**1184**) (40%).[1857] 4,8-Dimethyl-2-quinolone and related 2-quinolones are chlorinated at the 3-position on treatment with

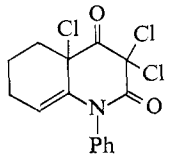


1184

sulphuryl chloride in acetic acid containing a small amount of iodine.[1863] 5-Fluoro-8-hydroxyquinoline with sulphuryl chloride in acetic acid yields 7-chloro-5-fluoro-8-hydroxyquinoline (61%).[1856] 8-Hydroxyquinoline on treatment with isotopically labelled sulphuryl chloride ($SO_2{}^{36}Cl_2$) yields a mixture of 5-^{36}chloro-8-hydroxyquinoline (21%) and 5,7-di^{36}chloro-8-hydroxyquinoline (79%).[1865]

Sulphuryl chloride has been found suitable for the polychlorination of quinoline.[1866] Held at 55–60 °C for 30 hours the reactants yield a mixture of 3,4,5,6,7,8-hexachloro- (57%), 3,4,6,8-tetrachloro-quinoline (37%), and a third product thought to be 2,3,5,6,7,8-hexachloroquinoline.

5,6,7,8-Tetrahydro-4-hydroxy-2-oxo-1-phenylquinoline reacts with sulphuryl chloride (2 equivalents) to yield the trichloro-compounds (**1185**) and (**1186**), while with sulphuryl chloride (4 equivalents) the pentachloro-derivative (**1187**) is formed.[1867]



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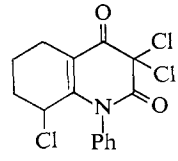
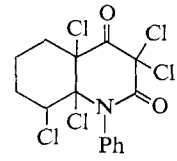


1186



1187

The trichloro-derivative (**1186**) and the pentachloro-derivative (**1187**) lose hydrogen chloride, when heated above their melting points giving 3-chloro- and 3,8-dichloro-4-hydroxy-1-phenyl-2-quinolone, respectively.

Quinoline with sodium hypochlorite (1.5–1.6M) at pH 12–13 gives a mixture of isophthalic acid (22.3%), 3,4-dichloro-2-quinolone (34.4%), and an unidentified trichloro-2-quinolone (39%).[1868]

5-Bromo-8-hydroxyquinoline[1858] and 8-hydroxy-2-methylquinoline-5-sulphonic acid[1864] with alkaline hypochlorite solution yield their 7-chloro-derivatives (60% and

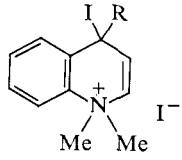
91% yield, respectively). The 7-bromo-derivative of the sulphonic acid is similarly prepared (85%) by using potassium hypobromite. 8-Hydroxy- and 8-hydroxy-2-methylquinoline react with iodine trichloride in hydrochloric acid to give their 5-chloro-derivatives.[1869]

8-Methoxyquinoline with *N*-chlorosuccinimide in warm acetic acid, chloroform, or pyridine solution gives mainly the 5-chloro-derivative.[1858] In 93% sulphuric acid solution good yields of the 5-chloro-compound may be obtained at ambient temperatures, whereas at higher temperatures (40–60 °C) and with an excess of halogenating agent 5,7-dichloro-8-methoxyquinoline becomes the major product. *N*-bromosuccinimide appears to be more reactive in that quantitative yields of 5-bromo-8-methoxyquinoline may be obtained at room temperature and in a wide range of solvents. High yields of 5,7-dibromo-8-methoxyquinoline are achieved by using an excess (3 mol) of reagent in acetic or sulphuric acid at higher temperatures (40–60 °C). In contrast to all the halogenation reactions of 8-methoxyquinoline so far discussed, Gershon and his co-workers[1858] found that *N*-iodosuccinimide, in 93% sulphuric acid,* glacial acetic acid, or chloroform solution, iodinates the methyl ether exclusively at the 7-position. In acetic acid yields are quantitative, while in warm sulphuric acid with 3 mol of iodinating agent a 95% yield of the 5,7-di-iodo-derivative is obtained.

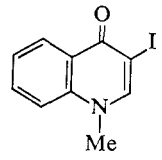
8-Hydroxy-2-methylquinoline in 90% sulphuric acid reacts with *N*-chlorosuccinimide to give 5-chloro-8-hydroxy-2-methylquinoline in 85% yield.[1864] The 5-bromo-derivative was prepared in a similar manner. The 5-bromo- and 5-iodo-derivatives of 7-fluoro-8-hydroxyquinoline have been prepared in high yield (88% and 95%) by treating the fluoro-compound with the appropriate *N*-halosuccinimide in chloroform solution.[1856]

N-Iodosuccinimide has also been used to prepare 8-hydroxy-5-iodo-2-methylquinoline-7-sulphonic acid, and the 7-iodo-derivatives of 8-hydroxy-2-methylquinoline and its 5-sulphonic acid.[1864]

4-Nitroquinoline is methylated normally at the ring-nitrogen by methyl fluorosulphonate ("Magic methyl"), whereas with methyl iodide the di-iodo-quaternary salt (**1188**; R = I) is formed, which on treatment with aqueous sodium hydroxide yields the hydroxyiodo-compound (**1188**; R = OH).[1870]



1188



1189

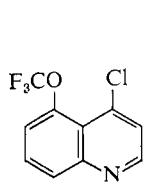
Attempts to estimate volumetrically the iodine content of this compound using silver nitrate in the presence of chromate indicator leads to formation of the 3-iodo-4-quinolone (**1189**), which is identical with the product obtained by treating 1-methyl-4-quinolone with iodine monochloride.

Addenda to II.1D. Preparation from Quinolones and Hydroxyquinolines

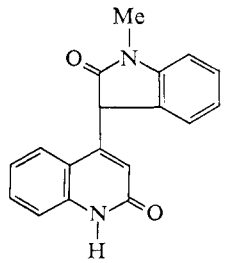
Several 6,7-dialkoxy-4-chloroquinoline-3-carboxylates have been prepared[1871–1873] by treating the corresponding 4-quinolones with boiling phosphorus oxychloride.

* Halogenation, particularly bromination, in sulphuric acid is often accompanied by formation of halo-8-hydroxyquinolines.

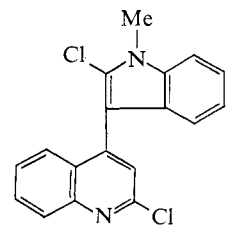
Phosphorus oxychloride–pentachloride mixture has been used to prepare a number of alkoxy substituted 4-chloro-2-(trifluoromethyl)quinolines.[1874, 1875] 6-Methoxy-8-nitro-2-quinolone gives more consistent and better yields of the 2-chloro-derivative with phosphorus oxychloride than with phosphorus pentachloride.[2029] 4-Chloro-substituted (trifluoromethoxy)quinolines, e.g. (**1190**), have been prepared by heating the corresponding 1,2,3,4-tetrahydro-4-oxoquinolines with phosphorus oxychloride in methylene chloride in the presence of iodine.[1876, 1877]



1190



1191



1192

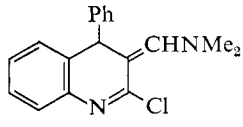
The 2-quinolone (**1191**) on treatment with phosphorus oxychloride is converted into the dichloro-compound (**1192**).[1878]

Gyul'budagyan and his co-workers,[1879, 1880] following on previous work,[508, 509, 1543, 1805] have prepared a further series of 4-chloro- and 2,4-dichloro-3-(3-chlorobut-2-enyl)- and 3-(3,3-dichloroallyl)quinolines.

1-Ethyl-6-nitro-4-quinolone reacts with thionyl chloride in dimethylformamide to give 4-chloro-1-ethyl-6-nitroquinolinium chloride.[1881] Under similar conditions 8-hydroxy-5,7-dinitroquinoline yields the 8-chloro-derivative.[1882] Apparently, if phosphorus pentachloride is used in the latter reaction then replacement of the nitro-groups is observed.

Several 2-(*tert*-butyl)- and 2-adamantyl-substituted 4-bromoquinolines have been prepared from the corresponding 4-quinolones.[1883] The reactions are smooth when phosphorus oxybromide is used. However, with phosphorus pentabromide or triphenylphosphine dibromide (Ph_3PBr_2)[1884] as the brominating agent, the 2-adamantyl compounds, in contrast to the 2-(*tert*-butyl) analogues, yield only tars.

2-Chloro-6-cyano-5,6,7,8-tetrahydro-6-phenylquinoline can be obtained by heating the 2-quinolone with phenylphosphonic dichloride.[2030]



1193

1,2,3,4-Tetrahydro-2-oxo-4-phenylquinoline with a mixture of phosphorus oxychloride and dimethylformamide gives the 2-chloro-3,4-dihydroquinoline (**1193**) (90%).[1885] A Vilsmeier–Haack reaction on 1,2,3,4-tetrahydro-2-oxo-4-phenylquinoline with phosphorus oxychloride in 1-methylpyrrolidone results in 2-chlorination and incorporation of the pyrrolidine unit at the 3-position.[2053]

Addenda to II.1E. Preparation from Aminoquinolines

5- and 7-Fluoro-8-hydroxy-2-methylquinoline[1864] and 5-chloro-7-fluoro-8-hydroxyquinoline[1856] have been prepared from the corresponding amines by the Balz–Schiemann reaction, while 6-chloro-3-(3,3-dichloroallyl)-2-methyl-4-quinolone has been prepared by a Sandmeyer reaction on the 6-amino-compound.[1879]

Diazotization of 4,6-diaminoquinoline with an equimolar amount of sodium nitrite followed by treatment with potassium iodide gave 4-amino-6-iodoquinoline.[1886] 4-Amino-7-iodoquinoline was prepared in an identical manner. By using isotopically labelled potassium iodide ($K^{131}I$) the authors were able, by means of the Sandmeyer reaction, to prepare the following ^{131}I-labelled quinolines; 5-iodo-, 6-iodo-, 7-iodo-, 4-amino-6-iodo-, 4-amino-7-iodo-, and 4-[3-(dimethylamino)-propylamino]-7-iodo-.

Addenda to II.1F. Preparation by Halogen–Halogen Exchange

A series of 6-mono- and 6,8-di-substituted 4-cyano-2-fluoroquinolines has been prepared[1887] by treating the 2-chloro-4-cyano-compounds with potassium fluoride in dimethyl sulphoxide at 180 °C. Gershon and his co-workers,[1888] using potassium fluoride in boiling dimethylformamide, were able to replace both chloro-groups from 5,7-dichloro-8-nitroquinoline and obtained 5,7-difluoro-8-nitroquinoline in good yield.

"Chloroquine" on treatment with isotopically labelled iodine (^{131}I) in potassium iodide undergoes chlorine–iodine exchange to yield the 7-^{131}iodo-derivative.[1889] The 7-^{125}iodo-derivative has also been prepared.[1889] A series of 7-^{125}iodo-substituted 4-amino- and 4-(aminoalkoxy)quinolines has been synthesized[1890] by treating the chloro-compounds with sodium ^{125}iodide. 8-Hydroxy-5-^{131}iodoquinoline and ^{125}I-labelled "Chinoform" have also been prepared.[2031]

Addenda to II.1G. Preparation from Quinoline *N*-Oxides

2-Chloro-6-methoxy-5-nitroquinoline, an intermediate in the synthesis of the antibiotic streptonigrin, has been obtained in 56.7% yield by treating 6-methoxy-5-nitroquinoline *N*-oxide with phosphorus oxychloride.[1891]

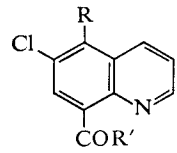
Japanese workers have shown[1892] that 2-cyanoquinoline *N*-oxides on photolysis in a mixture of sulphuric acid and methanol yield 2-cyano-6-methoxyquinolines. Photolysis in the presence of hydrochloric acid, however, leads to formation of 6-chloro-2-cyanoquinolines. The yield of chloroquinoline appears to depend on the acid–alcohol ratio (41% with a hydrochloric acid–methanol ratio of 1 : 1; 15% with a 1 : 17 mixture), and also on the nature of the alcohol. For example, 6-alkoxyquinolines appear to be favoured in methanol–acid mixtures, whereas the best yields (40%) of 6-chloro-2-cyanoquinolines were obtained when using *tert*-butyl alcohol–acid mixtures. Traces of 8-chloro-2-cyanoquinoline were also detected (maximum 6% in *tert*-butyl alcohol), and a mechanism involving an oxaziridine intermediate is proposed to explain the course of the reaction.

Reactions of 4-chloro- and 4-bromo-quinoline *N*-oxides with cyanogen bromide have been studied;[2032] photolysis of 4-substituted 2-(trifluoromethyl)quinoline *N*-oxides causes ring expansion that affords benzoxazepines in high yield.[2033]

Addenda to II.1H. Preparation by Displacement of Substituents Other than Halogen

Ready displacement of nitro-groups by halogen has been observed[1893] during attempts to prepare the acid chloride of the nitro-acid (**1194**; R = NO_2, R′ = OH)

by using thionyl chloride. After treatment of the reaction mixture with ethanol, only the dichloro ethyl ester (**1194**; R = Cl, R′ = OEt) (81%) was obtained. Further



1194

studies showed that the dichloro- and bromochloro-quinoline-8-carboxylic acids (**1194**; R = Cl, R′ = OH, and R = Br, R′ = OH, respectively) can be prepared by treating the nitro-acid in dimethylformamide solution with dry hydrogen chloride or hydrogen bromide, respectively. Displacement may be due to participation of the heteroatom in stabilizing the transition state, and also to relief of steric crowding at the 4, 5, and 6-positions.

4-Chloro-5-nitroquinoline *N*-oxide is obtained in quantitative yield by treating 4,5-dinitroquinoline *N*-oxide with hydrochloric acid.[1894]

Addenda to II.1J and II.1K. Haloquinolines by Skraup and Doebner–von Miller Reactions

5,7-Di-iodo- (62%),[1888] 5,7-difluoro- (78%),[1888] 6,8-dichloro-7-methyl, (51%),[1895] 6-chloro-8-methylquinoline,[1896] and 5,8-dibromo-6-nitroquinoline,[2034] have been prepared by Skraup reaction. 2,4-Dichloroaniline with methyl vinyl ketone yields 6,8-dichloro-4-methylquinoline,[1857] while 5-chloro-8-hydroxyquinoline is obtained[1897] on treatment of 5-chloro-2-hydroxyaniline with acrolein in a mixture of acetic and hydrochloric acid at 100–105 °C for 3 hours. 5-Bromo-2-methylaniline with 1,3-diethoxy-2-phenylpropan-2-ol in the presence of phosphoric and arsenic acid gives 5-bromo-8-methyl-2-phenylquinoline in 22% yield.[1898]

o-Fluoronitrobenzene with glycerol and concentrated hydrochloric acid yields a mixture of 6-chloro-8-fluoroquinoline, 8-fluoroquinoline, and *o*-fluoroaniline, whereas in the presence of hydrobromic acid only the last two products are obtained.[1899] Similarly *p*-fluoronitrobenzene with hydrobromic acid and glycerol yields only *p*-fluoroaniline and 6-fluoroquinoline. However *o*-iodonitrobenzene reacts with glycerol and hydrochloric acid to give a host of products (including 6-chloro-, 8-chloro-, and 6,8-dichloroquinoline), none of which contain iodine.

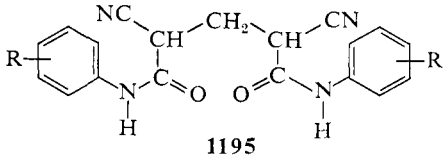
5-Chloro-2-hydroxyaniline with paraldehyde in the presence of hydrochloric acid gives 5-chloro-8-hydroxy-2-methylquinoline,[1900] while several 2,3,4-trialkyl-substituted 6-chloro-1,2-dihydroquinolines have been prepared by treating *p*-chloroaniline with an aldehyde or ketone (2 mol) under Doebner–von Miller conditions.[1901]

Addenda to II.1L and II.1M. Haloquinolines by Conrad–Limpach and Knorr Reactions

The Conrad–Limpach reaction has been used for the preparation of 6-iodo-4-quinolone-3-carboxylic esters[1886] and for a number of 2-(*tert*-butyl)- and 2-adamantyl-substituted halo-4-quinolone-3-carboxylates.[1883]

The dicyano-glutaric acid dianilides (**1195**; R = 2-Cl or 4-Cl) on treatment with polyphosphoric acid cyclize, presumably via the dicarboxylic acid, to give the

3,3′-methylenedi-(4-hydroxy-2-quinolones) (**1196**; R = 8-Cl or 6-Cl) in 48.7% and 52.5% yield, respectively.[1902]



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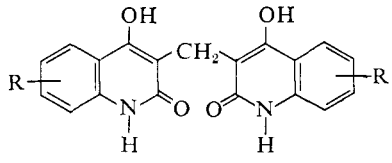
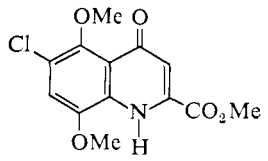
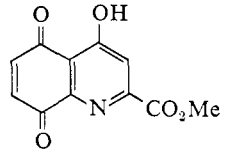


1196

The chlorodimethoxy-4-quinolone (**1197**) obtained by thermal cyclization of the appropriate iminosuccinate in diphenyl ether is identical with the product isolated after addition of hydrogen chloride to the quinoline-5,8-dione (**1198**) followed by treatment with diazomethane.[1903]

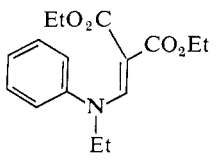


1197

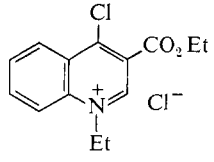


1198

Several chloro-4-quinolone-3-carboxylates have been prepared by Conrad–Limpach reaction,[1904] and diesters of type (**1199**), with phosphorus oxychloride yield the quaternary derivatives, e.g. (**1200**).[1905]



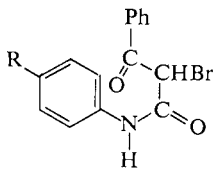
1199



1200

Gyul'budagyan and his co-workers[1879, 1880, 1906] have synthesised further examples of 4-quinolones bearing chloro- and dichloro-allyl side chains by cyclizing the corresponding 2-substituted acrylate esters in an inert solvent, generally paraffin oil, at high temperatures (ca. 280 °C). *m*-Chloroaniline reacts with ethoxymethylene-malonic ester, $EtOCH{=}C(CO_2Et)_2$, in the presence of zinc chloride to give ethyl 7-chloro-4-quinolone-3-carboxylate.[1907]

Egyptian[1862, 1908] and Indian workers[1863] have reported the synthesis of several 3-bromo-2-quinolones by treating α-bromoacetoacetanilides[1862, 1863] or α-bromo-α-benzoylacetanilides,[1908] e.g. (**1201**; R = Me) with either concentrated sulphuric acid



1201

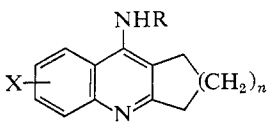
or polyphosphoric acid. The benzoylacetanilides (**1201**; R = Cl and NO_2) failed to cyclize, while the methoxy-compound (**1201**; R = MeO) gave only unidentified water-soluble products.[1908]

Two patents have appeared[1909, 1910] both of which describe the preparation of 6-chloro-1,2,3,4-tetrahydro-4-methyl-2-oxo-4-phenylquinoline (**377**) by cyclization of the cinnamanilide (**376**) (see p. 479).

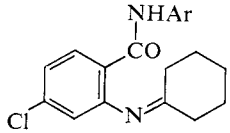
Addenda to II.1N and II.1O. Haloquinolines from *o*-Aminocarbonyl Compounds and by the Pfitzinger Reaction

Tricyclic halogenated 4-alkylamino- and 4-arylaminoquinolines of type (**1202**; X = Cl or Br, R = alkyl or aryl, n = 1 or 2) have been prepared[1911, 1912] by treating the corresponding *o*-amino-amides with cyclopentanone or cyclohexanone in the presence of base. Alternatively the anils, e.g. (**1203**), may be cyclized by phosphorus oxychloride.[1912]

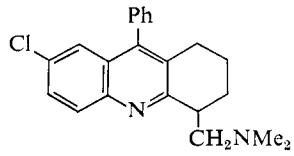
2-Amino-5-chlorobenzophenone has been condensed with a number of 2-(dialkylaminoalkyl)-cyclopentanones, -cyclohexanones, and -cycloheptanones in acetic acid in the presence of boron trifluoride–ether complex to give compounds of type



1202

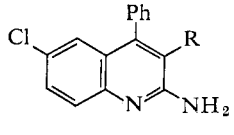


1203

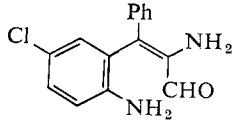


1204

(**1204**).[1913] 2-Amino-6-chloro-4-phenylquinolines (**1205**; R = H, Me, or Ph) have been prepared[1914, 1915] by condensing 2-amino-5-chlorobenzophenone with the appropriate nitrile (RCH_2CN; R = H, Me, or Ph) in the presence of sodium hydride. If malonodinitrile is used then the 3-cyano-derivative (**1205**; R = CN) is obtained.

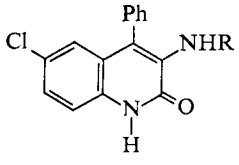


1205

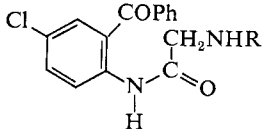


1206

3-Amino-6-chloro-4-phenylquinoline (**1205**; R = NH_2) has been prepared by cyclizing the amino-aldehyde (**1206**) (as the acetal) with ethanolic hydrogen chloride.[1916] 3-Amino-6-chloro-2-quinolones, e.g. (**1207**; R = Ac or CH_2CH_2OH)



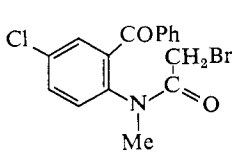
1207



1208

have been obtained[1917, 1918] by treating the amides (**1208**; R = Ac or CH_2CH_2OH) with aqueous sodium hydroxide.

The bromo-compound (**1209**), on treatment with aqueous base, cyclizes to give, not the 3-bromo-2-quinolone (**1210**; R = Br), but the 3-hydroxy-derivative (**1210**; R = OH) (10%).[1918]



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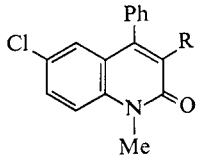
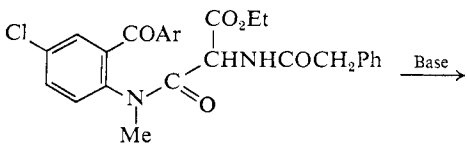
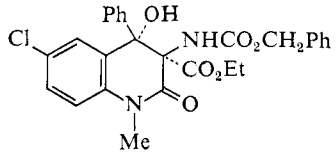


1210

A number of *o*-keto-amides such as (**1211**) have been shown to undergo stereoselective cyclization in the presence of base to yield halo-tetrahydro-2-oxo-quinolines (e.g. **1212**).[1919] Under acid conditions cyclization is accompanied by oxazole formation (e.g. **1213**).



1211



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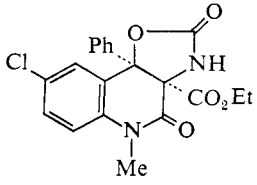
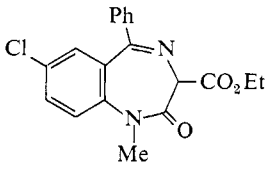


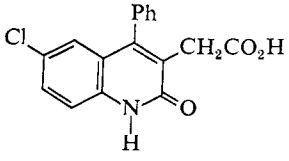
1213



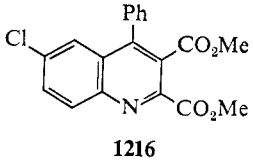
1214

In toluene solution in the presence of acetic acid the 2-oxoquinolines (e.g. **1212**) readily rearrange to give benzo[*e*]diazepine-3-carboxylates (e.g. **1214**) in high yields.

2-Amino-5-chlorobenzophenone reacts with diethyl succinate in the presence of potassium *tert*-butoxide to give the 2-quinolone (**1215**) in 75% yield,[1920] while with dimethyl acetylenedicarboxylate the chloro-dicarboxylic ester (**1216**) is obtained.[1921]



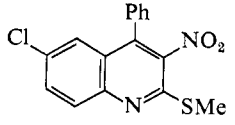
1215



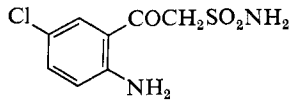
1216

2-Amino-5-chlorobenzophenone reacts also with 1,1-di(methylthio)-2-nitroethylene[$(MeS)_2C{=}CHNO_2$] at 140 °C to give the thioether (**1217**) in 52% yield.[1922]

6-Chloro-4-quinolone-3-sulphonamide (**1219**) has been prepared by heating the *o*-aminoacetophenone derivative (**1218**) with triethyl orthoformate at 110 °C for 2 hours.[1923]

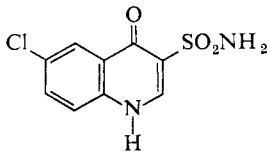


1217



1218

5-Iodoisatin with acetophenone in the presence of ethanolic potassium hydroxide gives 6-iodo-2-phenylquinoline-4-carboxylic acid in high yield.[1924] Under similar conditions 5-chloroisatin and cyclohexanone yield the acridine derivative (**1220**).[1925]



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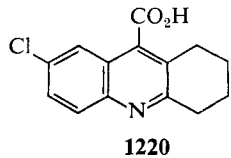
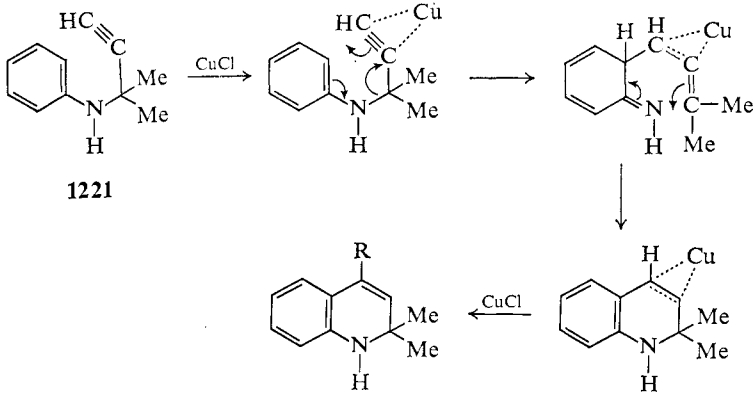


1220

2-Adamantyl-6,8-dichloroquinoline-4-carboxylic acid has been prepared by a Pfitzinger reaction with 5,7-dichloroisatin,[2042] as have various 8-chloro-2-heteroarylquinoline-4-carboxylic acids from 7-chloroisatin.[2043]

Addenda to II.1S.d,i,k. Miscellaneous Methods of Preparing Haloquinolines

The *N*-(butynyl)aniline (**1221**) in the presence of a large excess of cuprous chloride at 75 °C yields a mixture of 4-chloro-1,2-dihydro-2,2-dimethylquinoline (**1222**; R = Cl) (8.5%) and 1,2-dihydro-2,2-dimethylquinoline (**1222**; R = H) (41.5%).[1926] In the presence of cuprous bromide the 4-bromo-derivative (**1222**; R = Br) (4%) is obtained.



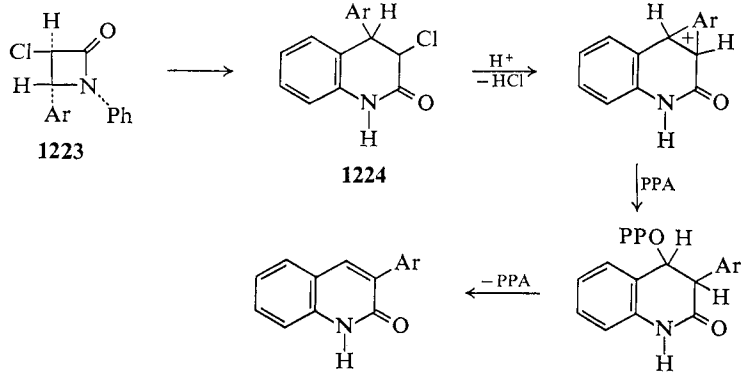
1221

1222

SCHEME 92

The authors show that the dihydroquinoline (**1222**; R = H) does not undergo halogenation on treatment with cuprous halide and suggest a mechanism to explain formation of the 4-halo-derivative, as outlined in Scheme 92.

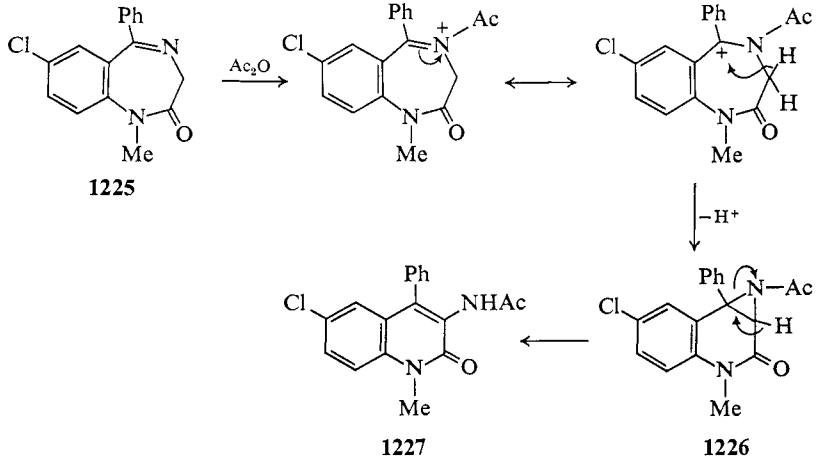
The *trans*-1,4-diaryl-3-chloroazetidin-2-ones (**1223**; Ar = Ph or *p*-$MeOC_6H_4$) in cold concentrated sulphuric acid or in polyphosphoric acid at 78 °C yield *trans*-4-aryl-3-chloro-1,2,3,4-tetrahydro-2-oxoquinolines (**1224**; Ar = as **1223**).[1927] In polyphosphoric acid at 140 °C, however, ring expansion of the azetidinone (**1223**; Ar = Ph) is accompanied by loss of chlorine and migration of the phenyl group to give 3-phenyl-2-quinolone in 75% yield.



1223 **1224**

SCHEME 93

As expected on the basis of the mechanism outlined in Scheme 93, the azetidinones (**1223**; Ar = *p*-$MeOC_6H_4$ or *p*-MeC_6H_4) rearrange at lower temperatures (110 °C) and in greater yield (88% and 79%, respectively). Evidence is presented for the intermediacy of cinnamanilides in these isomerizations. Azetidine intermediates are proposed in a reaction leading to the formation of 7-chloro-1,2,3,4-tetrahydro-2- and 4-thienylquinoline.[2044]

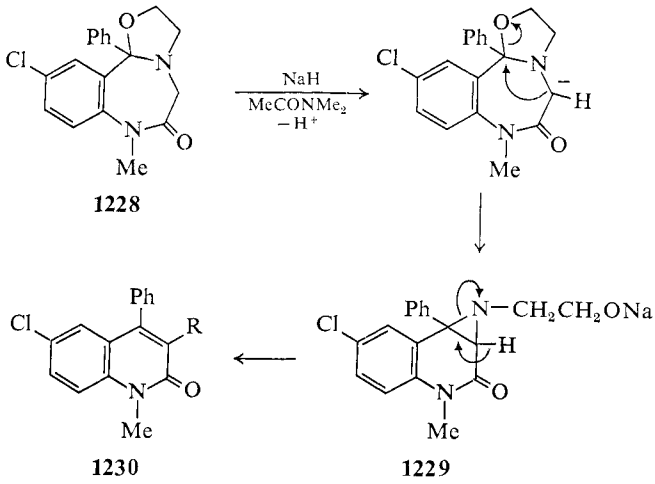


1225 **1227** **1226**

SCHEME 94

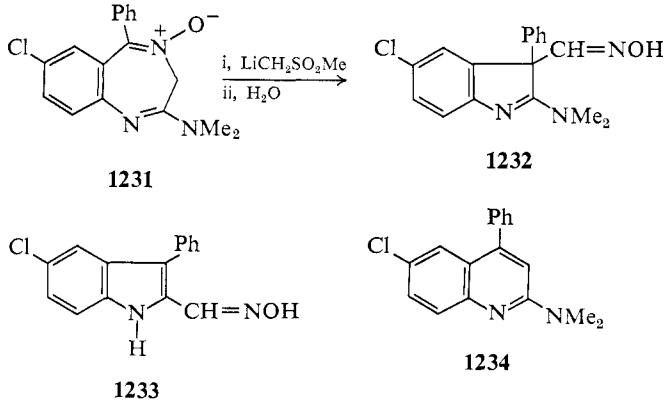
Several reports concerning the ring contraction of halobenzodiazepines to haloquinolines and quinolones have appeared.[2109] Heating 7-chloro-1-methylbenzo-1,4-diazepin-2-one ("Diazepam") (**1225**) with acetic anhydride yields the 6-chloro-2-quinolone (**1227**) by way of aziridine intermediate (**1226**), as outlined in Scheme 94.[1917, 1928]

10-Chloro-2,3,5,6,7,11b-hexahydro-7-methyl-11b-phenylbenzo[6,7]-1,4-diazepino-[5,4-*b*]oxazol-6-one (**1228**) on treatment with sodium hydride in *N*,*N*-dimethylacetamide gives a mixture of the 6-chloro-2-quinolone (**1230**; R = $NHCH_2CH_2OH$)



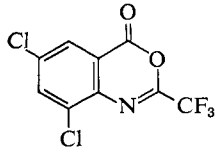
(10%) and the 6-chloro-3-hydroxy-2-quinolone (**1230**; R = OH) (10%).[1917] The former product is believed to arise via the aziridine intermediate (**1229**) similar to that proposed for the previous reaction, whereas the origin of the hydroxyquinolone is not clear.

A somewhat different reaction is observed[1929] when the chlorobenzo-1,4-diazepine *N*-oxide (**1231**) is treated with the lithium salt of dimethyl sulphoxide ($Li^+ {}^-CH_2SOCH_3$). Ring contraction occurs to give the chloroindoles (**1232**) and (**1233**) in



yields of 30% and 11%, respectively, along with a small amount (<1%) of the 6-chloro-2-dimethylaminoquinoline (**1234**). Possible mechanisms for this reaction are discussed.

2-(Trifluoromethyl)benzo-3,1-oxazin-4-ones, e.g. (**1235**), react exothermally with *N*,*N*-diethyl-1-propynylamine ($MeC{\equiv}CNEt_2$) in ether at −20 °C to give 4-(diethylamino)-2-(trifluoromethyl)quinolines, e.g. (**1236**), in high yields (94%).[1930] In acetonitrile or propan-2-ol a mixture of the aminoquinoline and the 4-quinolone (**1237**) is formed.



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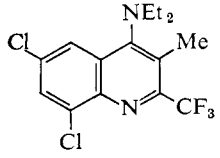

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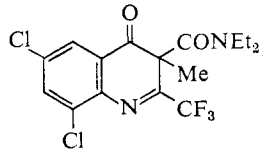
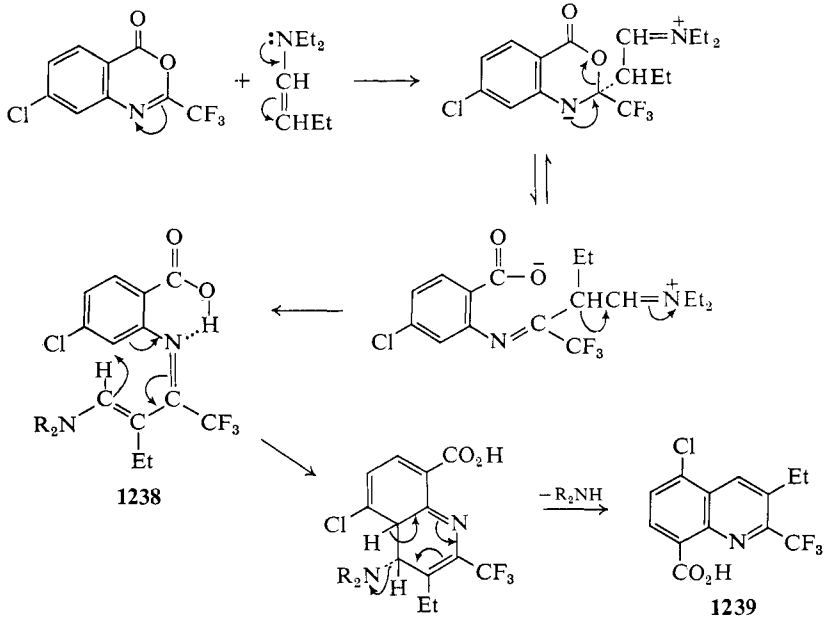


1237

It was also shown[1931] that 2-(trifluoromethyl)benzo-3,1-oxazin-4-ones react with enamines in diethyl ether or acetonitrile to give 2-(trifluoromethyl)quinoline-8-carboxylic acids of type (**1239**) as indicated in Scheme (**95**). Nucleophilic attack by



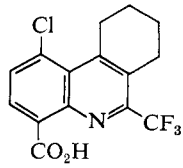
1238

1239

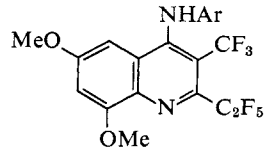
SCHEME 95

the enamine at the electron-deficient 2-position of the oxazinone ring is followed by ring opening and a proton shift to give the azabutadiene (**1238**), which undergoes a disrotatory 6π-ring closure with elimination of amine to yield the product (**1239**). *N*-(Trifluoroacetyl)anthranilic acids are formed as by-products, and if an enamine

derived from a cyclic secondary amine is employed (e.g. piperidine) then a good yield (48%) of the phenanthridine (**1240**) is obtained.



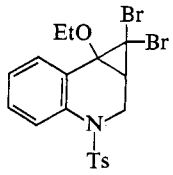
1240



1241

Haszeldine and his co-workers[1932] have shown that aromatic amines, particularly those bearing an electron-donating substituent (e.g. MeO), react with perfluoro-2-methylpent-2-ene at room temperature in tetrahydrofuran solution to give perfluoroalkylquinolines of type (**1241**). Similar reactions have been reported by Japanese workers.[2045]

Dibromocarbene with 4-ethoxy-1,2-dihydro-1-(*p*-toluenesulphonyl)quinoline gives the dibromocyclopropaquinoline (**1242**), which in boiling pyridine yields the benzoazepine (**1243**).[1933]



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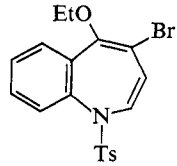

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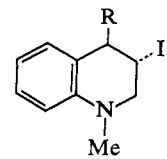
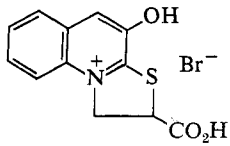


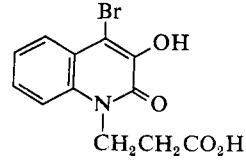
1244

1,2-Dihydro-1-methylquinoline under nitrogen in tetrahydrofuran solution at −78 °C undergoes *trans*-addition of iodine isocyanate (INCO) to yield the 3-iodo-derivative (**1244**; R = NCO), which in the presence of lithium methoxide in methanol yields a mixture of the carbamate (**1244**; R = $NHCO_2Me$) (23%) and the urea (**1244**; R = $NHCONHCO_2Me$).[1934] 7-Chloro-octahydro-Δ^6-4-oxoquinolines have been prepared in good yield by Diels–Alder cycloaddition of 2-chlorobutadiene to 2,3-dihydro-4-pyridones.[2046]

The thiazolo[3,2-*a*]quinolinium bromide (**1245**) with performic acid gives the 4-bromo-3-hydroxy-2-quinolone (**1246**) (73%).[1935] The authors presume that



1245



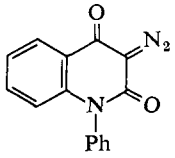
1246

bromonium ion is generated by oxidation of the hydrogen bromide present, and once formed attacks the 3-hydroxy-2-quinolone, obtained by hydrolysis of the initially produced *S*-oxide of the thiazole system (**1245**).

p-Chloronitrobenzene with ethylene at 150 °C in the presence of molybdenum and palladous chloride is reported[1936] to yield 6-chloro-2-methylquinoline together with traces of 6-chloro-2-(*n*-propyl)quinoline.

6-Chloro-2-dimethylamino-4-methylquinoline has been prepared in 40% yield by a new quinoline synthesis, which involves heating a primary aromatic amine with acetic acid and hexamethylphosphoric triamide at 250 °C for 16 hours.[2047] 4-Amino-3-chloro- and 4-amino-3-bromo-quinoline *N*-oxide are available in high yield from the rearrangement of 4-(hydroxyamino)quinoline *N*-oxide in the appropriate halo-acid.[2098]

The 3-diazo-2,4-dioxoquinoline (**1247**) with a mixture of *tert*-butyl hypochlorite and formic acid gives 3-chloro-3-formyloxy-1,2,3,4-tetrahydro-2,4-dioxo-1-phenylquinoline (**1248**) (62%).[1937] In the same paper oxiranes (**1249**; R = H or Me) are



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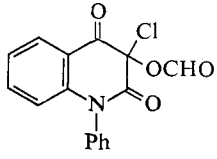

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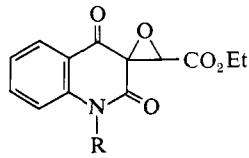


1249

shown to react with 6N-hydrochloric acid in ethanol to yield the corresponding 3-chloro-4-hydroxy-2-quinolones in 82% and 88% yield, respectively.

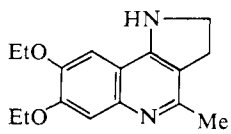
Addenda to II.2B.c. Nuclear Magnetic Resonance Spectra

The ^{13}C-nuclear magnetic resonance spectra of 3-bromoquinoline[1938] and 4-chloroquinoline[1939] have been recorded.

The π-electron densities in the ground and the first singlet excited states of 2-, 3-, 5-, 6-, 7-, and 8-fluoroquinoline have been predicted on the basis of an additivity model and accord well with experimentally determined ^{19}F-magnetic resonance chemical shifts.[2048]

Addenda to II.2C.d. Displacement by Nucleophilic Nitrogen

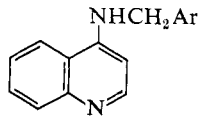
Various 4-chloroquinolines[1873, 1879] have been converted into the amino-derivatives by treatment with ammonia and phenol. 4-Chloro-3-(2-chloroethyl)-6,7-diethoxy-2-methylquinoline with ethanolic ammonia gives the dihydropyrroloquinoline (**1250**) (29%).[1873]



1250

Several 4-(dialkylamino)-3-nitroquinolines with herbicidal activity have been prepared[1940] by condensing 4-chloro-3-nitroquinolines with aliphatic secondary amines. Other 4-(alkylamino)quinolines have also been synthesized from 4-chloro

derivatives.[1873, 1911] The 4-(benzylamino)quinoline (**1251**; Ar = 2,3,4-triMeOphenyl), prepared by condensing 4-chloroquinoline with 2,3,4-trimethoxybenzylamine, is reported[1941] to have potassium permeability-regulating and antinicotinic acid action. 4,7-Dichloroquinoline condenses with 2-(methylamino)ethylamine to give the secondary base (**1252**),[1942] and several 3-substituted 2,7-dichloro-4-phenylquinolines have been condensed with ethanolamine and propanolamine to give the appropriate *N*-(2-quinolyl)-substituted amino-alcohols.[1914]



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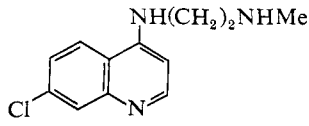

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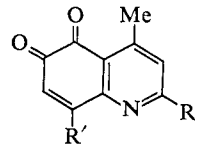


1253

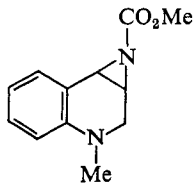
For condensations with other diamines and with triethylsilyl-substituted amines see refs. 2049 and 2050, respectively.

2-(Arylamino)quinolines have been prepared[1873, 1887, 1915, 1943, 1944] by condensing various arylamines with 2- and 4-chloroquinoline, and a large number of 4-(*o*-alkoxycarbonylanilino)quinolines possessing analgesic and anti-inflammatory properties have been obtained by heating a 4-chloroquinoline with an (*o*-alkoxycarbonyl)arylamine in dilute hydrochloric acid.[1877, 1945, 1946, 2051]

Various 4-piperidino-,[1947] 4-morpholino-,[1947] and 4-piperazino-quinolines[1948] have been synthesized, as have several 2- and 4-hydrazinoquinolines[1873, 1948–1951] by treating the appropriate base with a 2- or 4-chloroquinoline.

Oxidation of 2-chloro-6-hydroxy-4-methylquinoline in the presence of cupric acetate and an excess of piperidine or morpholine yields the dipiperidino- or dimorpholino-substituted quinoline-5,6-diones (**1253**; R = R′ = piperidino or morpholino).[1952] In the presence of 1 equivalent of secondary amine the chloroquinones (**1253**; R = Cl, R′ = piperidino or morpholino) are obtained.

The *N*-(3-iodoquinolyl)carbamate (**1244**; R = $NHCO_2Me$) on treatment with 50% aqueous sodium hydroxide and benzene undergoes intramolecular nucleophilic displacement of iodide to give the aziridine (**1254**) (73%).[1934] In contrast with pyridine elimination of hydrogen iodide occurs to give the 1,4-dihydroquinoline (**1255**), while with methanolic potassium hydroxide the *trans*-4-methoxy-carbamate (**1256**) is obtained, possibly by *trans*-ring opening of the aziridine initially produced.



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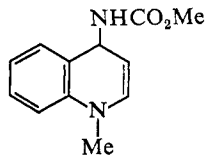

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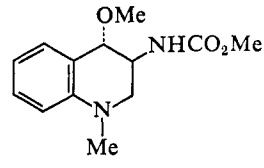
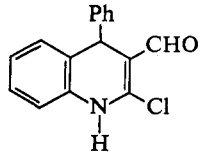


1256

The chloro-enamine (**1193**) (p. 678) on acid hydrolysis yields a mixture of products including 2-chloro-3-formyl-1,4-dihydro-4-phenylquinoline (**1257**) (39%) which in boiling formamide cyclizes to yield the pyrimido[4,5-*b*]quinoline (**1258**).[1885]



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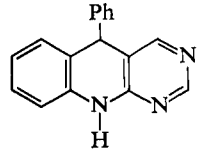
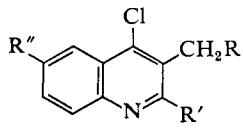


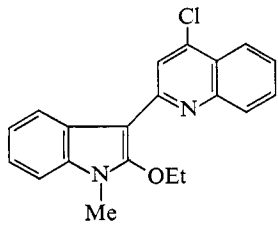
1258

Addenda to II.2C.e. Displacement by Nucleophilic Oxygen

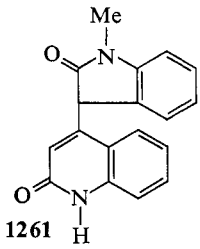
The trichloroquinoline (**1259**; R = CH=CClMe, R′ = Cl, R″ = H) may be selectively hydrolysed under acid conditions to give the dichloro-derivative (**1259**; R = CH_2COMe, R′ = Cl, R″ = H) or the "hydroxy" quinoline (**1259**; R = CH_2COMe, R′ = OH, R″ = H).[1880] Warming the tetrachloroquinoline (**1259**; R = $CH{=}CCl_2$, R′ = Me, R″ = Cl) with 85% sulphuric acid yields the (dichloroquinolyl)-propanoic acid (**1259**; R = CH_2CO_2H, R′ = Me, R″ = Cl).[1879] Selective hydrolysis is also observed[1878] with the 3-(4-chloroquinolyl)-2-ethoxyindole (**1260**) which, with dilute acid, yields the corresponding 3-(4-chloroquinolyl)oxindole.



1259



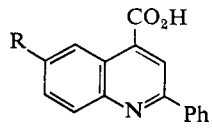
1260



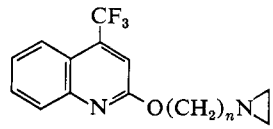
1261

The isomeric 3-(2-chloroquinolyl)-2-ethoxyindole, however, under the same conditions loses both the ethoxy- and the chloro-substituent to give the 2-quinolone (**1261**).

Bass[1924] (on the basis of an earlier observation by Al-tai *et al.*[1072] has prepared 6-hydroxy-2-phenylquinoline-4-carboxylic acid (**1262**; R = OH) in quantitative yield by heating the 6-iodo-derivative (**1262**; R = I) with 35% potassium hydroxide solution at 200 °C/15 atm. for 18 hours. Apparently 6-iodo-2-phenylquinoline does not react under these conditions and the author concludes that the 4-carboxylic acid group is aiding displacement of the iodide ion.



1262



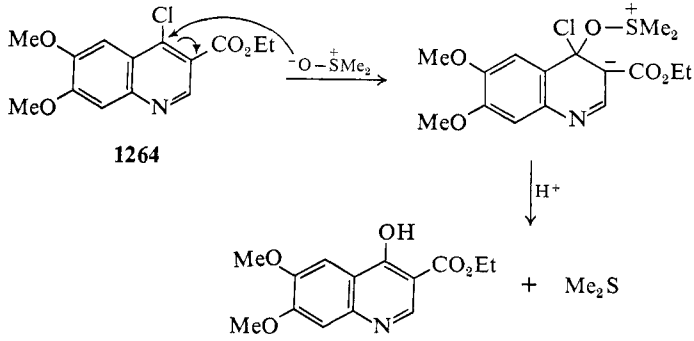
1263

Various 2-[1953] (e.g. **1263**) and 4-alkoxy-substituted[1954] quinolines have been prepared by treating 2- or 4-chloroquinolines with the appropriate alkoxides. In the former case reactions were carried out in boiling tetrahydrofuran and the products appear to have some potential as antiradiation agents.

The pentachlorotetrahydroquinoline (**1181**; R = Cl, R′ = Me) (p. 674) with sodium ethoxide yields 6,8-dichloro-2-ethoxy-4-methylquinoline.[1857] Many 2- and

4-(aryloxy)quinolines have been prepared by condensing 2- and 4-chloroquinolines with phenols.[1873, 1879, 1887, 1955]

Unusual hydroxydechlorination reactions are observed[1872] when 4-chloro-6,7-dimethoxyquinoline-3-carboxylates, e.g. (**1264**), are heated with dimethyl sulphoxide at 100 °C for 2 hours. The reactions fail with analogous "active halogen"-containing compounds such as 1-chloro-2,4-dinitrobenzene, ethyl *o*-chlorobenzoate, and ethyl 2-chloro-5-nitrobenzoate, and also on substituting diphenyl sulphoxide or dimethylformamide for dimethyl sulphoxide as solvent. The author suggests that the dechlorinations arise by way of a nucleophilic attack by the sulphoxide at the 4-position as indicated in Scheme 96.

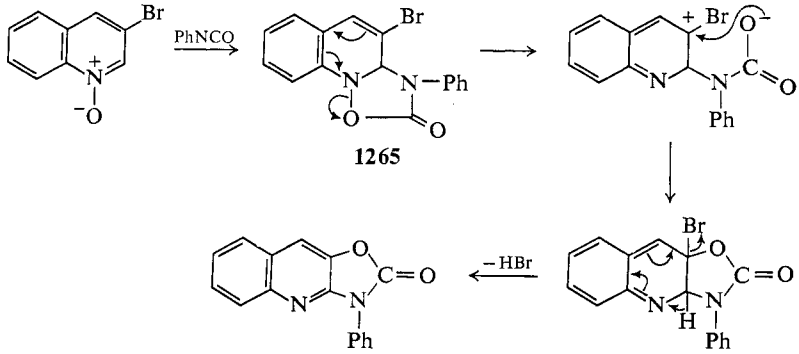


1264

SCHEME 96

A Japanese patent describes the preparation of 8-hydroxyquinoline, as the copper complex, by heating 8-chloroquinoline with diethylenetriaminecopper in 5% aqueous sodium hydroxide at 250–270 °C for 8 hours.[1956]

3-Bromo- and 3-nitro-quinoline *N*-oxides are reported[1957] to undergo an intriguing reaction with phenyl isocyanate in hot (80 °C) dimethylformamide. Initial 1,3-dipolar cycloaddition of isocyanate to yield the cyclic structure (**1265**) is followed by ring opening and nucleophilic attack at the 3-position of the quinoline ring to give the

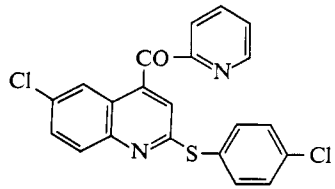


1265 **1266** **1267**

dihydro-oxazoloquinoline (**1266**) which readily loses hydrogen bromide to yield the final product 2(3*H*)-oxo-3-phenyloxazolo[4,5-*b*]quinoline (**1267**). 3,6-Dibromoquinoline *N*-oxide behaves similarly.

Addenda to II.2C.f. Displacement by Nucleophilic Sulphur

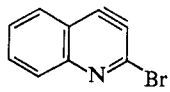
Quinoline-4-thiols have been prepared[1873, 1958] as has the 4-acyl-2-(*p*-chlorophenylthio)quinoline (**1268**),[1887] by treating 2- or 4-chloroquinolines with ethanolic sodium hydrogen sulphide and *p*-chlorothiophenol, respectively.



1268

Addenda to II.2C.h. Displacement Reactions Involving Aryne Intermediates

Peereboom and den Hertog[2061] have recorded the reaction of 3-bromoquinoline *N*-oxide with potassium amide in liquid ammonia; further, den Hertog and Buurman[1959] have extended their earlier investigations[620, 1598, 1602] of the reaction of bromo- and aminobromo-quinolines with potassium amide in liquid ammonia, to include 2,3-, 2,4-, and 3,4-dibromoquinoline. The authors argue that quinolyne (**1269**) is the chief product in all these reactions, and that with ammonia it gives



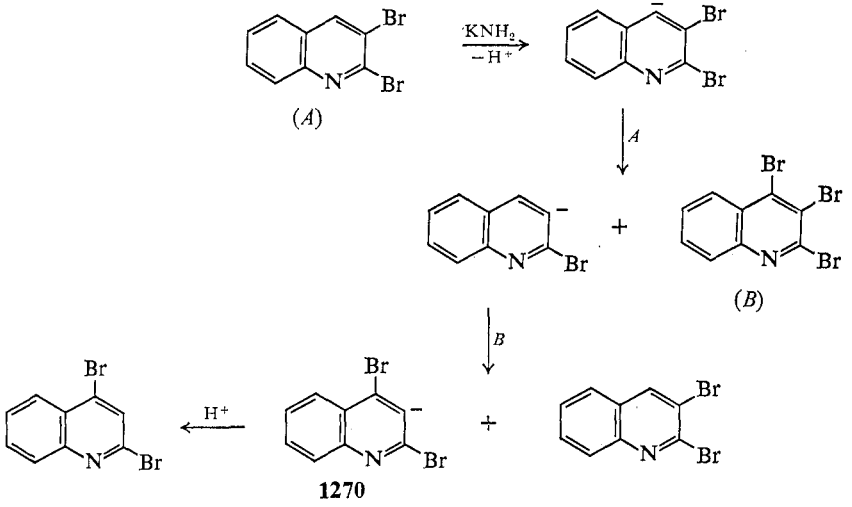
1269

4-amino-2-bromo- and 3-amino-2-bromoquinoline, the former in greater yield. Formation of these aminobromoquinolines explains the presence, in the reaction products, of 3-cyanopyrrole, 4-amino-2-methylquinazoline, and *o*-aminobenzonitrile, since these were isolated previously[1602] after reaction of 3- or 4-amino-2-bromoquinoline with potassium amide (see Scheme 76; p. 591). When 2,3- or 3,4-dibromoquinoline is allowed to react for 5 minutes with potassium amide in ether in the presence of only a small amount of ammonia, isomerization to 2,4-dibromoquinoline is observed; these isomerizations are envisaged as occurring as outlined in Scheme 97 for 2,3-dibromoquinoline.

Evidence for a scheme of this type comes from the isolation of 2,2′,4-tribromo-3,4′-biquinoline (**1271**) (35–40%) during the amination of 2,3-dibromoquinoline. The biquinoline presumably arises by attack of the anion (**1270**) on 2,3-dibromoquinoline as indicated in the Scheme 98.

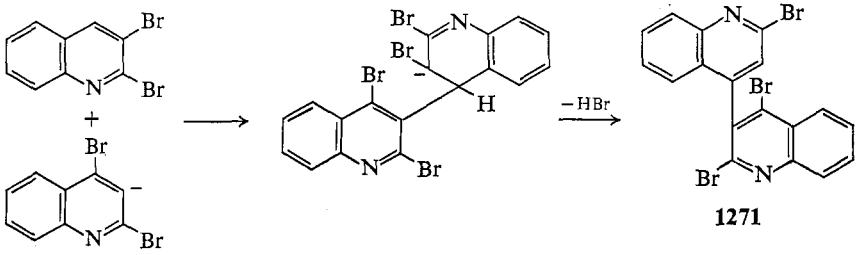
Amination of 3,4-dibromoquinoline gives, in addition to the products already mentioned, 2-amino-3,4-dibromoquinoline (ca. 5%), and (*o*-aminophenyl)acetylene (10%). The origin of these products is not as yet established, although the authors suggest several possibilities.

2-Amino-3-bromoquinoline with potassium amide in liquid ammonia at −33 °C gives mainly 2,3-diaminoquinoline (75%) together with a trace (3%) of the 2,4-diamino-isomer.[1960] In contrast, 3-bromo-2-ethoxy- and 2,3-dibromo-quinoline



1270

SCHEME 97



1271

SCHEME 98

under similar conditions yield 4-amino-2-ethoxyquinoline (95%) and 4-amino-2-bromoquinoline (30%) as the main products. (In the latter reaction the 4-amino-2-bromo-compound reacts further to give 4-amino-2-methylquinazoline (55%) and 2-aminobenzonitrile (5%)—see Section II.2C.h; Scheme 76.) All these reactions are thought to proceed via a 3,4-dehydroquinoline.

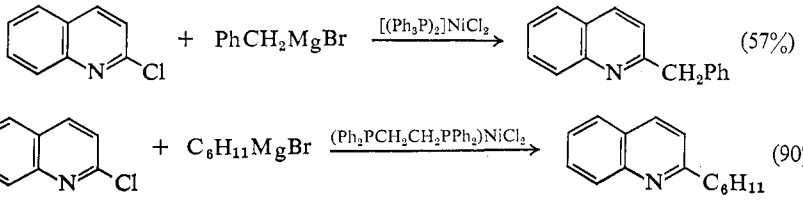
6-Chloroquinoline reacts with potassium amide (4 mol) in diethyl ether at −33 °C to give 6-amino- (50.5%) and 5-amino-quinoline (26.2%).[2062] 6-Bromoquinoline reacts similarly.

Addenda to II.2D. Reaction with Organometallic Compounds

On treatment with *n*-butyl-lithium in diethyl ether at −70 °C, and then with dimethylformamide in tetrahydrofuran, 5-bromo-8-methyl-3-phenylquinoline yields 5-formyl-8-methyl-3-phenylquinoline.[1898] If the reaction is carried out in the presence of ethanol rather than dimethylformamide, debromination to give 8-methyl-3-phenylquinoline is observed.

Recently a method of alkylating haloquinolines by means of Grignard reagents in the presence of nickel–phosphine complexes has been reported.[1961] For Grignard reagents possessing an sp^3-hybridized β-carbon centre (e.g. cyclohexylmagnesium

bromide), dichloro-1,2-bis(diphenylphosphino)ethanenickel(II) [$(Ph_2PCH_2CH_2PPh_2)_2NiCl_2$] is the recommended catalyst, while with Grignard reagents derived from benzyl and allyl halides (i.e. an sp^2-β-carbon centre) the catalyst of choice is the dichlorobis(triphenylphosphine)nickel(II) [$(Ph_3P)_2NiCl_2$]. The reaction fails completely with *n*-butylmagnesium halide, quinoline being the only product. Examples of these reactions are annexed. The authors also found that 4,7-dichloroquinoline may



be selectively alkylated at the 4-position (77%) with methylmagnesium bromide, and that alkylation is also possible with the generally unreactive 3-haloquinolines. For example, 3-bromoquinoline gives 3-methylquinoline (65%) accompanied by a trace of the 2,3-dimethyl compound.

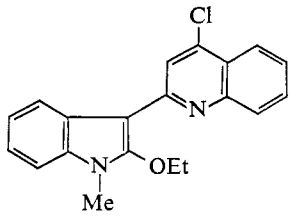
Addenda to II.2F. Nitration

6-Chloro-8-methylquinoline is nitrated at the 5-position (82%),[1896] while 5,7-diiodoquinoline in a mixture of fuming nitric acid and concentrated sulphuric acid gives the 8-nitro-derivative in 95% yield.[1888] 5-Iodoquinoline *N*-oxide is nitrated at the 4-position in 43% yield.[1886] Nitration of 4,5,7,8-tetrachloroquinoline in "mixed-acids" at 80 °C yields the 6-nitro-derivative.[1962]

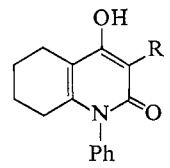
Addenda to II.2H. Dehalogenation

When heated, the pentachloroquinoline (**1181**; R = Cl, R′ = Me) (p. 674) loses hydrogen chloride to give 2,6,8-trichloro-4-methylquinoline, whereas with hydrogen and palladium–charcoal complete dehalogenation to give 4-methylquinoline is observed.[1857] Similarly the hexachloroquinoline (**1180**; R = Cl, R′ = Me) (p. 674) with hydrogen and palladium–charcoal yields 2-methylquinoline. 2,6,8-Trichloro-4-methylquinoline with zinc or tin and hydrochloric acid is selectively dehalogenated to give 6,8-dichloro-4-methylquinoline.

The 2-chloro-3-(2-chloro-4-quinolyl)indole (**1192**) (p. 678) with palladium–charcoal and hydrogen suffers dechlorination of both the quinoline and the indole nucleus.[1878] Under the same conditions the 3-(4-chloro-2-quinolyl)-2-ethoxyindole (**1272**) undergoes dechlorination, whereas with lithium aluminium hydride only the 2-ethoxy-group is lost.



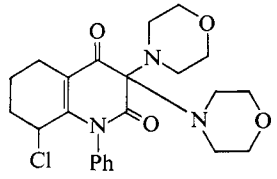
1272



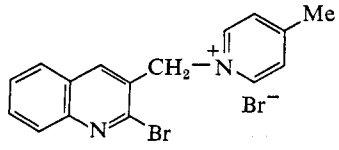
1273

Reduction of the tri- and penta-chloro-2,4-dioxoquinolines (**1186**) and (**1187**) (p. 676) with zinc and acetic acid yields in both cases 3-chloro-5,6,7,8-tetrahydro-4-hydroxy-1-phenyl-2-quinolone (**1273**; R = Cl).[1867]

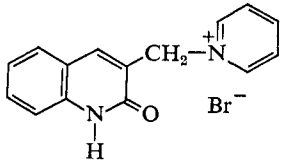
The aminal (**1274**), formed by condensing the trichloro-compound (**1186**) with morpholine, on reduction with sodium dithionite yields the 2-quinolone (**1273**; R = morpholino), whereas with zinc and hydrochloric acid the dihydroxy-derivative (**1273**; R = OH) is obtained.



1274



1275



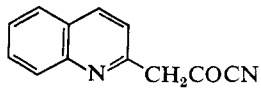
1276

1-(2-Bromo-3-quinolylmethyl)-4-methylpyridinium bromide (**1275**) on photolysis in hydrobromic acid loses bromine to give the 2-quinolone (**1276**).[1963] Debromination appears to be a light-induced process since no hydrolysis is observed when the bromo-compound is stirred with hydrobromic acid for 26 hours in the absence of ultraviolet radiation.

Photodebromination of 3-, 6-, 7-, and 8-bromoquinoline, and of 4-bromo-2-methylquinoline, has recently been reported.[1964] This process has been studied in some detail and the reaction appears to require the presence of both a hydrogen-donor and a proton-donor. Aqueous sodium hydroxide(0.1M)-methanol mixture appears to be the reaction medium of choice.

Addenda to IV.1. Side-chain Halogenation

2-(Trichloromethyl)quinoline may be prepared in high yield (88.3%) by heating 2-methylquinoline, in acetic anhydride solution in the presence of sodium acetate, with chlorine in acetic acid at 95 °C.[1965] In the absence of acetic anhydride the yield drops to 59.5%. 2-Quinolylacetyl cyanide (**1277**) with bromine in chloroform at

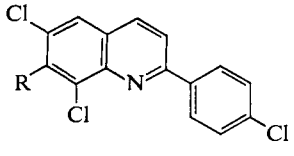


1277

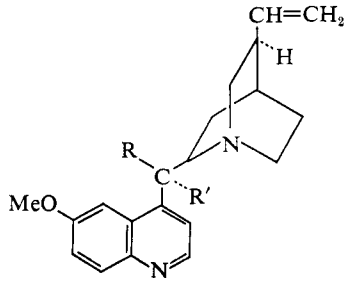
room temperature gives 2-(tribromomethyl)quinoline, whereas with potassium hypobromite 2-(dibromomethyl)quinoline is obtained.[1966]

6-Methyl-2-phenylquinoline reacts smoothly with bromine in acetic acid to give 6-(bromomethyl)-2-phenylquinoline.[1967] 2-(Tribromomethyl[2-^{13}C]quinoline has been prepared from 2-methyl[2-^{13}C]quinoline using bromine in acetic acid–sodium acetate mixture.[1968]

6,8-Dichloro-2-(*p*-chlorophenyl)-7-methylquinoline (**1278**; R = Me) with *N*-bromosuccinimide in carbon tetrachloride under ultraviolet irradiation is converted into the (bromomethyl) derivative (**1278**; R = CH_2Br).[1895]



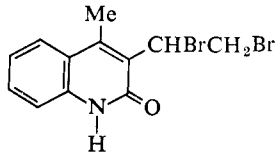
1278



1279

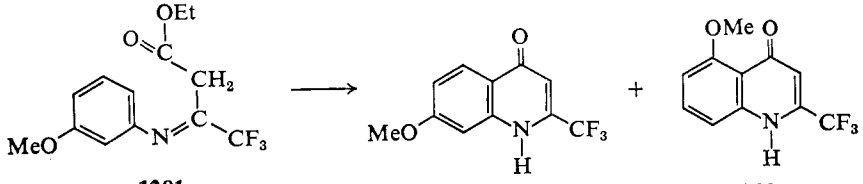
Early workers demonstrated that cinchona alkaloids, e.g. quinine (**1279**; R = OH, R′ = H), on treatment with phosphorus pentachloride are readily converted into the chloro-derivatives, e.g. (**1279**; R = Cl, R′ = H).[1969] More recently[1970] optical rotatory dispersion studies have shown that the chlorodehydroxylation may be carried out by using thionyl chloride and that reaction is accompanied by inversion of configuration at the reacting centre, i.e. the product has the configuration shown (**1279**; R = H, R′ = Cl).

4-Methyl-3-vinyl-2-quinolone with bromine in chloroform solution yields the dibromo-2-quinolone (**1280**).[1971]



1280

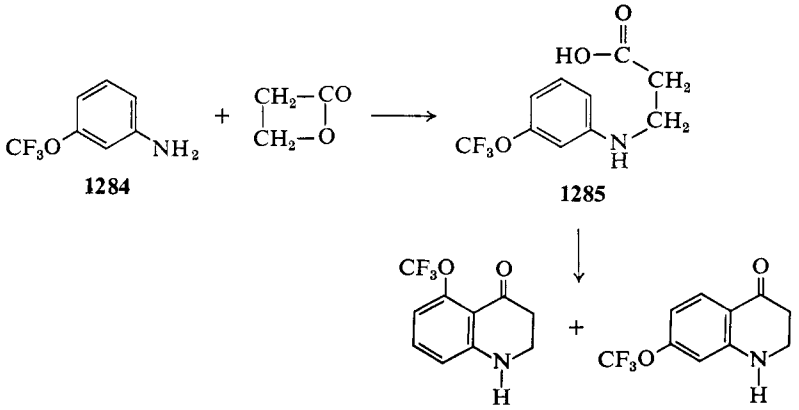
There is continuing interest in the synthesis of (trifluoromethyl)-substituted quinolines and several 2-(trifluoromethyl)-4-quinolones have been prepared by treating arylamines with ethyl (trifluoroaceto)acetate in the presence of polyphosphoric acid.[1874, 1875] *m*-Anisidine condenses with ethyl (trifluoroaceto)acetate to yield the anil (**1281**) which cyclizes in boiling diphenyl ether to give only the 7-methoxy-2-(trifluoromethyl)-4-quinolone (**1282**).[1972] However, when *m*-anisidine is condensed with ethyl



1281 **1282** **1283**

(trifluoroaceto)acetate in the presence of hot polyphosphoric acid a mixture of the 5- and 7-methoxy-2-(trifluoromethyl)-4-quinolones (**1282**) and (**1283**) is formed (31% and 43.5% yield, respectively). 4-(Trifluoromethyl)-2-quinolone has also been prepared.[1953]

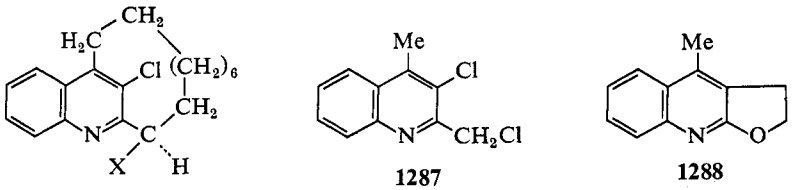
Several 1,2,3,4-tetrahydro-4-oxoquinolines bearing trifluoro-methyl- and trifluoro-methoxy-groups at the 5-, 6-, 7-, and 8-positions have been synthesized by condensing the corresponding arylamine (e.g. **1284**) with propiolactone in acetonitrile, and then cyclizing the resulting 3-(arylamino)propanoic acid (e.g. **1285**) with polyphosphoric acid.[1876, 1877]



1284 **1285**

2,4-Dimethylquinoline *N*-oxide reacts with *p*-toluenesulphonyl chloride in chloroform solution to give 2-(chloromethyl)-4-methylquinoline.[1973]

Parham and his co-workers[1974] have carried out further studies on the reactions of quinolinophane *N*-oxides. They have investigated the action of several acyl, sulphonyl, and phosphonyl halides with the 3-chloro-2,4-[10]quinolinophane (**1033**; R = Cl, R′ = H) (p. 647) and find that only in one case (with an excess of phosphorus oxychloride) is chlorination (albeit in low yield; 1–2%) at the 2-methylene group observed. The authors point out that the model compound, 3-chloro-2,4-dimethyl-quinoline *N*-oxide, with *p*-toluenesulphonyl chloride in chloroform yields the 2-(chloromethyl) derivative (**1287**) (74%), whereas the cyclophane yields exclusively the *syn*-tosylate (**1286**; X = *p*-$MeC_6H_4SO_2O$).



1286 **1287** **1288**

Addenda to IV.2C.a–e. Nucleophilic Displacement of Side-chain Halogen

2-(Chloromethyl)-4-methylquinoline reacts with potassium cyanide[1973] and with pyridine[1975] to give 2-(cyanomethyl)-4-methylquinoline and *N*-(4-methyl-2-quinolylmethyl)pyridinium chloride, respectively. Many *N*-(2-halo-3-quinolylmethyl)-pyridinium bromides (e.g. **1275**) have been prepared by Lyle and his co-workers[1963]

in their studies on the photocyclization of 1-(halomethyl)pyridinium salts. The quaternary salts were prepared by treating the 3-(bromomethyl)-2-haloquinoline with the appropriate pyridine in sulpholane at room temperature for varying periods depending on the nature of the pyridine base employed.

2-(Bromomethyl)quinoline condenses readily with thioglycollic acid and with 2-hydroxyethanethiol in the presence of base to give the corresponding 2-quinolylmethylthio-derivatives.[1976]

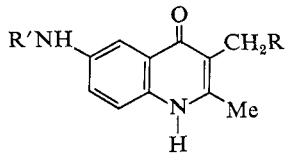
7-(Bromomethyl)-6,8-dichloro-2-(*p*-chlorophenyl)quinoline (**1278**; R = CH_2Br) reacts with sodium methoxide and 2-nitropropane (a method devised by Hass and Bender[1977]) to give the 7-formyl compound (**1278**; R = CHO) in 80% yield.[1895]

The (dibromoethyl)-2-quinolone (**1280**), on treatment with boiling triethylamine, undergoes cyclization and dehydrobromination to give the furoquinoline (**1288**).[1971]

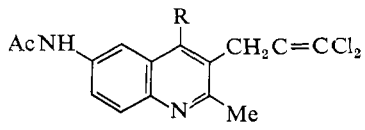
The chloroquinine (**1279**; R = H, R′ = Cl) with sodium thiosulphate in aqueous methanol gives the hemithiosulphuric acid derivative (**1279**; R = H, R′ = $S.SO_2OH$) in 18–25% yield.[1978] The authors attribute the poor yield to difficulty in displacing the sterically hindered chlorine atom.

Severe steric hindrance to S_N2 displacement has been demonstrated by Parham and his co-workers for the *syn*- and *anti*-isomers of the bromo-2,4-[10]quinolinophane (**1286**; X = Br).[1979] The isomers are recovered virtually unchanged when treated with lithium chloride in dimethylformamide or glacial acetic acid, or with thiourea in ethanol. Sodium methoxide gives mainly the debrominated material, whereas with silver acetate in acetic acid stereospecific S_N1 replacement of bromide to give the corresponding acetates is observed. In contrast, reaction of the *syn*-isomer with hot formic acid yields the *syn*-alcohol (60%) together with starting material containing some 10% of epimeric bromo-compound.[1979, 1980] The *anti*-bromo-isomer under the same conditions yields rather more epimer and a mechanism involving a tight ion-pair is proposed to account for the reaction.

The dichloroallylquinolone (**1289**; R = $CH{=}CCl_2$, R′ = Ac) on hydrolysis with dilute sulphuric acid yields the 2-(6-amino-3-quinolyl)propanoic acid (**1289**; R = CH_2CO_2H, R′ = H).[566, 1981]



1289



1290

Treatment of the 4-quinolone with phosphorus oxychloride yields the 4-chloroquinoline (**1290**; R = Cl)[1981] which with phenol condenses to give the 4-phenoxy-derivative (**1290**; R = PhO).[1982]

Haloquinolines prepared as described in the Addenda are collected in Table 39.

TABLE 39. Haloquinolines Prepared as Described in the Addenda

Haloquinoline	M.p. (°C)	Yield (%)	References
ALKOXY-SUBSTITUTED			
2-Chloro-6-methoxy-4-methyl-	144.5	87	1874
2-Chloro-6-methoxy-8-nitro-			2029
2,4-Dichloro-8-methoxy-	137*		1527

* Previously reported[586] as 92 °C.

TABLE 39 (*cont.*)

Haloquinoline	M.p. (°C)	Yield (%)	References
Et 4-chloro-6,7-methyleneoxy-3-carboxylate			2068
4-Chloro-5-methoxy-2-(trifluoromethyl)-	94	91	1874
4-Chloro-5,8-dimethoxy-2-(trifluoromethyl)-	140.5	89	1875
4-Chloro-6,7-dimethoxy-2-(trifluoromethyl)-	145	90	1875
4-Chloro-8-methoxy-2-(trifluoromethyl)-	92	95	1874, 1875
4-Chloro-5-(trifluoromethoxy)-	40		1876, 1877
4-Chloro-7-(trifluoromethoxy)-	40		1876, 1877
4-Chloro-6,7-diethoxy-	200	15	1873
4-Chloro-3-(2-chloroethyl)-6,7-diethoxy-2-methyl-	159	48	1873
Et 4-chloro-6,7-dimethoxy-3-carboxylate	160, 173.5	46	1872, 1873
Et 4-chloro-6-(*n*-decyl)-7-ethoxy-3-carboxylate	87	55	1872
4-Chloro-8-(trifluoromethoxy)-	Oil		1877
Me 4-chloro-7-benzyloxy-6-(*n*-butyl)-3-carboxylate	95	63	1872
Et 4-chloro-6,7-di-isobutoxy-3-carboxylate	103	55	1872
Et 4-chloro-6-(*n*-decyloxy)-7-ethoxy-3-carboxylate	83		1871
4-Chloro-8-methoxy-2-methyl-3-(*n*-propyl)-			2075
4-Chloro-6-methoxy-2-phenyl-	109		2076
5-Chloro-8-methoxy-		100	1858
5-Bromo-8-methoxy-		100	1858
6-Chloro-2-methoxy-3-methyl-4-phenyl-	255	60	1920
5,7-Dichloro-8-methoxy-		100	1858
5,7-Dibromo-8-methoxy-		63	1858
5,7-Di-iodo-8-methoxy-		95	1858
7-Iodo-8-methoxy-	113	100	1858
HYDROXY-SUBSTITUTED			
5-Fluoro-8-hydroxy-2-methyl-	58	37	1864
5,7-Difluoro-8-hydroxy-	172		1856
5,7-Dichloro-8-hydroxy-			2026
3-Chloro-4-hydroxy *N*-oxide	259	21	2098
4-Bromo-3-hydroxy-			2074
4-Chloro-3-hydroxy-			2074
5-Chloro-8-hydroxy-2-methyl-	64	85	1864, 1900
5-Chloro-7-fluoro-8-hydroxy-	170	5.5	1856
5-Bromo-8-hydroxy-2-methyl-	68		1864
5-Bromo-7-fluoro-8-hydroxy-	171.5	88	1856
5-Bromo-7-chloro-8-hydroxy-	201	60	1856
5-Bromo-8-hydroxy-7-iodo-	203 d	85	1856
8-Hydroxy-5-^{131}iodo-		40	2031
8-Hydroxy-5-iodo-2-methyl-	152	71	1864
7-Fluoro-8-hydroxy-5-iodo-	169	95	1856
7-Bromo-8-hydroxy-5-iodo-	204 d*	85	1856

* Previously reported[64] as 146 °C.

TABLE 39 (*cont.*)

Haloquinoline	M.p. (°C)	Yield (%)	References
5,6,7-Tribromo-8-hydroxy-	190	92	1858
6-Bromo-8-hydroxy-	145	33	1858
7-Fluoro-8-hydroxy-2-methyl-	83	1.7	1864
7-Chloro-5-fluoro-8-hydroxy-	172	61	1856
7-Chloro-8-hydroxy-2-methyl-	118	42	1864
7-Bromo-5-fluoro-8-hydroxy-	172	91	1856
7-Bromo-8-hydroxy-2-methyl-	136	57	1864
8-Hydroxy-7-iodo-2-methyl-	89	56	1864
2-QUINOLONES			
3-Chloro-4-hydroxy-6-methyl-	296	68.5	1863
3-Chloro-4-hydroxy-6-methoxy-	268	60.5	1863
3-Chloro-4-hydroxy-1-phenyl-	260	70	1867
3-Chloro-4-hydroxy-6,7-dimethyl-	228	69.4	1863
3-Chloro-5,6,7,8-tetrahydro-4-hydroxy-1-phenyl-	220	81	1867
3-Chloro-5,7-dimethyl-4-phenyl-			2065
3-Chloro-1-ethyl-5,7-dimethyl-4-phenyl-			2065
3-Chloro-4,8-dimethyl-	205	70.6	1863
3-Chloro-1-isopropyl-4-phenyl-			2065
3-Chloro-1,2,3,4-tetrahydro-4-phenyl-	159	90	1927
3-Chloro-1,2,3,4-tetrahydro-4-(*p*-methoxyphenyl)-		40	1927
3,4-Dichloro-		39	1868
3,8-Dichloro-6,7-dimethyl-			2065
3,8-Dichloro-4-hydroxy-	242	95	1867
3-Bromo-4-phenyl-	230	65	1908
3-Bromo-6-methyl-4-phenyl-	290	85	1908
3-Bromo-4-(*p*-bromophenyl)-	312	60	1908
3-Bromo-4-(*p*-nitrophenyl)-	320	65	1908
3-Bromo-4,6-dimethyl-	282	67.7	1862, 1863
3-Bromo-4,8-dimethyl-	255	92	1862, 1863
3-Bromo-4,6,8-trimethyl-	265	74.8	1863
3-Bromo-6-ethoxy-4-methyl-	252	80	1863
3-Bromo-4-methyl-	290	87	1862
3-Bromo-8-methoxy-4-methyl-	184	63	1862
3-Bromo-6-chloro-4-methyl-	232	62	1862
3-Bromo-4-hydroxy-6-methyl-	260	75.6	1863
3-Bromo-4-hydroxy-7-methyl-	237	75.4	1863
3-Bromo-6-chloro-4-hydroxy-	262	61.5	1863
3-Bromo-4-hydroxy-6-methoxy-	256	62.8	1863
3-Bromo-4-hydroxy-6,7-dimethyl-	255	73.6	1863
3-Iodo-4-methyl-	291	75	1863
3-Iodo-4,8-dimethyl-	232	63.6	1863
3-Iodo-4,6-dimethyl-	280	73.3	1863
3-Iodo-4,6,7-trimethyl-	273	68.4	1863
3-Acetamido-6-chloro-1-methyl-4-phenyl-	231		1928
7-Chloro-4-hydroxy-3-(2-phthalimidoethyl)-	> 270	94	1985
8-Chloro-4-methyl-	212	12	2070

TABLE 39 (*cont.*)

Haloquinoline	M.p. (°C)	Yield (%)	References
4-QUINOLONES			
3-Bromo-2-methyl-	277	70	1862
Et 6-bromo-2-carboxylate	257		2071
3-Iodo-1-methyl-	199	85	1870
Et 2-(*tert*-butyl)-6-chloro-3-carboxylate	266	63	1883
Et 2-(1-adamantyl)-6-chloro-3-carboxylate	318	73	1883
Me 6-chloro-5,8-dihydroxy-2-carboxylate	>300		1903
Me 6-chloro-5,8-dimethoxy-2-carboxylate	229		1903
6-Iodo-3-carboxylic acid	298		1886
6,8-Dichloro-1-ethyl-3-carboxylic acid	208.5	12	1904
Et 2-adamantyl-6,8-dichloro-3-carboxylate	160	74	1883
6,8-Dichloro-3-methyl-2-(trifluoromethyl)-3-carboxylic diethylamide	146	35	1930
6,8-Dibromo-3-methyl-2-(trifluoromethyl)-3-carboxylic diethylamide	146	39	1930
8-Chloro-3-carboxylic acid	242	83	1904
8-Chloro-2-methyl-	230	26	2070
8-Chloro-5-methyl-3-carboxylic acid	292	76	1904
Me 8-chloro-5-nitro-2-carboxylate	198		2071
8-Chloro-5-methoxy-2-(trifluoromethyl)-	219	95	1972
8-Chloro-1-ethyl-3-carboxylic acid	163	43	1904
Et 8-iodo-3-carboxylate	236		1877
ACYL-SUBSTITUTED AND CARBOXYLIC ACIDS			
2-Chloro-3-formyl-4-phenyl-	193	39	1885
Et 4-chloro-2-carboxylate			1986
Et 4-chloro-7-(4-pyridyl)-3-carboxylate			2072
4-Chloro-7-carboxylic acid	>250		1877
4-Chloro-2-phenyl-3-carbonyl chloride	103		2080
5-Chloro-3-ethyl-2-(trifluoromethyl)-8-carboxylic acid	147	48	1931
Et 5,6-dichloro-8-carboxylate	77	81	1893
5,6-Dichloro-8-carboxylic acid	223	69.5	1893
6,8-Dichloro-2-(1-adamantyl)-4-carboxylic acid			2042
5-Bromo-6-chloro-8-carboxylic acid	251	88	1893
3-Acetyl-6-fluoro-4-methyl-			1983
3-Acetyl-6-chloro-4-methyl-			1981
Me_2 6-chloro-4-phenyl-2,3-dicarboxylate	163	78	1921
Me_2 6-bromo-4-phenyl-2,3-dicarboxylate	170.5	70	1921
6-Iodo-2-phenyl-4-carboxylic acid	330	83	1924
8-Chloro-2-(2-pyridyl)-4-carboxylic acid			1984, 2043
NITRO-SUBSTITUTED			
2-Chloro-6-methoxy-5-nitro-		56.7	1891
4-Chloro-6-methoxy-2-methyl-3,5-dinitro-	210		2073
4-Chloro-3-nitro-	122	95	1951
4-Chloro-5-nitro *N*-oxide	148	100	1894
4-Chloro-2-methyl-6-nitro-	142		2076
4-Chloro-2-phenyl-6-nitro-	169		2076
4-Chloro-7-nitro-	173		1886
4-Chloro-2-methyl-7-nitro-	94		2076
4-Chloro-2-methyl-8-nitro-	113		2076
4-Bromo-2-(*tert*-butyl)-6-nitro-			1882
5-Iodo-4-nitro-	159		1886

TABLE 39 (*cont.*)

Haloquinoline	M.p. (°C)	Yield (%)	References
5-Iodo-4-nitro *N*-oxide	237 d	43	1886
5,7-Difluoro-8-nitro-	144		1888
5,7-Di-iodo-8-nitro-	172	95	1888
8-Chloro-5,7-dinitro-	158	90	1882
AMINO-SUBSTITUTED			
4-Amino-3-chloro *N*-oxide	220	88	2098
4-Amino-3-chloro-2-methyl *N*-oxide	222	79.5	2098
4-Amino-3-chloro-5-methyl *N*-oxide	218	54	2098
2-Amino-6-chloro-4-phenyl-	143	95	1915
3-Amino-6-chloro-4-phenyl-	162		1928
2-Amino-6-chloro-3-methyl-4-phenyl-	159	69	1915
2-Amino-6-chloro-3,4-diphenyl-	234	43	1915
2-Amino-6-chloro-3-cyano-4-phenyl-	270	95	1915
6-Chloro-2-dimethylamino-4-methyl-	83	40	2047
4-Amino-3-bromo *N*-oxide	203	71	2098
4-Amino-6-iodo-	223.5		1886
5,8-Dibromo-6-nitro-	161	67	2034
6,8-Dichloro-4-(diethylamino)-3-methyl-2-(trifluoromethyl)-	Oil	94	1930
6,8-Dibromo-4-(diethylamino)-3-methyl-2-(trifluoromethyl)-	Oil	82	1930
7-Chloro-4-(diethylamino)-3-methyl-2-(trifluoromethyl)-	74	85	1930
4-Amino-7-iodo-	198		1886
SULPHUR-CONTAINING SUSBTITUENTS			
4-Chloro-7-(methylthio)-	72		1877
4-Chloro-7-(methanesulphonyl)-	176		1877
8-Hydroxy-5-iodo-2-methyl-7-sulphonic acid	280 d	95	1864
6-Chloro-4-hydroxy-3-sulphonamide			1923
6-Chloro-(2-methylthio)-3-nitro-4-phenyl-	151	52	1922
7-Chloro-8-hydroxy-2-methyl-5-sulphonic acid	307 d	91	1864
7-Bromo-8-hydroxy-2-methyl-5-sulphonic acid	271 d	85	1864
7-Iodo-8-hydroxy-2-methyl-5-sulphonic acid	270 d	52	1864
MISCELLANEOUS			
2-Chloro-6-cyano-5,6,7,8-tetrahydro-6-phenyl-			2030
2-Chloro-4-(trimethylsilyl)-	69		2079
6-Chloro-2-cyano-	199		1892
6-Chloro-2-cyano-4-methyl-		41	1892
4-Chloro-3-cyano-2-phenyl-	214		2080
6-Acetamido-4-chloro-3-(3,3-dichloroallyl)-2-methyl-			1980, 1981
6-Acetamido-3-(3,3-dichloroallyl)-2-methyl-4-quinolone			556, 1981
Bis-(6-chloro-2,4-dihydroxyquinolyl)-methane	>400	52.5	1902
Bis-(8-chloro-2,4-dihydroxyquinolyl)-methane	>400	48.7	1902

VI. Tables of Haloquinolines

TABLE 40. Monohaloquinolines

Substituent	Compound M.p. (°C)[a]	Compound B.p. (°C/mm)	Compound *n*, *d*	Derivatives, m.p. (°C)	References
2-Fluoro-		133/30 75/2	n_D^{25} 1.5827–33		672, 679, 682, 749
3-Fluoro-		198–200/760 102/15 97/10	n_D^{25} 1.5902 d_4^{25} 1.194	Picrate, 185	672, 681, 683, 684
4-Fluoro-		119/30			672
5-Fluoro-		123/30 108/15	n_D^{25} 1.5916 d_4^{25} 1.197	Picrate, 200	672, 685, 870
6-Fluoro-		124/30	n_D^{25} 1.5908 d_4^{25} 1.200	Picrate, 219	672, 714, 846, 1899
7-Fluoro-		129/30 112/15	n_D^{25} 1.5845	Picrate, 229 Nitrate, 141	672, 870, 871
8-Fluoro-		148/30	n_D^{25} 1.6028 d_4^{25} 1.215	Picrate, 172	672, 678, 871, 1899
2-Chloro-	38	266/753 91/2 133/9 154/22	$n_\alpha^{56.3}$ 1.6125 n_D^{35} 1.62923 $d_4^{56.3}$ 1.215 d_4^{35} 1.2351	Picrate, 122 MeCl, 135	345, 622, 628, 629, 630, 634, 663, 665, 670, 733, 759, 785, 790, 835, 1140, 1213, 1219, 1990
3-Chloro-		255/743 97/7 141/15 85/0.5	n_D^{20} 1.63652 d_4^{20} 1.2490	Picrate, 189; MeI, 276; $H_2Cr_2O_7$, 126; H_2SO_4, 150; H_2PtCl_6, >300; HCl, 210	116, 236, 704, 1121, 1143, 1162, 1219
4-Chloro-	34	261/744 131/15 80/0.08	n_D^{20} 1.63609 d_4^{20} 1.2627	Picrate, 218; HCl, 242; $H_2Pt_2Cl_6$, 279; MeI, 208 d; EtI, 191 d; $H_2Cr_2O_7$, 75	241, 430, 431, 432, 433, 434, 481, 666, 700, 701, 731, 758, 759, 760, 785, 786, 789, 790, 799, 801, 807, 841, 1126, 1219, 1232, 1677, 2082

5-Chloro-	45	256/756 127.5/15 90/1	$n_\alpha^{57.6}$ 1.6108 $d_4^{57.6}$ 1.2158	H_2O, 42; Picrate, 223; Oxalate, 145; $H_2Cr_2O_7$, 121; MeI, 173; MeCl, 122; HNO_3, 161; $HClO_4$, 198	31, 32, 269, 690, 698, 699, 702, 820, 852, 866, 870, 1213, 1219, 1626
6-Chloro-	41 45	262/740 159/45 127/10	$n_\alpha^{56.4}$ 1.6110 $d_4^{56.4}$ 1.2146	Picrate, 215, 220.5; MeI, 248, 264; EtI, 169; HNO_3, 176; $H_2Cr_2O_7$, 168; p-$MeC_6H_4SO_3H$, 143; MeCl, 264	281, 730, 843, 852, 871, 876, 879, 881, 894, 1213, 1219, 1991, 1992, 1993
7-Chloro-	32	268/760 147.5/15 128/4	$n_\alpha^{57.6}$ 1.61923 n_D^{20} 1.63559 $d_4^{57.6}$ 1.2158 d_4^{20} 1.2503	Picrate, 222; $H_2Cr_2O_7$, 178 d; HNO_3, 199; Oxalate, 155; $H_2Pt_2Cl_6$, 253; MeI, 250 d; MeCl, 213 d	122, 268, 269, 698, 699, 852, 866, 870, 871, 942, 1136, 1213, 1219, 1994
8-Chloro-		288/760 171.5/26	$n_\alpha^{14.3}$ 1.6408 n_D^{20} 1.64403 $d_4^{14.3}$ 1.2834 d_4^{20} 1.2780	Picrate, 178; MeI, 165; HNO_3, 165; HCl, 97; $H_2Cr_2O_7$, 161; MeCl, 140; HBr, 223 d	31, 32, 844, 852, 871, 878, 881, 896, 1213, 1219, 1560, 1561, 1699
2-Bromo-	49.5	163/16.5		MeI, 210 d	2, 13, 605, 606, 622, 631
3-Bromo-	13 16	276/760 128/6 103.5/0.1	n_D^{20} 1,6652, 1.6645	HCl, 213; $H_2Cr_2O_7$, 145; HNO_3, 180; H_2SO_4, 183; HBr, 274; EtBr, 216; Picrate, 190; Oxalate, 107	2, 3, 10, 13, 21, 97, 99, 101, 109, 171, 234, 236, 280, 286, 287, 295, 299, 300, 683, 841, 1861, 2028
4-Bromo-	33	142/7 105–110/2	n_D^{23} 1.6662	MeI, 270 d; Picrate, 215	13, 171, 314, 608, 731, 807
5-Bromo-	48	280/756 105.7/1.2		Picrate, 238; HNO_3, 193 d, 186, $H_2Cr_2O_7$, 135; Oxalate, 152; MeI, 205	6, 7, 9, 13, 24, 176, 178, 287, 448, 669, 699, 715, 724, 725, 841, 867, 870, 1603

TABLE 40 (*cont.*)

Substituent	Compound M.p. (°C)	Compound B.p. (°C/mm)	Compound *n*, *d*	Derivatives, m.p. (°C)	References
6-Bromo-	24	284/760 164/22	n_D^{25} 1.6605	HBr, 256; MeI, 278; HCl, 213; $H_2Cr_2O_7$, 179; *p*-$MeC_6H_4SO_3H$, 152; Picrate, 217; Oxalate, 62	13, 287, 836, 841, 843, 871, 881, 1991
7-Bromo-	35.5	288/753		HNO_3, 199, 206; HCl, 213; $H_2Cr_2O_7$, 202; Oxalate, 168; Picrate, 238; MeI, 240	13, 287, 448, 699, 709, 715, 725, 841, 867, 870, 1603
8-Bromo-		304/760 310/760 d 113/0.5 166/18	n_D^{20} 1.6674	Picrate, 168; $H_2Cr_2O_7$, 168; HCl, 166–170; MeI, 281 d; EtI, 183 d; $H_2Pt_2Cl_6$, 252	6, 7, 13, 189, 287, 669, 717, 822, 823, 824, 841, 871, 881
2-Iodo-	53			EtI, 205 d; MeI, 212; Picrate, 143	586, 634, 642, 663, 732, 733, 734, 735, 737, 1993
3-Iodo-	62			MeI, 290 d; Picrate, 188.5	233
4-Iodo-	95.5 100			MeI, 251 d, 259 d; EtI, 243 d	314, 701, 731, 1603
5-Iodo-[b, c]	100 105			Picrate, 236; MeI, 245; HCl, 235	220, 221, 222, 728, 729, 870
6-Iodo-[b]	88 91			MeI, >300; HCl, 210	147, 690, 729, 1613
7-Iodo-[b]	103	179/10		HNO_3, 203 d	729, 870
8-Iodo-	36			MeI, 200; Picrate, 171	221, 222, 690, 1603

[b] Isotopically (^{131}I) labelled 5-, 6-, and 7-iodoquinoline have been prepared; see ref. 1886.

[c] Ref. 870 suggests that the so-called 7-iodoquinoline, reported in ref. 729, is in fact the 5-iodo-isomer.

TABLE 41. Monohalomonoalkylquinolines

Substituents	M.p. (°C) and/or b.p. (°C/mm)	Derivatives, m.p. (°C)	References
2-Fluoro-4-methyl-	140/16		656
3-Fluoro-2-methyl-	56		675
4-Fluoro-2-methyl-	40 114/16		656, 676
5-Fluoro-2-methyl-[a]			890
6-Fluoro-2-methyl-	51, 59		675, 1995
6-Fluoro-4-methyl-	45 135/23	Picrate, 231	1995, 1996
7-Fluoro-2-methyl-	56 120/15	H_2O, 38; HNO_3, 137	675, 890
8-Fluoro-2-methyl-		Picrate, 175	675
2-Chloro-3-methyl-	84, 90		658, 1749
2-Chloro-3-ethyl-	73		1997
3-Benzyl-2-chloro-	75		1655
4-(*n*-Butyl)-2-chloro-	72		2079
2-Chloro-4-ethyl-	77		643
2-Chloro-7-isopropyl-		$H_2Pt_2Cl_8$, 138	1651
2-Chloro-4-methyl-	59, 63 296/760		111, 346–350, 356, 428, 666, 1747, 1925
2-Chloro-5-methyl-			1140
2-Chloro-6-methyl-	115	MeCl, 153	259, 630, 631, 637, 640, 641, 642, 663
2-Chloro-7-methyl-	81		652, 1140, 1998
2-Chloro-8-methyl-	56, 61 286/734	Picrate, 135	259, 633, 1140, 1949, 2096
2-Chloro-4-(*n*-propyl)-	75		1953
2-Chloro-4-styryl-	121		765
3-Chloro-2-methyl-	66, 69, 72	Picrate, 224	788, 892, 946, 1142, 1162, 1649, 2100
3-Chloro-4-methyl-	55	Picrate, 208, 212	934, 1121, 1141, 1142, 1158, 1162, 1995, 2100
3-Chloro-6-methyl-	85.5		1146
3-Chloro-8-methyl-	55		1147
2-Benzyl-4-chloro-	51, 135		600, 601, 2095
4-Chloro-2-methyl-	26 270/760	Picrate, 178; H_2O, 43; MeI, 223	437, 518, 736, 768, 783, 791, 1403, 1404, 1413, 1513, 1999, 2000
4-Chloro-2-ethyl-	95/2		1340
4-Chloro-2-(*n*-propyl)-	88–90/0.1		2001
4-Chloro-2-(*n*-heptyl)-[b]	127/0.1		1339
4-Chloro-2-(2,2-diphenethyl)-	254		2002
3-Allyl-4-chloro-	154/3 102/9		446, 447
4-Chloro-3-methyl-	60		464, 543

[a] Obtained as mixtures with the 7-halo-isomer and apparently not isolated.[890, 904]
[b] n_D^{20} 1.5642.

TABLE 41 (*cont.*)

Substituents	M.p. (°C) and/or b.p. (°C/mm)	Derivatives, m.p. (°C)	References
4-Chloro-3-(*n*-propyl)-	115/0.09	Picrate, 155	1526
4-Chloro-3-(2-methylallyl)-	121/0.25		447
4-Chloro-3-(3-methylallyl)-	113/0.1		447
4-Chloro-3-(3,4-dimethoxybenzyl)-	96	MeI, 208	100
3-(2-Bromo-4,5-dimethoxybenzyl)-4-chloro-	112		100
4-Chloro-6-methyl-	55		484, 1232
6-(*tert*-Butyl-4-chloro-	41.5		1286
4-Chloro-6-(*n*-heptyl)-	35 137/0.15		1339
6-Benzyl-4-chloro-	44		455
4-Chloro-6-(diphenylmethyl)-	130		455
4-Chloro-6-(triphenylmethyl)-	188		455
4-Chloro-7-methyl-	28 142/9.5 100/1		321, 493, 777
4-Chloro-8-methyl-	99		484
8-(*tert*-Butyl)-4-chloro-	47.5		1286
5-Chloro-2-methyl-[c]	278/754 143/14	$3H_2O$, 53; Picrate, 243; HCl, 240; $HClO_4$, 164; Oxalate, 146	706, 870, 890, 904
5-Chloro-2-isopropyl-			1202
5-Chloro-4-methyl-	106.5		347, 943
4-Benzyl-5-chloro-	51.5		1304, 1305
5-Chloro-6-methyl-	47 110/2.5	Picrate, 210; Styphnate, 217	419, 707, 870, 901
6-Chloro-2-methyl-	96	Picrate, 208 d, 214; HCl, 165	272, 489, 886, 887, 902, 904, 921, 925, 951, 1180, 1936, 2093
6-Chloro-2-(2,2-diphenethyl)-	116	Picrate, 214	1188
6-Chloro-2-styryl-	157	Picrate, 256	1188
6-Chloro-2-(1-methylvinyl)-	50		925
6-Chloro-2-cyclopropyl-	163/12	Picrate, 203	1068
6-Chloro-3-methyl-	82		240
6-Chloro-4-methyl-	66.5, 71	Picrate, 222	367, 949, 2094
6-Chloro-4-styryl-	85		950
6-Chloro-8-methyl-	65.5 138/10	Picrate, 224	647, 877, 1896
6-Chloro-8-ethyl-	142.5/7		632, 903
6-Chloro-8-isopropyl-[d]	147/10	Picrate, 157.5	880
7-Chloro-2-methyl-	78 282/761 87/0.5	Picrate, 193; HCl, 249	706, 769, 870, 887, 890, 904, 942
7-Chloro-2-isopropyl-			1202
7-Chloro-2-styryl-	131		769

[c] n^{20} 1.6198.
[d] n_D^{20} 1.6002.

TABLE 41 (*cont.*)

Substituents	M.p. (°C) and/or b.p. (°C/mm)	Derivatives, m.p. (°C)	References
7-Chloro-3-methyl-	84.5 144/10	Picrate, 187.5; EtI, 270	887
7-Chloro-4-methyl-	61		943, 1961, 2094
7-Chloro-4-(*n*-propyl)-	49.5		1296
4-Benzyl-7-chloro-	94	MeI, 225 d	1304, 1305
7-Chloro-6-methyl-	78 122/35	Picrate, 280	419, 870, 901
7-Chloro-8-methyl-	48 278/759	HNO_3, 149; Oxalate, 146; $HClO_4$, 171; $H_2Cr_2O_7$, 148	699
8-Chloro-2-methyl-	64, 70		886, 902, 904, 922, 951, 1177, 1178, 1179, 1227
8-Chloro-4-methyl-	107 115/0.5		401, 875, 920, 935, 936
8-Chloro-5-methyl-	49, 54	Picrate, 172	848, 905
8-Chloro-6-methyl-	49, 61.5 192/26	Picrate, 220	419, 848, 877
8-Chloro-6-ethyl-[e]	301/760 177/8		878, 903
8-Chloro-6-isopropyl-[f]	178/11	Picrate, 90	880
8-Chloro-7-methyl-	45 162/2		927
2-Bromo-3-methyl-	97		1749
2-Bromo-4-methyl-	81.5 126/1		607, 610
2-Bromo-4-ethyl-	81		612
2-Bromo-6-methyl-	118, 126	Picrate, 140.5, EtI, 111	616, 630
2-Bromo-8-methyl-	79 143/0.3		617
2-Bromo-8-ethyl-	27 175/0.2		617
3-Bromo-2-methyl-	78	Picrate, 225	892, 1141, 1142
3-Bromo-4-methyl-	59.5, 45	Picrate, 215	1141, 1142, 1995, 2100
3-Bromo-6-methyl-	51		99
4-Bromo-2-methyl-	90		607
5-Bromo-2-methyl-[a]			890, 924, 2077
5-Bromo-4-methyl-	113.5		347
5-Bromo-7-methyl-	24	HCl, 216	99
5-Bromo-8-methyl-	38	HCl, 103; $H_2Cr_2O_7$, 119	99, 850
6-Bromo-2-methyl-	101	MeI, 237; EtI, 218; Picrate, 205	190, 191, 904, 921, 924, 1066, 1180, 1184
6-Bromo-2-isobutyl-	46 215/14	Picrate, 192	1066

[a] See footnote *a* on p. 707. [e] n_D^{25} 1.6190; d_4^{20} 1.188. [f] n_D^{20} 1.6066.

TABLE 41 (*cont.*)

Substituents	M.p. (°C) and/or b.p. (°C/mm)	Derivatives, m.p. (°C)	References
6-Bromo-2-(*n*-pentyl)-	208/14	Picrate, 192	1067
6-Bromo-2-(*n*-hexyl)-[g]	240/25	Picrate, 154	1066
6-Bromo-2-(*n*-heptyl)-[h]	231/20	Picrate, 150	1070
6-Bromo-2-(*n*-nonyl)-		Picrate, 137	1066
6-Bromo-2-(*n*-undecyl)-[i]	272/14	Picrate, 137	1070
6-Bromo-3-methyl-	103		888
6-Bromo-8-methyl-	59 290/760 115/15	Picrate, 226	647, 849, 900
6-Bromo-8-ethyl-	146/8		903
7-Bromo-2-methyl-	77	HNO_3, 102; Picrate, 207	890, 924
7-Bromo-5-methyl-	67		99
7-Bromo-8-methyl-	48.5	HCl, 224; $H_2Cr_2O_7$, 210	850
8-Bromo-2-methyl-	69.5		926
8-Bromo-5-ethyl-	40		425
8-Bromo-6-methyl-	53, 58 166–179/ 11–16		99, 650, 719
8-Bromo-6-ethyl-	184/14	Picrate, 158	903
8-Bromo-7-methyl-	97.5		99
2-Iodo-3-methyl-	89		1749
2-Iodo-4-methyl-	90	EtI, 219 d	111, 427, 586
2-Iodo-6-methyl-		MeI, 225 d	642
4-Iodo-2-methyl-	110.5	MeI, 230 d	736, 2001
5-Iodo-2-methyl-[a]			890
6-Iodo-2-methyl-	108, 112	Picrate, 195	147, 379, 675
6-Iodo-4-methyl-			2003
7-Iodo-2-methyl-	81	HNO_3, 135 d	890
8-Iodo-6-methyl-	66	H_2SO_4, 180; HNO_3, 151; HCl, 216; $H_2Pt_2Cl_6$, 226; $H_2Cr_2O_7$, 112	337

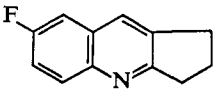
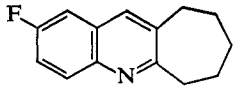
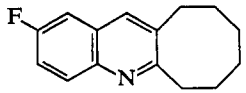
[a] See footnote *a* on p. 707.
[g] $n_D^{18.1}$ 1.5910. [h] $n_D^{22.5}$ 1.5982. [i] n_D^{29} 1.5700.

TABLE 42. Monohalodialkylquinolines

Substituents	M.p. (°C) and/or b.p. (°C/mm)	Derivatives, m.p. (°C)	References
4-Fluoro-2,8-dimethyl-	41		677
6-Fluoro-2-isobutyl-3-isopropyl-	165/15	Picrate, 209	1195
3-Ethyl-6-fluoro-2-(*n*-propyl)-[a]	163/15		1197

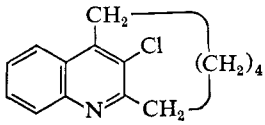
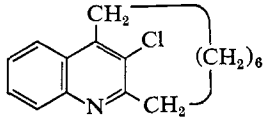
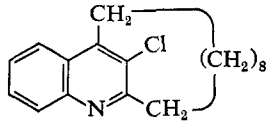
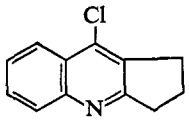
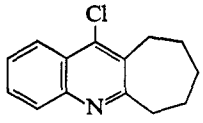
[a] n_D^{25} 1.5588.

TABLE 42 (*cont.*)

Substituents	M.p. (°C) and/or b.p. (°C/mm)	Derivatives, m.p. (°C)	References
	88	Picrate, 231	1069
7-Fluoro-1,2,3,4-tetrahydroacridine[b]	71		1069
7-Fluoro-1,2,3,4-tetrahydro-2-methylacridine[b]	88		1069
	97	Picrate, 194	1068
		Picrate, 201	1068
7-Fluoro-2,4-dimethyl-	46		1172
2-Chloro-3,4-dimethyl-	131		351, 353
2-Chloro-4-ethyl-3-methyl-	73		643, 1664
2-Chloro-4-methyl-3-vinyl-	69		2105
2-Chloro-3-ethyl-4-methyl-	85.5		416
2-Chloro-6-ethyl-4-methyl-			2096
2-Chloro-3,4-diethyl-	205/25		643
2-Chloro-3-ethyl-4-(*n*-propyl)-	88.5		1664
2-Chloro-4-methyl-3-(*n*-propyl)-	80		416
2-Chloro-4-(*n*-pentyl)-3-(*n*-propyl)-			1664
3-(*n*-Butyl)-2-chloro-4-methyl-	183.5/5		416
3-(*n*-Butyl)-2-chloro-4-(*n*-pentyl)-			1664
2-Chloro-4,6-dimethyl-	96, 104		403, 511, 1953
2-Chloro-4,8-dimethyl-	67		352, 353, 403, 511
2-Chloro-6,8-dimethyl-	56		259
2-Chloro-7,8,9,10-tetrahydrobenzo[*f*]quinoline[c]	90	Picrate, 214	2023, 2024
3-Chloro-2,4-dimethyl-	75	Picrate 210; MeI, 230 d	1150, 1151, 1152, 1156, 1157, 1158, 1160, 1162, 1163, 2100
3-Chloro-2,5-dimethyl-	97.5		892
3-Chloro-2,6-dimethyl-	84		89
3-Chloro-2,7-dimethyl-			892

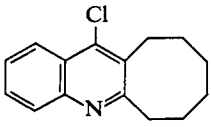
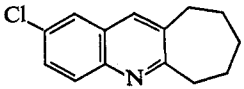
[b] Acridine derivatives are dealt with in more detail in Vol. 9 of this series;[2011] c.f. ref. 2012.
[c] Phenanthridine-type derivatives are dealt with in more detail in Vol. 12 of this series.[2025]

TABLE 42 (*cont.*)

Substituents	M.p. (°C) and/or b.p. (°C/mm)	Derivatives, m.p. (°C)	References
	68	Picrate, 193.5	1163, 1164
	66	Picrate, 203	1163, 1164
	82.5	Picrate, 178; HCl, 221	1163, 1164, 1939
4-Chloro-2,3-dimethyl-	78		643
4-Chloro-3-ethyl-2-methyl-	36		511
3-Benzyl-4-chloro-2-methyl-	79		511
	235		832, 1897, 2078
4-Chloro-3-(*p*-methoxybenzyl)-2-methyl-	60		508
4-Chloro-3-(*p*-ethoxybenzyl)-2-methyl-	61		508
4-Chloro-2-methyl-3-vinyl-		HCl, 234 d	833
4-Chloro-2-ethyl-3-methyl-	23, 43		599, 643
2-(But-3-enyl)-4-chloro-3-methyl-	58.5		1671
2-(1-Allylbut-3-enyl)-4-chloro-3-methyl	128/0.14	Picrate, 145	1671
9-Chloro-1,2,3,4-tetrahydroacridine[b]	70		2004, 2005, 2006, 2007, 2008, 2078
9-Chloro-1,2,3,4-tetrahydro-2-methylacridine[b]	64		987
9-Chloro-1,2,3,4-tetrahydro-4-methylacridine[b]	56		987
	97.5		987, 1163

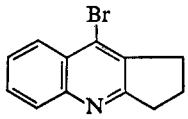
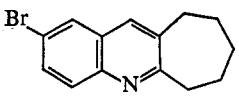
[b] See footnote *b* on p. 711.

TABLE 42 (*cont.*)

Substituents	M.p. (°C) and/or b.p. (°C/mm)	Derivatives, m.p. (°C)	References
	83		1164
4-Chloro-2,5-dimethyl-	73, 78	Picrate, 189	474, 598, 769
4-Chloro-2,6-dimethyl-	63.5, 70 119/3.5		661, 1514
4-Chloro-2-(2,2-diphenylethyl)-6-methyl-	140		1653
4-Chloro-2,7-dimethyl-	57	Picrate, 210	769
4-Chloro-2,8-dimethyl-	72		661
4-Chloro-3,5-dimethyl-	62.5 145–152/5		321, 485
4-Chloro-3,6-dimethyl-	58		464
4-Chloro-3,7-dimethyl-		Picrate, 218	485
4-Chloro-3,8-dimethyl-	63		352, 482
4-Chloro-5,6-dimethyl-[d]			968
4-Chloro-5,7-dimethyl-	59		484
4-Chloro-5,8-dimethyl-	51		484
4-Chloro-6,7-dimethyl-	88 149/0.6		493, 968
4-Chloro-6,8-dimethyl-	90		484
5- or 7-Chloro-1,2,3,4-tetrahydroacridine[b]	92 203/15	Picrate, 205 d	2009
5-Chloro-2,6-dimethyl-	45		687, 710, 711
5-Chloro-4,6-dimethyl-	34.5 290/624	Picrate, 218; Styphnate, 222	419
5-Chloro-6,8-dimethyl-	44 122/2.5	Picrate, 176	705
6-Chloro-3-ethyl-2-(*n*-propyl)-[e]	174/12		1197
6-Chloro-2-isobutyl-3-isopropyl-	177/15	Picrate, 203	1195
7-Chloro-1,2,3,4-tetrahydroacridine[b]	96/20	Picrate, 189 d	2009
	109	Picrate, 192	1067, 1927
6-Chloro-2,4-dimethyl-	99	H_2O, 85.5	91, 2093
6-Chloro-3,4-dimethyl-	130		875
7-Chloro-2,4-dimethyl-	48.5	H_2O, 61; HCl, 277	91
7-Chloro-2,6-dimethyl-	92		687, 710, 711
7-Chloro-4,6-dimethyl-	104	Picrate, 248; Styphnate, 244	419

[b] See footnote *b* on p. 711.
[c] Not purified. [e] n_D^{25} 1.5870.

TABLE 42 (*cont.*)

Substituents	M.p. (°C) and/or b.p. (°C/mm)	Derivatives, m.p. (°C)	References
7-Chloro-6,8-dimethyl-	41 131/2.5	Picrate, 213	705
5-Chloro-1,2,3,4-tetrahydroacridine[b]	95.5 220/20	Picrate, 198 d	2009
8-Chloro-2,4-dimethyl-	74 185/15		91
8-Chloro-2,7-dimethyl-	65		687
2-Bromo-3,4-dimethyl-	139 151–158/5		610
2-Bromo-4,6-dimethyl-	113 161/5		610
2-Bromo-4,7-dimethyl-	38		610
2-Bromo-4,8-dimethyl-	65.5		610
2-Bromo-4-ethyl-6-methyl-	117		612
2-Bromo-4-ethyl-7-methyl-	76		612
2-Bromo-4-ethyl-8-methyl-	53		612
3-Bromo-2,4-dimethyl-	70	Picrate, 213	1156, 1158
3-Bromo-2,5-dimethyl-			892
3-Bromo-2,7-dimethyl-			892
3-Bromo-6,8-dimethyl-	60		944
4-Bromo-2-(*tert*-butyl)-6-methyl-	80		1883
			2078
9-Bromo-1,2,3,4-tetrahydroacridine[b]	80		2008, 2078
6-Bromo-2,3-dimethyl-	82	Picrate, 225	1066
6-Bromo-3-methyl-2-(*n*-pentadecyl)-	55	Picrate, 114	1067
2-Bromo-7,8,9,10-tetrahydrobenzo[*f*]quinoline[c]	110	Picrate, 221	2023
6-Bromo-3-ethyl-2-(*n*-propyl)-[f]	185/15		1197
6-Bromo-2-isobutyl-3-isopropyl-	184/18	Picrate, 199	1195
7-Bromo-1,2,3,4-tetrahydroacridine[b]	94 224/18	Picrate, 195; 214.5	2009, 2010
7-Bromo-1,2,3,4-tetrahydro-4-methylacridine[b]		Picrate, 197	1067
7-Bromo-4-ethyl-1,2,3,4-tetrahydroacridine[b]	92		1067
	128	Picrate, 201	1067

[b] See footnote *b* on p. 711. [c] See footnote *c* on p. 711. [f] n_D^{25} 1.6022.

TABLE 42 (*cont.*)

Substituents	M.p. (°C) and/or b.p. (°C/mm)	Derivatives, m.p. (°C)	References
5- or 7-Bromo-1,2,3,4-tetrahydroacridine[b]	87 218/15	Picrate, 214.5	2009
7-Bromo-2,4-dimethyl-	47		1172
8-Bromo-2,6-dimethyl-	97		929
5-Bromo-1,2,3,4-tetrahydroacridine[b]	80 228/15	Picrate, 192 d	2009
4-Ethyl-2-iodo-3-methyl-	103		643
2-Ethyl-4-iodo-3-methyl-	65		643
3-Ethyl-6-iodo-2-(*n*-propyl)-	44		1197
6-Iodo-2-(isobutyl)-3-(isopropyl)-	207/14	Picrate, 184	1195
7-Iodo-1,2,3,4-tetrahydroacridine[b]	87.5	Picrate, 220.5	2009
7-Iodo-2,4-dimethyl-	55		1172

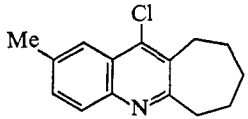
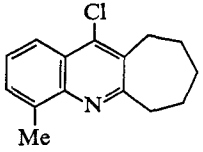
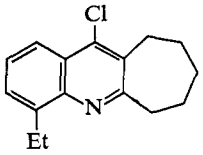
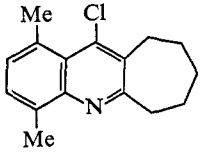
[b] See footnote *b* on p. 711.

TABLE 43. Monohalopolyalkylquinolines

Substituents	M.p. (°C) and/or b.p. (°C/mm)	References
2-Chloro-3-ethyl-4,5- or -4,7-dimethyl-	83	511
2-Chloro-4,7-dimethyl-3-vinyl-	84	2105
2-Chloro-4,5,8-trimethyl-	77	403
2-Chloro-4,6,8-trimethyl-	131	403
2-Chloro-5-isopropyl-4,8-dimethyl-	197	2013
3-Chloro-2,6,8-trimethyl-	68	89
4-Chloro-2,3,5-trimethyl-	96	511
4-Chloro-2,3,6-trimethyl-	91	511
4-Chloro-2,3,7-trimethyl-	85	511
4-Chloro-2,3,8-trimethyl-	52	511
4-Chloro-2,5,7-trimethyl-	73[a]	598
4-Chloro-2,6,8-trimethyl-	114 298/760	2014
4-Chloro-3,5,6-trimethyl-	68	961
4-Chloro-3,6,7-trimethyl-	107	961
4-Chloro-3-ethyl-2,5-dimethyl-	68	511
4-Chloro-3-ethyl-2,6-dimethyl-	61	511
4-Chloro-3-(*p*-methoxybenzyl)-2,6-dimethyl-	64	508
4-Chloro-3-(*p*-ethoxybenzyl)-2,6-dimethyl-	58	508
9-Chloro-1,2,3,4-tetrahydro-7-methylacridine[b]	85	987

[a] Picrate, m.p. 226 °C.
[b] See footnote *b* on p. 711.

TABLE 43 (*cont.*)

Substituents	M.p. (°C) and/or b.p. (°C/mm)	References
	80	987
4-Chloro-3-ethyl-2,8-dimethyl-	42	511
4-Chloro-3-(*p*-methoxybenzyl)-2,8-dimethyl-	51	508
4-Chloro-3-(*p*-ethoxybenzyl)-2,8-dimethyl-	50	508
9-Chloro-1,2,3,4-tetrahydro-5-methylacridine[b]	47	987
	86	987
	72	987
4-Chloro-6-(*n*-pentyl)-3,8-di-(*n*-propyl)-		564
3-(*n*-Butyl)-4-chloro-6,8-di-(*n*-propyl)-		564
9-Chloro-1,2,3,4-tetrahydro-6,8-dimethylacridine[b]	90	987
9-Chloro-1,2,3,4-tetrahydro-5,8-dimethylacridine[b]	70	987
	90	987
9-Chloro-1,2,3,4-tetrahydro-5,7-dimethylacridine[b]	94	117
4-Chloro-2,3,6,8-tetramethyl-	89	117
4-Chloro-3-ethyl-2,6,8-trimethyl-	84	511
4-Chloro-3,5,6,7-tetramethyl-	72	493
5-Chloro-2,4,6-trimethyl-	50[c]	419
5-Chloro-2,4,8-trimethyl-	55	1172
5-Chloro-2,6,8-trimethyl-	64[d] 135/4	705
6-Chloro-2,4,7-trimethyl-	90	1172
6-Chloro-2,5,8-trimethyl-	95	687
7-Chloro-2,4,6-trimethyl-	82	1172
7-Chloro-2,4,8-trimethyl-	69	1172
7-Chloro-2,5,8-trimethyl-	109	687
8-Bromo-2,5,6-trimethyl-	91	933

[c] Picrate, m.p. 207 °C. [d] Picrate, m.p. 179 °C.

TABLE 44. Monohaloarylquinolines

Substituents	M.p. (°C) and/or b.p. (°C/mm)	Derivatives, m.p. (°C)	References
6-Fluoro-2-phenyl-	86	Picrate, 176	1069, 2086
6-Fluoro-2-(*p*-fluorophenyl)-	128	Picrate, 172	1069, 2086
2-Chloro-3-phenyl-	55		1528
2-Chloro-3-(*p*-nitrophenyl)-	153		359
2-Chloro-3,4-diphenyl-	171		360
2-Chloro-4-phenyl-	92		358, 377, 764, 1036
2-Chloro-6-phenyl-	110 180/0.6		637
2-Bromo-4-phenyl-	95		609, 615
2-Bromo-4,6-diphenyl-	168.5		614
2-Bromo-8-phenyl-	175/0.2		617
3-Chloro-2-phenyl-	92		686, 1149, 2100
3-Chloro-2-(*o*-chlorophenyl)-	147.5		2015
3-Bromo-2-phenyl-	86, 92		686, 1174, 2100
4-Chloro-2-phenyl-	52, 65	Picrate, 177	478, 480, 518, 600, 689, 764, 794, 1017, 1021, 1515, 1516, 2016, 2080, 2095
4-Chloro-2-(*o*-methoxyphenyl)-	98	Picrate, 201	769
4-Chloro-2-(*p*-nitrophenyl)-	150		477
4-Chloro-2-(*o*-tolyl)-	68		478
4-Chloro-2-(*p*-tolyl)-	80		478
4-Chloro-2-(1-naphthyl)-	121		478
4-Chloro-2-(*o*-bromophenyl)-	141		2015
4-Chloro-2-(*p*-methoxyphenyl)-	135		486
4-Chloro-2-(*p*-chlorophenyl)-	129.5		739, 2095
4-Chloro-2-(3,4-methylenedioxyphenyl)-			1517
4-Chloro-2,3-diphenyl-	121		2017
4-Chloro-3-phenyl-	64, 75 168/0.3		471, 993, 1556
4-Chloro-3-(*o*-aminophenyl)-	253 d	*N*-Ac, 229	343
4-Chloro-3-(*o*-hydroxyphenyl)-	210		343
4-Chloro-6-phenyl-	90.5	Picrate, 207	1665
4-Chloro-7-phenyl-	90	Picrate, 200	1665
4-Chloro-7-(*o*-chlorophenyl)-	95	Picrate, 169	1665
4-Chloro-7-(*p*-chlorophenyl)-	131		1665
7-(*p*-Bromophenyl)-4-chloro-	135		1665
4-Chloro-8-phenyl-	93		1338
4-Chloro-8-(*p*-nitrophenyl)-	224		1338
5-Chloro-3-phenyl-	113		359
5-Chloro-3-(*p*-nitrophenyl)-	184		359
6-Chloro-2-phenyl-	111	Picrate, 190	1067, 2110
6-Chloro-2-(*p*-dimethylaminophenyl)-	201		1610
6-Chloro-2-(*p*-diethylaminophenyl)-	123		1610
6-Chloro-2-(2-fluoro-5-methylphenyl)-	73	Picrate, 195	1084

TABLE 44 (*cont.*)

Substituents	M.p. (°C) and/or b.p. (°C/mm)	Derivatives, m.p. (°C)	References
6-Chloro-2-[3-chloro-4-(methylthio)-phenyl]-	124		1085
6-Chloro-2-(4-fluoro-1-naphthyl)-	132		1086
6-Chloro-3-phenyl-2-(*p*-tolyl)-	125	Picrate, 188	1087
6-Chloro-2-(2-chloro-4-methylphenyl)-3-phenyl-	149	Picrate, 172	1087
6-Chloro-2,4-diphenyl-	131	Picrate, 189	1047
6-Chloro-4-phenyl-2-(*p*-tolyl)-	133	Picrate, 234	1047
2-(*p*-Bromophenyl)-6-chloro-4-phenyl-	175	Picrate, 229	1047
6-Chloro-2-(*p*-chlorophenyl)-4-phenyl-	160	Picrate, 224	1047
6-Chloro-2-(*p*-methoxyphenyl)-4-phenyl-	136	Picrate, 235	1047
6-Chloro-2-(*o*-methoxyphenyl)-4-phenyl-	157	Picrate, 188	1047
6-Chloro-2-(3,4-dimethoxyphenyl)-4-phenyl-	159	Picrate, 223	1047
6-Chloro-4-phenyl-2-(3,4,5-trimethoxyphenyl)-	193	Picrate, 212	1047
2-(*p*-Aminophenyl)-6-chloro-4-phenyl-	185	Picrate, 239d	1047
6-Chloro-2-(1-naphthyl)-4-phenyl-	124	Picrate, 250	1047
6-Chloro-2-(2-naphthyl)-4-phenyl-	155	Picrate, 252	1047
6-Chloro-4-phenyl-		Picrate, 210.5	1170
7-Choro-2-phenyl-	106		2110
7-Chloro-2-(2,4-dihydroxyphenyl)-	256		1230
7-Chloro-3-phenyl-	112		359
8-Chloro-2-phenyl-		HCl, 242	938
2-Bromo-4-phenyl-	95		609, 615
2-Bromo-4,6-diphenyl-	168.5		614
2-Bromo-8-phenyl-	175/0.2		617
3-Bromo-2-phenyl-	86		686, 1174
4-Bromo-2-phenyl-	90.5	Picrate, 170	213, 720
4-Bromo-2-(*p*-bromophenyl)-	120.5		213
6-Bromo-2-phenyl-	113 183–190/7.5		1185, 1186
6-Bromo-2-(3-methyl-4-methoxyphenyl)-	171		1062
6-Bromo-2-(3-methyl-4-ethoxyphenyl)-	175		1062
6-Bromo-2-(2-methyl-4-methoxyphenyl)-	126		1062
6-Bromo-2-(*p*-fluorophenyl)-	152		1063
6-Bromo-2-(3-fluoro-4-methoxyphenyl)-	186		1064
6-Bromo-2-(6-methoxy-2-naphthyl)-	163		1065
6-Bromo-2-(4-biphenylyl)-	222	Picrate, 225	1067
6-Bromo-2-(6-tetralyl)-	133	Picrate, 212	1067
6-Bromo-2-(3,4-dimethylphenyl)-	135	Picrate, 207	1067
6-Bromo-2-(2,4-dimethylphenyl)-	98	Picrate, 194	1067
6-Bromo-2-(2,5-dimethylphenyl)-	124	Picrate, 205	1067
6-Bromo-2-(*p*-isopropylphenyl)-	143	Picrate, 194	1067
6-Bromo-2-(3-pyrenyl)-	205	Picrate, 242	1067
6-Bromo-2-(*p*-chlorophenyl)-	177		900, 1067
6-Bromo-2-(*p*-bromophenyl)-	188	Picrate, 207	1067
6-Bromo-2-(3,4-dichlorophenyl)-	169	Picrate, 192	1067

TABLE 44 (*cont.*)

Substituents	M.p. (°C) and/or b.p. (°C/mm)	Derivatives, m.p. (°C)	References
6-Bromo-2-(*p*-iodophenyl)-	185	Picrate, 198	1067
6-Bromo-2-(4-fluoro-2-methylphenyl)-	118		1084
6-Bromo-2-(2-fluoro-5-methylphenyl)-	72	Picrate, 207	1084
6-Bromo-2-[3-chloro-4-(methylthio)-phenyl]-	145		1085
6-Bromo-2-(3-chloro-4-methoxyphenyl)-	169	Picrate, 220	1095
6-Bromo-2-(2-bromo-4-chlorophenyl)-	178		1105
6-Bromo-2-(2-bromo-5-chlorophenyl)-	163		1105
6-Bromo-2-[*m*-(trifluoromethyl)phenyl]-	82	Picrate, 212	1105
6-Bromo-2-(*p*-chlorophenyl)-3-phenyl-	161	Picrate, 194	1067
6-Bromo-2-(*p*-bromophenyl)-3-phenyl-	172	Picrate, 193	1067
6-Bromo-2-(*p*-hydroxyphenyl)-3-phenyl-	237		1089
6-Bromo-3-phenyl-2-[*m*-(trifluoromethyl-phenyl]-	102	Picrate, 171	1104
6-Bromo-2-(2,4-dimethoxyphenyl)-3-phenyl-	89	Picrate, 203	1067
6-Bromo-2-(4-methoxy-3-methyl-phenyl)-3-phenyl-	135		1062
6-Bromo-2-(4-fluoro-2-methyl-phenyl)-3-phenyl-	136	Picrate, 182	1084
6-Bromo-2-(2-fluoro-5-methylphenyl)-3-phenyl-	154		1084
6-Bromo-2-(6-methoxy-2-naphthyl)-3-phenyl-	160		1065
6-Bromo-8-phenyl-	72	Picrate, 186	900
8-Bromo-6-phenyl-	68		900
6-Iodo-2-phenyl-	144 210–220/0.5		379, 1185

TABLE 45. Monohaloalkylarylquinolines

Substituents	M.p. (°C) and/or b.p. (°C/mm)	Derivatives, m.p. (°C)	References
2-Chloro-3-methyl-4-phenyl-	118		377
2-Chloro-3-ethyl-4-phenyl-	99		377
2-Chloro-4-phenyl-3-vinyl-	79		2105
2-Chloro-4-(*p*-tolyl)-3-vinyl-	123		2105
2-Benzyl-4-chloro-3-phenyl-	91	Picrate, 174	625
4-Chloro-3-methyl-2-phenyl-	97		688
2-Benzyl-4-chloro-6-methyl-3-phenyl-	93		625
4-Chloro-5 (or 7)-methyl-2-phenyl-	82		480, 2095
4-Chloro-7 (or 5)-methyl-2-phenyl	67		480, 2095
4-Chloro-5,8-dimethyl-2-phenyl-	89		480
4-Chloro-6-methyl-2-phenyl-	95, 100		479, 480, 1017, 1021, 1548
4-Chloro-2-(*p*-methoxyphenyl)-6-methyl-	109, 141		486, 770

TABLE 45 (*cont.*)

Substituents	M.p. (°C) and/or b.p. (°C/mm)	Derivatives, m.p. (°C)	References
4-Chloro-2-(*m*-chlorophenyl)-6-methyl-	116		771
4-Chloro-2-(*p*-chlorophenyl)-6-methyl-	139		771
4-Chloro-6,8-dimethyl-2-phenyl-	83		478, 480
4-Chloro-2-(*p*-methoxyphenyl)-7-methyl-	91		770
4-Chloro-2-(*p*-chlorophenyl)-7-methyl-	135.5		771
4-Chloro-8-methyl-2-phenyl-	85		478, 479, 480, 1017, 1021
4-Chloro-2-(*p*-methoxyphenyl)-8-methyl-	116		486
6-Chloro-2-(2-fluoro-5-methylphenyl)-3-methyl-	128	Picrate, 194	1084
6-Chloro-2-[3-chloro-4-(methylthio)-phenyl]-3-methyl-	135		1085
6-Chloro-2-(*p*-hydroxyphenyl)-3-methyl-	202	Picrate, 198	1089
6-Chloro-2-methyl-4-phenyl-	90	Picrate, 217	1048
6-Chloro-2-ethyl-4-phenyl-	71	Picrate, 195	1048
6-Chloro-4-phenyl-2-(*n*-propyl)-	98	Picrate, 177	1048
6-Chloro-2-(isobutyl)-4-phenyl-	66	Picrate, 173	1048
6-Chloro-2-(*n*-pentyl)-4-phenyl-	135/0.08	Picrate, 156	1048
6-Chloro-2-(3-methylbutyl)-4-phenyl-	187/0.5	Picrate, 150	1048
6-Chloro-2-(*p*-methoxybenzyl)-4-phenyl-	97	Picrate, 166	1048
6-Chloro-2-phenethyl-4-phenyl-	72	Picrate, 198	1048
6-Chloro-4-methyl-2-phenyl-	91.5		947
6-Chloro-4-ethyl-2-phenyl-	66	Picrate, 170	948
6-Chloro-2,3-dimethyl-4-phenyl-	118	Picrate, 216	1048
6-Chloro-3-ethyl-2-methyl-4-phenyl-	140	Picrate, 195	1048
3-(*n*-Butyl)-6-chloro-2-methyl-4-phenyl-	79	Picrate, 178	1048
6-Chloro-3-(isobutyl)-2-methyl-4-phenyl-	112	Picrate, 190	1048
6-Chloro-2-methyl-3,4-diphenyl-	197		1048
6-Chloro-3-(*p*-methoxyphenyl)-2-methyl-	177	Picrate, 228	1048
3-Benzyl-6-chloro-2-methyl-4-phenyl-	131	Picrate, 194	1048
8-Chloro-4-methyl-2-phenyl-	80		947
8-Chloro-5-methyl-2-phenyl-	129		906
8-Chloro-6-methyl-2-phenyl-	95.5		900
2-Bromo-6-methyl-4-phenyl-	101		609
2-Bromo-7-methyl-4-phenyl-	67		609
2-Bromo-8-methyl-4-phenyl-	70.5		609
2-Bromo-4-methyl-5-phenyl-	165		612
2-Benzyl-4-bromo-3-phenyl-	126.5	Picrate, 184	625
5-Bromo-8-methyl-3-phenyl-	153	HBr, 237	1898
6-Bromo-3-methyl-2-phenyl-	129		1067
6-Bromo-2-(*p*-fluorophenyl)-3-methyl-	105		1063
6-Bromo-2-(*p*-methoxyphenyl)-3-methyl-	139		1065
6-Bromo-2-(*p*-isopropylphenyl)-3-methyl-	130	Picrate, 185	1067
6-Bromo-2-[*p*-(*tert*-butyl)phenyl]-3-methyl-	132	Picrate, 154	1067
6-Bromo-2-(*p*-chlorophenyl)-3-methyl-	160	Picrate, 207	1067
6-Bromo-2-(*p*-bromophenyl)-3-methyl-	190	Picrate, 163	1067
6-Bromo-2-(*p*-ethylphenyl)-3-methyl-	115		1067
6-Bromo-2-(*p*-hydroxyphenyl)-3-methyl-	225		1089

TABLE 45 (*cont.*)

Substituents	M.p. (°C) and/or b.p. (°C/mm)	Derivatives, m.p. (°C)	References
6-Bromo-3-methyl-2-[*m*-trifluoromethyl)-phenyl]-	73	Picrate, 206	1105
6-Bromo-2-[*p*-(*n*-butoxyphenyl)]-3-methyl-	133	Picrate, 194	1110
6-Bromo-3-methyl-2-(*p*-tetradecyl-oxyphenyl)-	>300/20	Picrate, 124	1065
6-Bromo-2-(*p*-hexadecyloxyphenyl)-3-methyl-	50		1065
6-Bromo-2-(4-methoxy-3-methylphenyl)-3-methyl-	172		1062
6-Bromo-2-(4-methoxy-2-methylphenyl)-3-methyl-	115		1062
6-Bromo-2-(3-fluoro-4-methoxyphenyl)-3-methyl-	136	Picrate, 187	1064
6-Bromo-2-(4-fluoro-2-methylphenyl)-3-methyl-	130		1084
6-Bromo-2-(2-fluoro-5-methylphenyl)-3-methyl-	132	Picrate, 185	1084
6-Bromo-2-[3-chloro-4-(methylthio)-phenyl]-3-methyl-	182		1085
2-(4-Biphenylyl)-6-bromo-3-methyl-	196		1067
6-Bromo-3-methyl-2-(6-tetralyl)-	123	Picrate, 216	1067
6-Bromo-2-(2,4-dimethylphenyl)-3-methyl-	122	Picrate, 209	1067
6-Bromo-2-(2,5-dimethylphenyl)-3-methyl-	109	Picrate, 192	1067
6-Bromo-3-methyl-2-(4-methyl-1-naphthyl)-	181	Picrate, 228	1067
6-Bromo-2-(6-methoxy-2-naphthyl)-3-methyl-	169		1065
6-Bromo-3-ethyl-2-(*p*-fluorophenyl)-	121		1063
6-Bromo-3-ethyl-2-(*p*-isopropylphenyl)-	93	Picrate, 204	1067
6-Bromo-2-(*p*-chlorophenyl)-3-ethyl-	147	Picrate, 196	1067
6-Bromo-2-(*p*-bromophenyl)-3-ethyl-	110		1067
6-Bromo-3-ethyl-2-[*m*-(trifluoromethyl)-phenyl]-	56	Picrate, 196	1105
6-Bromo-3-ethyl-2-(3-fluoro-4-methoxyphenyl)-	125	Picrate, 181	1064
2-(4-Biphenylyl)-6-bromo-3-ethyl-	172	Picrate, 215	1067
6-Bromo-3-ethyl-2-(6-tetralyl)-	97	Picrate, 218	1067
6-Bromo-3-ethyl-2-(6-methoxy-2-naphthyl)-	185		1065
6-Bromo-3-(*n*-propyl)-2-[*m*-(trifluoro-methyl)phenyl]-	42	Picrate, 160	1105
6-Bromo-4-methyl-2-phenyl-	100		947
6-Bromo-8-methyl-2-phenyl-	96		900
6-Bromo-4-methyl-3-(*o*-nitrophenyl)-	151		1049
8-Bromo-6-methyl-2-phenyl-	105		900
8-Bromo-5,6-dimethyl-2-phenyl-	183		375
6-Iodo-4-methyl-2-phenyl-	50		947

TABLE 46. Monohaloheteroarylquinolines

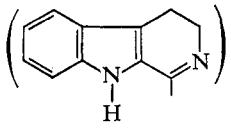
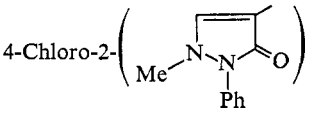
Substituents	M.p. (°C)	Derivative, m.p. (°C)	References
2-Chloro-4-(1-methyl-3-indolyl)-			429
2-Chloro-4-(2-chloro-1-methyl-3-indolyl)-			1878
2-Chloro-4-methyl-3-	216		385
			
4-Chloro-2-(1-methyl-3-indolyl)-	158		429
4-Chloro-2- 	201		789
4-Chloro-2-(2-ethoxy-1-methyl-3-indolyl)-			1878
4,4′-Dichloro-2,2′-biquinoline	297, 307		614, 795
6-Chloro-4-phenyl-2-(2-pyridyl)-	180	Picrate, 205	1047
6-Chloro-4-phenyl-2-(3-pyridyl)-	195	Picrate, 237	1047
6-Chloro-4-phenyl-2-(4-pyridyl)-	187	Picrate, 261	1047
6-Chloro-2-(2-methyl-5-pyridyl)-4-phenyl-	171	Picrate, 250 d	1047
7-Chloro-1,2,3,4-tetrahydro-4-(2-thienyl)-	89		2044
7-Chloro-1,2,3,4-tetrahydro-2-(2-thienyl)-			2044
6,6′-Dichloro-5,5′-biquinoline	205		730
6,6′-Dichloro-4,4′-dimethyl-2,2′-biquinoline	280.5		614
7,7′-Dichloro-4,4′-dimethyl-2,2′-biquinoline	278.5		614
8,8′-Dichloro-4,4′-dimethyl-2,2′-biquinoline	254		614
4,4′-Dibromo-2,2′-biquinoline	292, 320		614, 795
6-Bromo-2-(2-thienyl)-	124		1067
6-Bromo-2-(5-bromo-2-thienyl)-	176		1067
6-Bromo-2-(5-ethyl-2-thienyl)-	107	Picrate, 188	1098
6-Bromo-3-methyl-2-(2-thienyl)-	90		1067
6-Bromo-2-(5-bromo-2-thienyl)-3-methyl-	148		1067
6-Bromo-2-(5-ethyl-2-thienyl)-3-methyl-	80		1098
2-(2-Benzo[*b*]furyl)-6-bromo-3-methyl-	140	Picrate, 213	1109
3,3′,8′,8′-Tetrabromo-4,4′-bis-(dibromomethyl)-1,1′,2,2′-tetrahydro-2,2,2′,2′-tetramethyl-6,6′-biquinoline	210 d		1501

TABLE 47. Monohalohydroquinolines

Substituents	M.p. (°C) and/or b.p. (°C/mm)	Derivatives, m.p. (°C)	References
2-Chloro-5,6,7,8-tetrahydro-[a]	137/12		361, 362, 384
3-Chloro-1,2-dihydro-1,4-dimethyl-2-methylene-	142/18 75d		1158
3-Chloro-1,2,3,4-tetrahydro-1-(1-naphthyl)-			1987
4-Chloro-1,2-dihydro-5-methyl-[b]		1-Ts, 100	1125, 1126
4-Chloro-1,2-dihydro-6-methyl-[b]		1-Ts, 177	1125, 1126
4-Chloro-1,2-dihydro-7-methyl-[b]		1-Ts, 138	1125, 1126
4-Chloro-1,2-dihydro-2,2-dimethyl-	38		1926
4-Chloro-1,2-dihydro-2,2,6-trimethyl-	67		1926
4-Chloro-1,2-dihydro-2,2,8-trimethyl-			1926
4-Chloro-5,6,7,8-tetrahydro-	114/10	Picrate, 166.5	435
4-Chloro-5,6,7,8-tetrahydro-2-methyl-	104/0.3	Picrate, 139	1667
4-Chlorodecahydro-2-methyl-, all isomers			2092
5-Chloro-1,2,3,4-tetrahydro-[c]	110–120/1	Picrate, 146	1194
5-Chloro-1,2,3,4-tetrahydro-1-methyl-[d]			1203
5-Chloro-1,2,3,4-tetrahydro-6-methyl-	158/11	Picrate, 146	707, 708, 901
5-Chloro-1,2,3,4-tetrahydro-6,8-dimethyl-	131/2.5		705
5-Chloro-2,3,4,6,7,8-hexahydro-1,7-dimethyl-	160/11	$HClO_4$, 167	597, 1663
6-Chloro-1,2-dihydro-2,2-dimethyl-	80/0.2		1181
6-Chloro-2-ethyl-1,2-dihydro-2,3,4-trimethyl-			1901, 2089
6-Chloro-1,2-dihydro-2,2,4-trimethyl-	61.5	HCl, 196 d	202, 204, 1169 1901, 2018, 2081, 2089
6-Chloro-1,2,3,4-tetrahydro-	43 127/34 160/11	Picrate, 152.5; HCl, 195 d	250, 1634, 1660, 1661

[a-d] See footnotes on p. 724.

TABLE 47 (*cont.*)

6-Chloro-1,2,3,4-tetrahydro-1-methyl-[a]			1203
6-Chloro-1,2,3,4-tetrahydro-2,4-dimethyl-4-phenyl-	170/0.01		1207
7-Chloro-1,2-dihydro-2,2-dimethyl-	113/2.2		1168
7-Chloro-1,2-dihydro-2,2,4-trimethyl-	38.5 172/18	HCl, 202; HNO_3, 132 d; MeI, 144; 1-Ac, 77	202, 2083
7-Chloro-1,2-dihydro-2,2,8-trimethyl-	70/0.05		1926
7-Chloro-1,2,3,4-tetrahydro-	63.5	HCl, 208	1194
7-Chloro-1,2,3,4-tetrahydro-6-methyl-	77.5 129/3		901, 1130
8-Chloro-1,2-dihydro-2,2-dimethyl-			1926
8-Chloro-1,2-dihydro-2,2,4-trimethyl-			202, 1169
8-Chloro-1,2,3,4-tetrahydro-	95–110/1	Picrate, 131; 1-Bz, 134	1194
4-Bromo-1,2-dihydro-2,2-dimethyl-			1926
5-Bromo-2,3,4,6,7,8-hexahydro-1,7-dimethyl-	$HClO_4$		597
6-Bromo-1,2-dihydro-2,2,4-trimethyl-	89		204, 2018
6-Bromo-1,2,3,4-tetrahydro-	35	HBr, 192; 1-Ac, 60	182, 187
6-Bromo-1,2,3,4-tetrahydro-1-methyl-		HBr	186
6-Bromo-1-ethyl-1,2,3,4-tetrahydro-		HBr, 150	186
6-Bromo-1,2,3,4-tetrahydro-1-isopropyl-		HBr, 167	186
6-Bromo-1,2,3,4-tetrahydro-2-methyl-		HBr, 201	184
6-Bromo-1,2,3,4-tetrahydro-8-methyl-			849
6-Bromo-1,2,3,4-tetrahydro-2,2,4-trimethyl-		1-Ac	1636
6-Bromo-1,2,3,4-tetrahydro-2-phenethyl-	184		185
8-Bromo-1,2,3,4-tetrahydro-2,6-dimethyl-		1-Bz, 144	929
4-(α-Cyanobenzyl)-1,4-dihydro-3-iodo-1-methyl-	131.5		233

[a] $n_D^{19.5}$ 1.5608, n_D^{20} 1.5595, d_D^{20} 1.1760.
[b] Named incorrectly in ref. 1125 as 3-chloro-4-oxo-derivatives.
[c] n_D^{20} 1.6137.
[d] Not separated; estimated by infrared spectroscopy.

TABLE 48. Dihaloquinolines

Substituents	M.p. (°C) and/or b.p. (°C/mm)	Derivatives, m.p. (°C)	References
2,4-Difluoro-	91.5/11		656
5,7-Difluoro-	78		1888
5,8-Difluoro-	71		1248
6,8-Difluoro-	67		1248
2,3-Dichloro-	105		364, 383, 1504
2,4-Dichloro-	67		365, 396, 562, 583, 584, 585, 586, 772, 784, 806, 808, 1282, 1504
2,5-Dichloro-[a]	99		633, 1140
2,6-Dichloro-	156, 161.5 172/13		404, 633, 637, 757, 1140
2,7-Dichloro-	120		366, 775, 1140
2,8-Dichloro-	103		639, 1140
3,4-Dichloro-	69	Picrate, 180	45, 122
3,6-Dichloro-	113		55
4,5-Dichloro-	117 134/5.5		472, 494, 959
4,6-Dichloro-	104		212, 472, 481, 489, 757, 1019, 1232
4,7-Dichloro-	86, 93 125/5	MeI, 218; Me_2SO_4, 176 d; $HClO_4$, 230	54, 438, 439, 441, 472, 493, 494, 496, 565, 775, 803, 804, 959, 968, 1120, 1123, 1460
4,8-Dichloro-	156		54, 472, 1019
5,6-Dichloro-	86.5		33, 281, 870
5,7-Dichloro-	115	MeI, 257; HCl, 216; H_2SO_4, 162; $H_2Cr_2O_7$, 159; $H_2Pt_2Cl_6$, >300 d	49, 703, 860
5,8-Dichloro-	94, 98	Picrate, 151; $H_2Cr_2O_7$, 131; $H_2Pt_2Cl_6$, 252	31, 32, 33, 268, 843, 844, 895, 898
6,7-Dichloro-	134		838, 870
6,8-Dichloro-	104	Picrate, 206.5; $H_2Pt_2Cl_6$, 250 d	235, 238, 281, 648, 843, 879, 895
7,8-Dichloro-	85.5		698
2,3-Dibromo-	97		284, 1602
2,4-Dibromo-	93[b]		619, 1602
2,5-Dibromo-	86		618
2,6-Dibromo-	167		618, 633
2,7-Dibromo-	134		618
3,4-Dibromo-	77, 82		13, 118, 124, 171
3,5-Dibromo-	86	MeI, 253; HCl, 183; HNO_3, 147	7, 94, 177, 282
3,6-Dibromo-	130	HCl, 185; HNO_3, 158	7, 13, 21, 94, 95, 96, 97, 177, 208, 287, 797
3,7-Dibromo-	127	MeI,222	94, 96, 287

[a] Listed in ref. 633 as the 2,7-dichloro-isomer.
[b] M.p. 265° in ref. 127.

TABLE 48 (*cont.*)

Substituents	M.p. (°C) and/or b.p. (°C/mm)	Derivatives, m.p. (°C)	References
3,8-Dibromo-	90, 102, 108	HCl, 142; H_2SO_4, 206; $HCrO_4$, 158	13, 95, 287, 717
5,6-Dibromo-	81, 95	MeI, 250	33, 176, 217
5,7-Dibromo-	112	MeI, 287; HBr, 288	49, 175, 217, 283
5,8-Dibromo-	128, 130[c]	MeI, 166	6, 7, 9, 217, 655, 716, 717, 725, 899
6,7-Dibromo-	69		298
6,8-Dibromo-	101	MeI, 178 d	175, 189, 217, 655, 843
7,8-Dibromo-	112		725
2,4-Di-iodo-	132	MeI, 237 d; EtI, 236 d	586, 713
5,6-Di-iodo-	125		690
5,7-Di-iodo-	132	MeI, 250 d	845, 1888
5,8-Di-iodo-	165		220, 221, 222, 690

[c] Listed in ref. 716 as the 5,6-dibromo-isomer; see ref. 718.

TABLE 49. Mixed Dihaloquinolines

Substituents	M.p. (°C) and/or b.p. (°C/mm)	Derivatives, m.p. (°C)	References
3-Bromo-2-chloro-	91		774
2-Chloro-4-iodo-	109		713
4-Chloro-2-iodo-	108		713
6-Bromo-2-chloro-	158 175/8		55, 633, 637, 1140
7-Chloro-2-fluoro-	50		748
3-Bromo-4-chloro-	70	Picrate, 185.5	118, 122, 212, 396
4-Chloro-3-iodo-	97	Picrate, 189	122
3-Bromo-6-chloro-	112	HCl, 168; MeI, 287	96, 109, 171, 281
5-Chloro-4-iodo-		MeI, 248	1372
4-Chloro-6-fluoro-	77		495, 1232
6-Bromo-4-chloro-	110, 113		212, 1232, 1272
4-Chloro-6-iodo-	143		1886
4-Chloro-7-fluoro-	69, 74		495, 496
7-Bromo-4-chloro-	101.5, 106		494, 965
4-Chloro-7-iodo-	97, 102		493, 494, 753, 754, 965
4-Bromo-7-chloro-	102		739
7-Chloro-4-iodo-	126	MeI, 266	739, 1372
4-Chloro-8-iodo-	106		1877
5-Chloro-6-iodo-	141		690
5-Bromo-6-chloro-	63		33

TABLE 49 (*cont.*)

Substituents	M.p. (°C) and/or b.p. (°C/mm)	Derivatives, m.p. (°C)	References
6-Chloro-5-iodo-	136		730
5-Chloro-8-fluoro-	62		1248
5-Chloro-8-iodo-	138		690
8-Chloro-5-iodo-	118		690
8-Chloro-6-fluoro-	102.5	Picrate, 219	714
8-Bromo-6-fluoro-	77 121/0.25		900
6-Chloro-8-fluoro-			1899
8-Bromo-6-chloro-	94	Picrate, 202	881, 900
6-Bromo-8-chloro-	120	Picrate, 209	881

TABLE 50. Dihalomonoalkylquinolines

Substituents	M.p. (°C) and/or b.p. (°C/mm)	Derivatives, m.p. (°C)	References
2,4-Dichloro-3-methyl-	84, 91	MeCl, 115; MeI, 178	399, 437, 1401, 1402, 2084
2,4-Dichloro-3-ethyl-	184/21		399, 1401, 1402
2,4-Dichloro-3-(*p*-methoxybenzyl)-	87		596
2,4-Dichloro-3-(*p*-ethoxybenzyl)-	106		596
2,4-Dichloro-5-methyl-[a]	134		582, 595
2,4-Dichloro-6-methyl-	95		582, 589, 763
2,4-Dichloro-7-methyl-	108		120
2,4-Dichloro-8-methyl-	86		582, 589
2,5-Dichloro-4-methyl-	105		347
2,6-Dichloro-4-methyl-	149		839, 1953
2,6-Dichloro-8-methyl-	122		647
2,6-Dichloro-8-ethyl-	60		632
2,7-Dichloro-4-methyl-	97		990, 2019
2,8-Dichloro-4-methyl-	88, 105		420, 697, 1953
2,8-Dichloro-6-methyl-	116		646
2,8-Dichloro-6-ethyl-	93		645
3,4-Dichloro-2-methyl-[b]	67		598
4,5-Dichloro-2-methyl-	76, 89	Picrate, 143	474, 769, 777, 958, 1016
4,5-Dichloro-3-methyl-	72 146/3		463, 543, 959, 1008
4,5-Dichloro-3-(*n*-propyl)-[c]	117/0.4	Picrate, 214	961
4,6-Dichloro-2-methyl-	85		476, 489, 839, 1337, 2087
4,6-Dichloro-2-(2,2-diphenylethyl)-	145	Picrate, 150	1188

[a] Quoted in error as the 7-methyl isomer in ref. 582.
[b] In ref. 599 m.p. 322 °C is inexplicably quoted for this compound.
[c] n_D^{25} 1.6122.

TABLE 50 (*cont.*)

Substituents	M.p. (°C) and/or b.p. (°C/mm)	Derivatives, m.p. (°C)	References
4,6-Dichloro-3-methyl-	119		321, 464, 543
4,7-Dichloro-2-methyl-	103	Picrate, 178	769, 777, 791, 957, 958, 961, 1000, 1016, 1533, 2095
4,7-Dichloro-3-methyl-	88 150/5.5		463, 493, 959, 1008
4,7-Dichloro-3-(*n*-propyl)-	52.5	Picrate, 219	961
4,7-Dichloro-6-methyl-	109.5 137/0.3		493, 967
4,7-Dichloro-8-methyl-	89		966
4,8-Dichloro-2-methyl-	82, 88		422, 541, 839, 1002
4,8-Dichloro-3-methyl-	98, 103		321, 482, 543
5,8-Dichloro-2-methyl-	46 300/760		1061 1061
6,8-Dichloro-2-methyl-	122		954
6,8-Dichloro-2-(*n*-hexyl)-		Picrate, 141	1066
6,8-Dichloro-4-methyl-	128		1857
6,8-Dichloro-5-methyl-	119		906
6,8-Dichloro-7-methyl-	98.5		1895
7,8-Dichloro-2-methyl-	71		706
3,4-Dibromo-2-methyl-	85.5		607
3,4-Dibromo-2-styryl-	147		607
5,8-Dibromo-6-ethyl-	72		33
6,8-Dibromo-2-methyl-	100	Picrate, 155	192, 1114
6,8-Dibromo-5-ethyl-	95.5		425

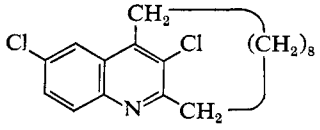
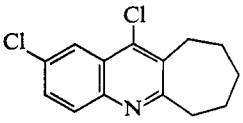
TABLE 51. Mixed Dihalomonoalkylquinolines

Substituents	M.p. (°C)	References
2-Chloro-6-fluoro-4-methyl-	115	994
6-Bromo-2-chloro-4-methyl-	143	511
6-Bromo-2-chloro-8-methyl-	121	647
6-Bromo-2-chloro-8-ethyl-	47	653
8-Bromo-2-chloro-5-ethyl-	84	425
8-Bromo-2-chloro-6-methyl-	111	650
8-Bromo-2-chloro-6-ethyl-	91	644
4-Chloro-5-fluoro-3-methyl-	71	961
5-Bromo-4-chloro-3-methyl-	100.5	463
4-Chloro-6-fluoro-2-methyl-	78	994
6-Bromo-4-chloro-2-methyl-	75	452, 2090
4-Chloro-6-fluoro-3-methyl-	58	961
6-Bromo-4-chloro-3-methyl-	144	464
4-Chloro-6-iodo-3-methyl-	138	960
4-Chloro-7-fluoro-2-methyl-	48	994, 2095
4-Chloro-7-fluoro-3-methyl-	89	961
7-Bromo-4-chloro-3-methyl-	105.5	463

TABLE 51. (*cont.*)

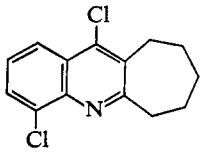
Substituents	M.p. (°C)	References
4-Chloro-7-iodo-3-methyl-	110	960
4-Chloro-8-fluoro-2-methyl-	78	994
8-Bromo-4-chloro-2-methyl-	75	511
4-Chloro-8-fluoro-3-methyl-	102	961
8-Bromo-4-chloro-3-methyl-	111	482
4-Chloro-8-iodo-3-methyl-	137	960
2-Bromo-6-chloro-4-methyl-	167	614
2-Bromo-7-chloro-4-methyl-	123	614
2-Bromo-8-chloro-4-methyl-	99	614
4-Bromo-2-(*tert*-butyl)-6-chloro-	85	1883
2-Adamantyl-4-bromo-6-chloro-	173	1883
4-Bromo-7-chloro-3-methyl-	82.3	739

TABLE 52. Dihalopolyalkylquinolines

Substituents	M.p. (°C)	References
6,7-Difluoro-1,2,3,4-tetrahydroacridine [a]	70	1069
6,7-Difluoro-1,2,3,4-tetrahydro-2-methylacridine [a]	80	1069
2,4-Dichloro-3-(*p*-ethoxybenzyl)-6-methyl-	112	596
2,4-Dichloro-3,6-dimethyl-		2096
2,4-Dichloro-5,8-dimethyl-	80.5	581
2,4-Dichloro-6,8-dimethyl-	115.5	589
2,4-Dichloro-7,8-dimethyl-	73	589
3-Benzyl-2,4-dichloro-5,8-dimethyl-	95	589
2,4-Dichloro-3-(*n*-pentyl)-6,8-di-(*n*-propyl)-		564
6-(*n*-Butyl)-2,4-dichloro-3,8-di-(*n*-propyl)-		564
2,4-Dichloro-8-(*n*-pentyl)-3,6-di-(*n*-propyl)-		564
3-Benzyl-2,4-dichloro-6,8-dimethyl-	92	589
3-Benzyl-2,4-dichloro-7,8-dimethyl-	97	589
2,5-Dichloro-4,6-dimethyl-	122.5	419
2,7-Dichloro-4-methyl-3-vinyl-	87	2105
2,7-Dichloro-4,6-dimethyl-	139	419
	79	793
4,5-Dichloro-2,3-dimethyl-	91	990
4,5-Dichloro-3-ethyl-2-methyl-	85.5	511
4,5-Dichloro-2,8-dimethyl-	88	991
4,6-Dichloro-2,3-dimethyl-	126	511
4,6-Dichloro-3-ethyl-2-methyl-	78	511
7,9-Dichloro-1,2,3,4-tetrahydroacridine[a]	85[b]	2006
	111	987, 1955

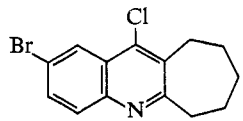
[a] See footnote *b* on p. 711. [b] Hydrochloride, m.p. 230 °C (decomp.).

TABLE 52 (*cont.*)

Substituents	M.p. (°C)	References
4,6-Dichloro-2,8-dimethyl-	123	991
4,7-Dichloro-2,3-dimethyl-	89	990
4,7-Dichloro-3-ethyl-2-methyl-	80.5	511
4,7-Dichloro-3-cyclopentyl-2-methyl-	88	992
6,9-Dichloro-1,2,3,4-tetrahydroacridine[a]	89	2006
4,7-Dichloro-2,8-dimethyl-	93	991
4,7-Dichloro-3,6-dimethyl-	130	321
4,8-Dichloro-2,3-dimethyl-	88.5	511
4,8-Dichloro-3-ethyl-2-methyl-	43	511
	83	987
4,8-Dichloro-2,5-dimethyl-	86	511
4,8-Dichloro-2,3,5-trimethyl-	131	511
4,8-Dichloro-3-ethyl-2,5-dimethyl-	40	511
5,6-Dichloro-2,4-dimethyl-	120	91
5,7-Dichloro-2,4-dimethyl-	86	91
5,8-Dichloro-2,4-dimethyl-	118.5	91
5,8-Dichloro-2,6-dimethyl-	84	687
5,8-Dichloro-2,7-dimethyl-	97	687
6,7-Dichloro-2,4-dimethyl-	120	91
6,8-Dichloro-2,4-dimethyl-	148.5	91
7,8-Dichloro-2,4-dimethyl-	104.5	91
7,8-Dichloro-2,5-dimethyl-	124[c]	932
5,7-Dibromo-1,2,3,4-tetrahydroacridine[a]	107	2010

[c] Picrate, m.p. 154 °C.

TABLE 52a. Mixed Dihalopolyalkylquinolines

Substituents	M.p. (°C)	References
6-Bromo-4-chloro-2,3-dimethyl-	103	511
6-Bromo-4-chloro-3-ethyl-2-methyl-	73	511
7-Bromo-9-chloro-1,2,3,4-tetrahydroacridine[a]	99	117
		1955
9-Chloro-6-iodo-1,2,3,4-tetrahydroacridine[a]	116	2006
8-Bromo-4-chloro-2,3-dimethyl-	96	511
8-Bromo-4-chloro-3-ethyl-2-methyl-	48.5	511

[a] See footnote *b* on p. 711.

TABLE 53. Dihalo-aryl- and -arylalkyl-quinolines

Substituents	M.p. (°C)	References
2,4-Dichloro-3-phenyl-	94	357, 1528, 2084
2,4-Dichloro-3-(*o*-nitrophenyl)-	142	343
3-(*o*-Aminophenyl)-2,4-dichloro-	[a]	343
3-(*o*-Acetamidophenyl)-2,4-dichloro-	235	343
2,6-Dichloro-4-phenyl-	115	1027, 1043, 1915
2,6-Dichloro-3,4-diphenyl-	172	1914, 1915
2,6-Dichloro-3-methyl-4-phenyl-	177	1914
4,5-Dichloro-2-phenyl-	103	480, 1017
4,5-Dichloro-3-phenyl-		993
4,6-Dichloro-2-phenyl-	112, 120	479, 480, 1021
4,6-Dichloro-3-phenyl-	144.5	471
4,7-Dichloro-2-phenyl-	101.5	454, 477, 480, 1017, 1055, 1366
4,7-Dichloro-2-(*p*-chlorophenyl)-	163, 168	1000, 1366
4,7-Dichloro-2-(*p*-tolyl)-	125	1366
4,7-Dichloro-2-(*p*-methoxyphenyl)-	121.5	1366
4,7-Dichloro-3-phenyl-	122	471, 493, 993
4,8-Dichloro-3-phenyl-	113.5	471
6,8-Dichloro-2-(3-chloro-4-ethoxyphenyl)-	152	1095
6,8-Dichloro-5-methyl-2-phenyl-	149	906
6,8-Dichloro-2-(*p*-chlorophenyl)-7-methyl-		1895
3,4-Dibromo-2-phenyl-	150	623, 1212, 2099
3,4-Dibromo-2-(*p*-bromophenyl)-	223	623
4,6-Dibromo-2-phenyl-	122	213

[a] At 160 °C hydrogen chloride is evolved and a product of undetermined structure is obtained.

TABLE 53a. Mixed Dihaloarylquinolines

Substituents	M.p. (°C)	References
3-Bromo-4-chloro-2-phenyl-	135	2015
3-Bromo-2-(*o*-bromophenyl)-4-chloro-	149	2015
6-Bromo-4-chloro-2-phenyl-	114	213
6-Bromo-8-chloro-2-phenyl-	92	900

TABLE 54. Trihaloquinolines

Substituents	M.p. (°C)	Derivative, m.p. (°C)	References
5,6,8-Trifluoro-	87		271, 721
6,7,8-Trifluoro-	101.5		721
2,3,4-Trichloro-	107.5		575, 576, 1344
2,3,6-Trichloro-	161		55
2,4,6-Trichloro-	120, 126		582, 593
2,4,7-Trichloro-	100, 107.5		565, 582, 585, 593, 594, 775, 1460, 1505

TABLE 54 (*cont.*)

Substituents	M.p. (°C)	Derivatives, m.p. (°C)	References
2,4,8-Trichloro-	104		593
2,6,8-Trichloro-	166		648, 1140
3,4,5-Trichloro-	85.5	Picrate, 220 d	122
3,4,6-Trichloro-	114		45, 212
3,4,7-Trichloro-	84, 114.5	Picrate, 146.5	122, 604
3,4,8-Trichloro-	122		45
4,5,6-Trichloro-	122.5	Picrate, 169.5	691, 1009
4,5,7-Trichloro-	106	Picrate, 171	54, 493
4,5,8-Trichloro-	141		691, 1009
4,6,7-Trichloro-	155	Picrate, 192.5	493, 691, 1009
4,6,8-Trichloro-	169		691, 1009, 1013, 1014
4,7,8-Trichloro-	126	Picrate, 152	691, 694
5,6,7-Trichloro-	159		895
5,6,8-Trichloro-	125, 135		33, 895
5,7,8-Trichloro-	150		703
2,3,4-Tribromo-	130[a]		1959
2,6,8-Tribromo-	165		655
3,5,6-Tribromo-	149		177, 298, 798, 836
3,5,7-Tribromo-	126		283
3,5,8-Tribromo-	172		7, 95, 296, 297, 798, 1640
3,6,7-Tribromo-	116.5		298
3,6,8-Tribromo-	169.5, 175, 185		7, 13, 21, 94, 96, 103, 182, 183, 189, 297, 716, 797, 798, 836
5,6,7-Tribromo-	124		298
5,6,8-Tribromo-	159, 175		7, 9, 96, 175, 217, 296, 298
5,7,8-Tribromo-	141		175, 283
6,7,8-Tribromo-	84		298
5,6,7-Tri-iodo-	102		845

[a] In ref. 127, m.p. is given as 288 °C.

TABLE 54a. Mixed Trihaloquinolines

Substituents	M.p. (°C)	Derivative, m.p. (°C)	References
3-Bromo-2,4-dichloro-	95[a]		120
6-Bromo-3,4-dichloro-	131		212
3,6-Dibromo-4-chloro-	131.5		212
3-Bromo-4,5-dichloro-	87	Picrate, 220 d	122
4,5-Dichloro-3-iodo-	111	Picrate, 218	122, 534
3-Bromo-4,6-dichloro-	124.5		212
3-Bromo-4,7-dichloro-	108	Picrate, 144.5	122
4,7-Dichloro-3-iodo-	112	Picrate, 162.5	122, 534
5,7-Dibromo-4-chloro-	132	Picrate, 179	691

[a] B.p. 158 °C/1 mm.

TABLE 55. Polyhaloquinolines

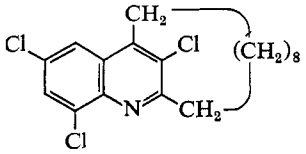
Substituents	M.p. (°C)	References
TETRAHALO		
5,6,7,8-Tetrafluoro-	95	271, 721
2,3,4,6-Tetrachloro-	127	411
2,4,5,8-Tetrachloro-	134	582
3,4,6,8-Tetrachloro-	190, 203	45, 1857
4,5,7,8-Tetrachloro-		2091
4,6,7,8-Tetrachloro-	156	484
5,6,7,8-Tetrachloro-	187	9
3,5,6,8-Tetrabromo-	198, 205	94, 95, 96, 297, 798, 836
5,6,7,8-Tetrabromo-	243	9
7-Bromo-5,6,8-trifluoro-	99.3	271, 721
PENTAHALO		
3,5,6,7,8-Pentafluoro-	50.5	750
3,4,5,6,7-Pentachloro-	144	45
3,4,5,6,8-Pentachloro-		45
3,4,6,7,8-Pentachloro-	203	45
3,5,6,7,8-Pentachloro-		1678
HEXAHALO		
3,4,5,6,7,8-Hexafluoro-	64.5	751
2,3,5,6,7,8-Hexachloro-		1678
2,4,5,6,7,8-Hexachloro-	185.5	271
HEPTAHALO		
2,3,4,5,6,7,8-Heptafluoro-[a]	95.5	35, 36, 1218
2,3,4,5,6,7,8-Heptachloro-	152, 157	35, 36, 37, 38, 41, 46, 47, 1989
2-Chloro-3,4,5,6,7,8-hexafluoro-		750, 752
2-Bromo-3,4,5,6,7,8-hexafluoro-		750, 752
2,4-Dichloro-3,5,6,7,8-pentafluoro-	77.5	750, 752
2,4-Dibromo-3,5,6,7,8-pentafluoro-	86	750, 752
3,5,6,7,8-Pentafluoro-2,4-di-iodo-	119	750
2,8-Dibromo-3,4,5,6,7-pentafluoro-		752
3,4,5,6,7-Pentafluoro-2,8-di-iodo-		752

[a] B.p. 205 °C/760 mm; SbF_6^- salt, m.p. 104 °C (dec.).

TABLE 56. Polyhalo-alkyl- and -aryl-quinolines

Substituents	M.p. (°C)	References
2,3,4-Trichloro-6-methyl-	134	577, 578
2,3,4-Trichloro-8-methyl-	112.5	577
2,4,6-Trichloro-3-(*p*-methoxybenzyl)-	84	596
2,4,7-Trichloro-3-methyl-	106	990
2,6,8-Trichloro-4-methyl-	200	1857

TABLE 56 (*cont.*)

Substituents	M.p. (°C)	References
	160	793
4,5,7-Trichloro-3-methyl-	151	493
4,5,8-Trichloro-2-methyl-	122	511, 1857
4,5,8-Trichloro-2,3-dimethyl-	159	511
4,5,8-Trichloro-3-ethyl-2-methyl-	64	511
4,6,8-Trichloro-2-methyl-	154	511, 1857
4,6,8-Trichloro-2,3-dimethyl-	113	511
4,6,8-Trichloro-3-ethyl-2-methyl-	74	511
5,6,8-Trichloro-2,4-dimethyl-	114	91
6-Bromo-2,4-dichloro-3-(*p*-methoxybenzyl)-	126	596
5,7-Dibromo-9-chloro-1,2,3,4-tetrahydroacridine[a]	173	117
3,4,6-Tribromo-2-phenyl-	195	2099
2-Adamantyl-4-bromo-6,8-dichloro-	233	1883
5,6,7,8-Tetrafluoro-2-methyl-	52	271, 721
5,6,7,8-Tetrafluoro-4-methyl-	81.5	271, 721
3,5,6,7,8-Pentachloro-2,4-dimethyl-	127	91

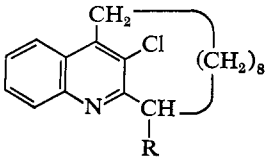
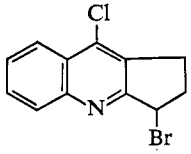
[a] See footnote *b* on p. 711.

TABLE 57. Polyhalohydroquinolines

Substituents	M.p. (°C)	References
Heptadecafluorodecahydro-[a]		29
2,2-Dichloro-1,2-dihydro-1-methyl-		662, 664
3,4-Dichloro-1,2,3,4-tetrahydro-2,6-dimethyl-[b]		89
4,6-Dichloro-1,2-dihydro-2,2-dimethyl-		1926
2,5,6,8-Tetrachloro-5,8-dihydro-4-methyl-	101	1857
2,5,6,7,8-Pentachloro-5,6,7,8-tetrahydro-	132	1857
2,5,6,7,8-Pentachloro-5,6,7,8-tetrahydro-4-methyl-	153	1857
5,6,7,8,8-Pentachloro-5,6,7,8-tetrahydro-4-methyl-	188	1857
4,5,6,7,8,8-Hexachloro-5,6,7,8-tetrahydro-2-methyl-	175.5	1857
5,7-Dibromo-1,2,3,4-tetrahydro-[c]		104
3,4,6,8-Tetrabromo-1,2,3,4-tetrahydro-2,2,4-trimethyl-	160	202

[a] B.p. 130 °C/760 mm; n_D^{25} 1.302.
[b] 1-Bz-derivative, m.p. 128 °C.
[c] Hydrobromide, m.p. 185 °C.

TABLE 58. Monohalo(haloalkyl)quinolines

Substituents	M.p. (°C)	References
7-Fluoro-2-(chloromethyl)-6-methyl-		2088
2-Chloro-3-(trifluoromethyl)-	100	395
3-(Bromomethyl)-2-chloro-	125	1749
2-Chloro-3-(2-chloroethyl)-4-methyl-	139	354
3-(2-Bromoethyl)-2-chloro-	92	831
2-Chloro-4-(trifluoromethyl)-	39.5, 42	390, 395, 1953
2-Chloro-4-(chloromethyl)-	97, 102	1747, 1827
4-(Bromomethyl)-2-chloro-	98	1747
2-Chloro-4-(dibromomethyl)-	58	1747
2-Chloro-7-(trifluoromethyl)-	118	390
3-Chloro-2-(chloromethyl)-4-methyl-	103	1974
	145 *syn* R = Cl *anti* R = Cl 151 *syn* R = Br *anti* R = Br	1974 2038 1164 2038
4-Chloro-2-(trifluoromethyl)-	34, 39	390, 395, 453
4-Chloro-6-methyl-2-(trifluoromethyl)-	68	453
4-Chloro-8-methyl-2-(trifluoromethyl)-	[a]	453
4-Chloro-6,8-dimethyl-2-(trifluoromethyl)-	101	627
4-Chloro-2-(trichloromethyl)-	65	1349
4-Chloro-2-(dibromomethyl)-	164	1349
4-Chloro-3-(2-chloroethyl)-2-(dibromomethyl)-	141.5	1452
4-Chloro-3-(1,2-dibromoethyl)-2-(dibromomethyl)-	174	1452
4-Chloro-2-(tribromomethyl)-	122	1349
	196	1452
4,9-Dichloro-1,2,3,4-tetrahydroacridine[b]	141	2020
4-Chloro-3-(chloromethyl)-	122	460, 1761
4-Chloro-3-(chloromethyl)-2-methyl-	64	624
4-Chloro-3-(chloromethyl)-7-(trifluoromethyl)-[c]		460
4-Chloro-3-(2-chloroethyl)-2-methyl-	60, 64[d]	624, 829, 830, 831, 833, 1562, 1563
4-Chloro-3-(2-chloroethyl)-2,6-dimethyl-	96, 127	829, 830, 832
4-Chloro-3-(2-chloroethyl)-2,8-dimethyl-	76	829
4-Chloro-3-(3-chloroallyl)-2-methyl-	54	2021

[a] B.p. 60 °C/0.2 mm.
[b] See footnote *b* on p. 711.
[c] Hydrochloride recorded without m.p.
[d] B.p. 156 °C/2 mm.

TABLE 58 (*cont.*)

Substituents	M.p. (°C)	References
4-Chloro-3-(3-chloroallyl)-2,6-dimethyl-	83	2021
4-Chloro-3-(3-chloroallyl)-2,8-dimethyl-	61	2021
4-Chloro-3-(3,3-dichloroallyl)-2-methyl-	102	1805
4-Chloro-3-(3,3-dichloroallyl)-2,6-dimethyl-	105	1805
4-Chloro-3-(3,3-dichloroallyl)-2,8-dimethyl-	76	1805
4-Chloro-3-(3-chlorobut-2-enyl)-2-methyl-	54	508
4-Chloro-3-(3-chlorobut-2-enyl)-2,6-dimethyl-	62	508
4-Chloro-3-(3-chlorobut-2-enyl)-2,8-dimethyl-	43	508
4-Chloro-3-(1,2-dibromoethyl)-2-methyl-	88	1452
4-Chloro-3-methyl-5-(trifluoromethyl)-	102.5	1368
4-Chloro-6-(trifluoromethyl)-	48	1877
4-Chloro-7-(trifluoromethyl)-	72, 81	493, 495, 496, 1368, 2095
4-Chloro-2-methyl-7-(trifluoromethyl)-	47	994, 2095
4-Chloro-3-methyl-7-(trifluoromethyl)-	66.5	1368
4-Chloro-8-(trifluoromethyl)-	78	1421, 1428, 1877
5-Chloro-2-(tribromomethyl)-	103	769
6-Chloro-4-(chloromethyl)-1,2-dihydro-2,2-dimethyl-[e]		204
6-Chloro-2-(tribromomethyl)-	60	925
2-(Bromomethyl)-7-chloro-6-methyl-	142	711
7-Chloro-2-(tribromomethyl)-	175	769
7-Chloro-6-methyl-2-(tribromomethyl)-	148	711
8-Chloro-4-(chloromethyl)-		1843
2-Bromo-3-(bromomethyl)-	138	1749
3-Bromo-6-(dibromomethyl)-	141	290
3-Bromo-8-(chloromethyl)-	106	291
3-Bromo-8-(bromomethyl)-	145	292, 1829
4-Bromo-2-(trifluoromethyl)-	39	627
4-Bromo-3-(2-bromoethyl)-2-methyl-	96	624
2-Adamantyl-4-bromo-8-(trifluoromethyl)-	157	1883
6-Bromo-4-(bromomethyl)-1,2-dihydro-2,2-dimethyl-[f]		203, 204, 1501
4-Bromo-6-methyl-2-(trifluoromethyl)-	71	627
4-Bromo-6,8-dimethyl-2-(trifluoromethyl)-	116	627
3-(Bromomethyl)-2-iodo-	128	1749
8-Iodo-5-(trifluoromethyl)-	63	726
8-Iodo-7-(trifluoromethyl)-	112	726

[e] Hydrochloride, m.p. 180 °C (decomp.).
[f] Hydrobromide, m.p. 194 °C (decomp.).

TABLE 59. Dihalo(haloalkyl)quinolines

Substituents	M.p. (°C)	References
2,4-Dichloro-3-(dichloromethyl)-	126	567, 568
2,4-Dichloro-3-(2-chloroethyl)-	114	414, 572, 573, 1361
2,4-Dichloro-3-(3,3-dichloroallyl)-		1543
2,4-Dichloro-3-(3-chlorobut-2-enyl)-		1876

TABLE 59 (*cont.*)

Substituents	M.p. (°C)	References
4-(Bromomethyl)-2,8-dichloro-	96	511
3,4-Dichloro-2-(chloromethyl)-	120	599
4,6-Dichloro-2-(trifluoromethyl)-	104.5	627
4,6-Dichloro-3-(chloromethyl)-[a]		460
4,6-Dichloro-3-(2-chloroethyl)-2-methyl-	117	829
4,6-Dichloro-3-(3-chloroallyl)-2-methyl-	94	2021
4,6-Dichloro-3-(3,3-dichloroallyl)-2-methyl-		1879
4,6-Dichloro-3-(3-chlorobut-2-enyl)-2-methyl-	59	1840
4,7-Dichloro-2-(dibromomethyl)-	190	1123
4,7-Dichloro-2-(tribromomethyl)-	143	1123
4,8-Dichloro-2-(trifluoromethyl)-	59.5	627
4,8-Dichloro-3-(2-chloroethyl)-2-methyl-	70	624, 830, 832
4,8-Dichloro-3-(3-chloroallyl)-2-methyl-	56	2021
6,8-Dichloro-2-(dibromomethyl)-	119.5	954
7-(Bromomethyl)-6,8-dichloro-2-(*p*-chlorophenyl)-	181	1895
3,6-Dibromo-4-(bromomethyl)-1,2-dihydro-2,2-dimethyl-[b]		203, 204
5,8-Dibromo-4-(tribromomethyl)-	178	1349

[a] Hydrochloride, m.p. 191 °C.
[b] Hydrobromide, m.p. 182 °C (decomp.).

TABLE 59a. Mixed Dihalo(haloalkyl)quinolines

Substituents	M.p. (°C)	References
6-Bromo-4-chloro-2-(trifluoromethyl)-	98	453
6-Bromo-4-chloro-(2-chloroethyl)-2-methyl-	115	829, 830
6-Bromo-4-chloro-3-(3-chloroallyl)-2-methyl-	102	2021
6-Bromo-4-chloro-3-(3-chlorobut-2-enyl)-2-methyl-	78	1840
8-Bromo-4-chloro-3-(3-chloroallyl)-2-methyl-	67	2021
8-Bromo-4-chloro-3-(3-chlorobut-2-enyl)-2-methyl-	32	1840
4-Bromo-6-fluoro-2-(trifluoromethyl)-	95	995
4-Bromo-6-chloro-2-(trifluoromethyl)-	120	627
4-Bromo-8-fluoro-2-(trifluoromethyl)-	69	995

TABLE 60. Polyhalo(haloalkyl)quinolines

Substituents	M.p. (°C) or b.p. (°C/mm)	References
2,4,6-Trichloro-3-(2-chloroethyl)-	117	1361
2,4,6-Trichloro-3-(3-chlorobut-2-enyl)-	148	596
2,4,7-Trichloro-3-(2-chloroethyl)-	100	1361
4,5,8-Trichloro-3-(2-chloroethyl)-2-methyl-	115.5	829
4,6,8-Trichloro-2-(trifluoromethyl)-	76	627
4,6,8-Trichloro-3-(2-chloroethyl)-2-methyl-	115	624

TABLE 60 (*cont.*)

Substituents	M.p. (°C) or b.p. (°C/mm)	References
3,6,8-Tribromo-4-(bromomethyl)-1,2-dihydro-2,2-dimethyl-	162	203, 204, 1501
3,6,8-Tribromo-4-(dibromomethyl)-1,2-dihydro-2,2-dimethyl-	188	203, 204, 1501
3,6,8-Tribromo-4-(bromomethylene)-1,2,3,4-tetrahydro-2,2-dimethyl-	159	1501
3,5,7,8-Tetrafluoro-2,4,6-tris(perfluoroisopropyl)-	> 260/760	1250
3,5,6,7,8-Pentafluoro-2,4-di(perfluoroisopropyl)-	Oil	1250
3,4,5,7,8-Pentafluoro-2,6-di(perfluoroisopropyl)-	Oil	1250
2,3,5,6,7,8-Hexafluoro-4-(perfluorisopropyl)-	228/754	1250
3,4,5,6,7,8-Hexafluoro-2-(perfluoroisopropyl)-	220/763	1250

TABLE 60a. Mixed Polyhalo(haloalkyl)quinolines

Substituents	M.p. (°C)	References
6-Bromo-2,4-dichloro-3-(3-chlorobut-2-enyl)-	152	596
6,8-Dibromo-4-chloro-3-(2-chloroethyl)-2-methyl-	[a]	829
4-Bromo-6,8-difluoro-2-(trifluoromethyl)-	85	995
4-Bromo-6,8-dichloro-2-(trifluoromethyl)-	76	627

[a] Hydrochloride, m.p. 161.5 °C.

TABLE 61. (Monohaloalkyl)quinolines

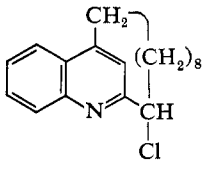
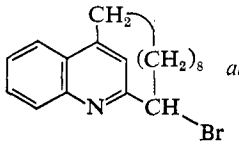
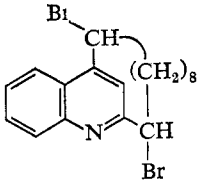
Substituents	M.p. (°C)	Derivatives, m.p. (°C)	References
2-(Chloromethyl)-	57.5	Picrate, 172–173; HCl, 192 d	787, 1722, 1727, 1734, 1735, 1750, 1766, 1770, 1811
2-(Chloromethyl)-4-methyl-	60	Picrate, 187	1973, 1975
2-(Chloromethyl)-6-methyl-	110		711, 1736, 2088
2-(Chloromethyl)-4,6-dimethyl-			2088
	110		793

TABLE 61 (*cont.*)

Substituents	M.p. (°C)	Derivatives, m.p. (°C)	References
3-(Chloromethyl)-	34	HCl, 131	1761, 1771
3-(2-Chloroethyl)-2-methyl-	62		833
4-(Chloromethyl)-	57	Picrate, 188	787, 1747, 1811
4-(Chloromethyl)-1,2-dihydro-2,2-dimethyl-		HCl, 180 d	203, 204
4-(1-Chloroethyl)-		Picrate, 180	401
5-(Chloromethyl)-	89.5		1761
6-(Chloromethyl)-	70	Picrate, 206; HCl, 184.5	1759, 1760, 1761, 1767
7-(Chloromethyl)-	54		1761
8-(Chloromethyl)-	56		292, 1761
2-(Bromomethyl)-	57, 83	Picrate, 178; MeBr, 205 d	1725, 1727, 1733, 1744, 1750, 1781, 1823, 1826, 1828
2-(1-Bromoethyl)-			1758
2-(3-Bromopropyl)-		HBr, 117	1764
2-(1-Bromo-2,2-diphenylethyl)-	132.5		1732
 *anti*-			2038
3-(Bromomethyl)-	54.5		1727
4-(Bromomethyl)-	65, 91	Picrate, 193; HBr, 230	1727, 1745, 1746, 1747, 1770, 1820
4-(Bromomethyl)-1,2,3,4-tetrahydro-		HBr, 163; Picrate, 135	1757
4-(Bromomethyl)-1,2-dihydro-2,2-dimethyl-		HBr, 191 d; *N*-Ac, 109; *N*-Bz, 126; *N*-$PhSO_2$, 117	203, 204, 1748
5-(Bromomethyl)-	76.5		1761
6-(Bromomethyl)-	75	Picrate, 198	1759, 1761
6-(Bromomethyl)-2-phenyl-			1967
6-(Bromomethyl)-2-(*p*-chlorophenyl)-			1967
6-(Bromomethyl)-2-(*p*-fluorophenyl)-			1967
6-(Bromomethyl)-2-(2-thienyl)-			1967
7-(Bromomethyl)-	70.5		1761
8-(Bromomethyl)-	84		107, 292, 1743, 1753, 1754, 1755
4-(2-Iodoethyl)-[a]		HI, 173	1756
4-(2-Iodoethyl)-1,2,3,4-tetrahydro-		HI, 105	1756
6-(Iodomethyl)-	205 ?	Picrate, 198	1759
8-(Iodomethyl)-	84		292, 1788

[a] Free base polymerizes on distillation.

TABLE 62. (Dihaloalkyl)quinolines

Substituents	M.p. (°C)	Derivatives, m.p. (°C)	References
2-(Dichloromethyl)-	83	Picrate, 119	1722, 1727, 1734
2-(3,3-Dichloropropyl)-	[a]		1797, 1819
2-(3,3-Dichloropropyl)-1,2,3,4-tetrahydro-			1797, 1819
2-(3,3-Dichloroallyl)-	131		1797, 1819
2-(Dibromomethyl)-	120	Picrate, 151; MeI, 120	1725, 1727, 1729, 1731, 1733, 1750, 1784, 1785, 1787, 1823, 1966
2-(Dibromomethyl)-6-methyl-	86		1729
2-(1,1-Dibromoethyl)-			1730
2-(1,2-Dibromoethyl)-	64		1773
2-(α,β-Dibromo-*p*-chlorophenethyl)-	175		1732
	135	Picrate, 185	1164
4-(Dibromomethyl)-1,2-dihydro-2,2-dimethyl-		1-Bz, 167	1748
6-(Dibromomethyl)-	160		290
8-(Dibromomethyl)-	108		1754
4-(1,3-Di-iodo-2-propyl)-	140 d		1723

[a] Amorphous.

TABLE 63. (Trihaloalkyl)quinolines

Substituents	M.p. (°C) and/or b.p. (°C/mm)	Derivatives, m.p. (°C)	References
2-(Trifluoromethyl)-	62.5 233/760 120–130/20	HCl, 145	453, 1790, 1810, 1817
6-Methyl-2-(trifluoromethyl)-	93		453, 995
8-Methyl-2-(trifluoromethyl)-	50/0.35		453
1,2,3,4-Tetrahydro-2-(trifluoromethyl)-	120/22		1790
3-(Trifluoromethyl)-	110/15		395, 1817
4-(Trifluoromethyl)-	139/25	Picrate, 162	395, 1817
5-(Trifluoromethyl)-[a]	−7 217/760	Picrate, 186; Oxalate, 136	726, 868, 869, 870
5,7-Bis(trifluoromethyl)-	98/17		1802

[a] n_{Di}^{32} 1.5379; d_4^{32} 1.272.

TABLE 63 (*cont.*)

Substituents	M.p. (°C) and/or b.p. (°C/mm)	Derivatives, m.p. (°C)	References
6-(Trifluoromethyl)-	39 224/714		1799, 1817
4-Methyl-6-(trifluoromethyl)-	56	Picrate, 220	1996
7-(Trifluoromethyl)-	60, 67 221/731	HNO_3, 171	726, 868, 869, 870, 1790, 1791, 1801
1,2,3,4-Tetrahydro-7-(trifluoromethyl)-	33.5 256.5/758 140/22		869, 1790, 1791
2-Methyl-7-(trifluoromethyl)-			1790, 1791
1,2,3,4-Tetrahydro-2-methyl-7-(trifluoromethyl)-			1790, 1791
2-(*p*-Tolyl)-7-(trifluoromethyl)-	133		868
8-(Trifluoromethyl)-	66 252/728		1799
2-(Trichloromethyl)-	56, 64		1724, 1825, 1965
2-(3,3,3-Trichloroallyl)-	148		1774, 1818
4-Methyl-2-(3,3,3-trichloroallyl)-	124		1776
4-Methyl-2-(2,2-dibromo-3,3,3-trichloropropyl)-	155		1776
2-Methyl-4-(trichloromethyl)-	69		1804
2-(Tribromomethyl)-	130, 205 ?		942, 1724, 1733, 1750, 1966
3-Methyl-2-(tribromomethyl)-	158		1730
4-Methyl-2-(tribromomethyl)-	162		1727
6-Methyl-2-(tribromomethyl)-	133		1729
4-(Tribromomethyl)-		MeBr, 159	1727

TABLE 64. Miscellaneous Haloquinolines

Compound	M.p. (°C)	Derivatives, m.p. (°C)	References
1-Chloro-1,2-di-(2-quinolyl)ethylene	110	Dipicrate, 236	1782
1-Bromo-1,2-di-(2-quinolyl)ethylene	116	Dipicrate, 212	1782
cis-1,2-Dichloro-1,2-di-(2-quinolyl)ethylene	95	Picrate, 185	1781
trans-1,2-Dichloro-1,2-di-(2-quinolyl)-ethylene	173	Picrate, 224	1781
cis-1,2-Dibromo-1,2-di-(2-quinolyl)-ethylene	142	Picrate, 189; 2HBr, 263 d	1781, 1782
trans-1,2-Dibromo-1,2-di-(2-quinolyl)-ethylene	223	Picrate, 239	1781
1,2-Dibromo-1,2-di-(2-quinolyl)ethane	173 d		1780
1,1,2-Trichloro-1,2-di-(2-quinolyl)ethane	139		1782
1,1,2-Tribromo-1,2-di-(2-quinolyl)ethane	151 d		1782
1,2-Di-(4-chloro-2-methyl-6-quinolyl)-ethylene	276		444
2,3-Di-(4-chloro-2-methyl-6-quinolyl)-but-2-ene	234		444

TABLE 64 (*cont.*)

Compound	M.p. (°C)	Derivatives, m.p. (°C)	References
Di-(8-bromo-2-quinolyl)methane	237		1312
2,2′,4-Tribromo-3,4′-biquinoline	237		1959
trans-(−)-1-Chlorodecahydroquinoline[a]			339
1-Chlorodecahydroquinoline	125.5		336
8-(Dichloroiodo)-6-methylquinoline	138		337
8-Iodosylquinoline	175 d		337
8-Iodylquinoline	187		337
2-(4-Chloro-2-quinolyl)cyclohexanone	99		1317
2-(4,7-Dichloro-2-quinolyl)cyclohexanone	135		1317
2-(2-Chloro-4-quinolyl)cyclohexanone	101		1317

[a] $[\alpha]_D^{20}$ +134.5 °C.

TABLE 65. Haloquinolines of Uncertain Structure

Compound	M.p. (°C) and/or b.p. (°C/mm)	References
(? 6)-Chloro-2-methyl-	94.5	272
(5 or 7)-Chloro-6,8-dimethyl-	42 168/0.4	259
(? 5)-Bromo-2-methyl-	56	99
(? 3)-Bromo-6-methyl-	51	99
(? 5)-Bromo-6-methyl-	85	98
x-Bromohexahydro-[a]		200
(? 3)-Iodo-	63	218
(? 3)-Iodo-8-methyl-	74	218
2,*x*-Dichloro-6,8-dimethyl-	109	259
x,*x*-Dichloro-6-methyl-	81	98
(? 2, ? 6)-Dibromo-	171	2
3,*x*-Dibromo-	166	287
(?3, ? 7)-Dibromo-	108	287
x,*x*-Dibromo-1,2,3,4-tetrahydro-	66	92
(? 6, ? 8)-Dibromo-1,2,3,4-tetrahydro-[b]	Oil	103, 104, 182
x,*x*-Dibromo-6-methyl-	136	98
x,*x*-Dibromo-2-ethyl-3,6-dimethyl-	144	93
x,*x*-Di-iodo-	90	92
(? 5, ? 8)-Di-iodo-	165	220
x,*x*-Di-iodo-6-methyl-	136	98
x,*x*-Di-iodo-8-methyl-	171	219
x-Bromo-4-chloro-2,6,8-trimethyl-	107	117
x,*x*,*x*-Trichloro-	135/0.7	46
x,*x*,*x*-Trichloro-	186	236, 237
2,(? 3, ? 6)-Trichloro-	160.5	110
2,*x*,*x*-Trichloro-	ca. 140	800
2,4,(7 or 8)-Trichloro-	105	562

[a] Hydrobromide, m.p. 184 °C. [b] Hydrobromide, m.p. 185 °C.

TABLE 65 (*cont.*)

Compound	M.p. (°C) and/or b.p. (°C/mm)	References
5,8,*x*-Trichloro-	68	158
4,*x*,*x*-Trichloro-2-methyl-	102	470
x,*x*,*x*-Trichloro-6-methyl-	159	98
7,*x*,*x*-Trichloro-2,4-dimethyl-	195	91
(? 3, ? 6, ? 8)-Tribromo-	166	234, 236
2,*x*,*x*-Tribromo-	248	605, 1639
2,3,*x*-Tribromo-	174	284
2,4,*x*-Tribromo-	276 ?	127
2,(? 6), 8-Tribromo-	165	651
x,*x*,*x*-Tribromo-2-phenyl-	150	213
x,*x*,*x*-Tri-iodo-	189	219
x,*x*,*x*,*x*-Tetrachloro-	121	235, 238
x,*x*,*x*,*x*-Tetrachloro-	150/0.7	46
x,*x*,*x*,*x*-Tetrachloro-		35, 36
(? 4, ? 6, ? 7, ? 8)-Tetrachloro-	158	759
x,*x*,*x*,*x*-Tetrachloro-		254
2,*x*,*x*,*x*-Tetrachloro-	155	252
2,*x*,*x*,*x*-Tetrachloro-	199.5	1857
4,*x*,*x*,*x*-Tetrachloro-2-methyl-	159.5	1857
5,6,*x*,*x*-Tetrachloro-2,4-dimethyl-	158	91
6,*x*,*x*,*x*-Tetrachloro-2,4-dimethyl-	75.5–81	91
8,*x*,*x*,*x*-Tetrachloro-2,4-dimethyl-	152	91
x,*x*,*x*,*x*-Tetrabromo-	119	92
x,*x*,*x*,*x*-Tetrabromo-	255	189
3,4,*x*,*x*-Tetrabromo-2-phenyl-	167	213
4,6,*x*,*x*-Tetrabromo-2-phenyl-	179	213
x,*x*,*x*,*x*,*x*-Pentachloro-	184/0.7	46
x,*x*,*x*,*x*,*x*-Pentachloro-	206	35, 36
5,8,*x*,*x*,*x*-Pentachloro-2,4-dimethyl-	128	91
6,8,*x*,*x*,*x*-Pentachloro-2,4-dimethyl-	125	91
5,6,7,8,*x*,*x*-Hexachloro-	185.5	271, 721
x,*x*,*x*,*x*,*x*,*x*-Hexabromo-	90	2022
x-Chloro-*x*,*x*,*x*,*x*,*x*,*x*-hexafluoro-	90	35, 36

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Dedication

This chapter is dedicated to the proud memory of my son, Andrew John, during whose all too short lifetime it was composed and written.

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Author Index

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Subject Index

Notes on the use of this index

To avoid duplication, compounds listed in the tables at the end of Chapters 2 and 3 are not listed in this index unless they also appear in the text of those chapters. Page numbers in ordinary type refer to an entry in the text, while numbers in italic refer to an entry in a table within the text.

The following conventions have been adopted in the organization of the index:

(a) In Chapters 1 and 2 compounds are listed as derivatives of a major class, e.g.

2 (1H)-Quinolone, 6-hydroxy

but simple derivatives of quinoline appear throughout the index, e.g.

2-Allylquinoline

6-Nitroquinoline, etc.

(b) All substituted haloquinolines are listed as derivatives of the haloquinoline, and where two or more different halogens are present, listing is by alphabetical order, e.g. 5-chloro-8-hydroxy-7-iodoquinoline is listed as the 8-hydroxy-7-iodo derivative of 5-chloroquinoline, and not as a derivative of 7-iodoquinoline.

(c) Nuclear halogen derivatives are given precedence over side-chain halogen derivatives, e.g. 5-(bromomethyl)-6-chloroquinoline is indexed as the 5-(bromomethyl) derivative of 6-chloroquinoline.

(d) Substituents are listed under the parent haloquinoline in strictly alphabetical order, i.e. dimethyl before tetrahydro before triamino-, and not in recommended IUPAC order, as adopted in the text.

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