ISOQUINOLINES

PART ONE

This is the thirty-eighth 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



ISOQUINOLINES

PART ONE

Edited by

Guenter Grethe

CHEMICAL RESEARCH DEPARTMENT

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To Inge, Nadine, and Jeffrey

The Chemistry of Heterocyclic Compounds

The chemistry of heterocyclic compounds is one of the most complex 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 editions.

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ARNOLD WEISSBERGER

EDWARD C. TAYLOR

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Preface

The isoquinoline skeleton is found abundantly in the plant world and is widely incorporated into medicinally important compounds. Several excellent books on isoquinoline alkaloids and reviews on certain aspects of isoquinoline chemistry have been written but the significance of isoquinolines among heterocyclic compounds clearly merits a comprehensive and detailed study. This is the purpose of the books on isoquinolines. They are intended to serve a dual function, as an introduction for the beginner interested in the general chemistry of isoquinolines and as a source of detailed data for the frequent user. The individual chapters constitute a complete source on a specific subject of isoquinoline chemistry. They have been arranged in such a manner as to avoid overlapping as much as possible and to simplify literature searching.

The first two chapters deal with the general aspects of the chemistry of isoquinolines. A broad discussion of the physical and chemical properties of the ring system in the opening chapter is followed by a detailed coverage of the general and specific methods of synthesizing the isoquinoline nucleus. The other two chapters in Part I deal with the more specific subjects of isoquinoline biosynthesis and the chemistry of quaternary isoquinolinium derivatives. Subsequent chapters in future volumes will give a detailed coverage of the chemistry of substituted and fused isoquinolines and should be considered reference sources. To this purpose each of these chapters closes with an exhaustive tabulation of derivatives containing only the substituents discussed in that particular chapter and in the preceding ones.

These books are made possible only because of the untiring efforts of the expert authors, whose work I acknowledge with deep admiration and gratitude.

I thank Hoffmann-La Roche, Inc. for the use of the excellent library and the staff of the library for their continuous help. I owe my gratitude to Mrs. Claudette Czachowski for helping with the extensive correspondence connected with the editorial work. Special thanks are due to my family for their understanding and support during this long and sometimes difficult task.

GUENTER GRETHE

Nutley, New Jersey
November 1980

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XVIII. Isoquinolines Containing More Than Three Added Rings

P. H. GRAYSHAN and J. V. GREENHILL

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PART ONE

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CHAPTER I

Properties and Reactions of Isoquinolines and Their Hydrogenated Derivatives

S. F. DYKE* AND R. G. KINSMAN

School of Chemistry, University of Bath, Bath, United Kingdom

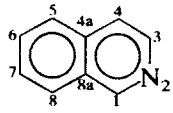
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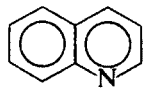
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I. INTRODUCTION

Isoquinoline (**1**)[1] is the name given to 2-azanaphthalene, the benzopyridine in which a benzene ring is fused to the C-3 and C-4 atoms of the pyridine system. The numbering scheme of the atoms used throughout this chapter is in accordance with that currently accepted by *Chemical Abstracts*, although in earlier literature the atoms **4a** and **8a** at the ring junction were numbered both 9, 10 and 10, 9, respectively.



1



2

Isoquinoline, which occurs in the crude quinoline (**2**) fraction of coal tar, was first reported[2] in 1885. It has been isolated by exploiting the greater basicity compared to quinoline and by the selective precipitation of certain isoquinoline salts. 1-Methyl-, 3-methyl-, and 1,3-dimethylisoquinolines have also been identified in coal-tar bases. Oxidation with alkaline potassium permanganate results[2] in degradation to phthalic acid and pyridine-3,4-dicarboxylic acid (cinchomeronic acid). Certain chemical and physical properties of isoquinoline resemble those of both quinoline and naphthalene. Isoquinoline has been classified[3] as a π-deficient system in common with quinoline and pyridine, and its properties reflect this definition.

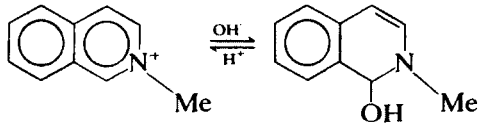
This chapter is intended as an introduction to the general physical and

chemical properties of this heterocyclic system. Some characteristics of isoquinoline derivatives are incorporated, but a more detailed description is given in the appropriate chapters.

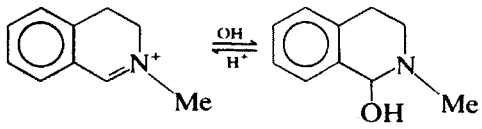
II. PHYSICAL PROPERTIES

A. General

Isoquinoline is[4] a colorless, crystalline substance with melting point (m.p.) 26.48±0.1°C. It has a density at 30°C of 1.09101 g/ml, and its viscosity is 3.2528 cP at the same temperature. The boiling point at 760 mm pressure is 243.25°C, and the heat of vaporization is 11.7 kcal/mole. The refractive index is n_D^{30} 1.62078. Critical temperatures of quinoline and isoquinoline, measured[5] by observation of the disappearance and reappearance of the liquid–vapor meniscus, are 509±2°C and 530±5°C, respectively. A heat of atomization ($-\Delta H_a$) of 85.32 eV and a resonance energy (E_R) of 34.1 kcal/mole were calculated[6] for isoquinoline by the SCF MO π-approximation method. By a different approach, using pK_a values for equilibria **3** and **4**, a value for the resonance energy of 48±9 kcal/mole was suggested.[7] Molar Cotton-Mouton constants for a series of solutes were determined[8] and a value for the magnetic susceptibility for isoquinoline of 94.2×10^{-6} derived (cf. quinoline, 112×10^{-6}).



3

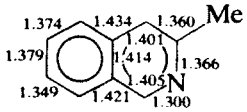


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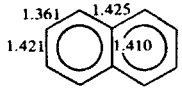
B. X-Ray Crystallography

The structural analysis[9] of 3-methylisoquinoline (**5**) shows it to be essentially planar, and the bond lengths resemble those of naphthalene (**6**)[10]. The three principal valence-bond structures of isoquinoline (**7**) are similar to those for naphthalene; and predictions of $\frac{2}{3}$ double-bond character for C_1–N, C_3–C_4, C_5–C_6, and C_7–C_8 bonds and $\frac{1}{3}$ double-bond character for all other bonds follow accordingly. The two C–N bond lengths, 1.300 Å for C_1–N and 1.366 Å for N–C_3, have the expected relationship to the 1.340-Å C–N

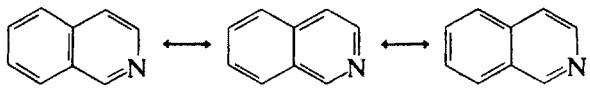
distance ($\frac{1}{2}$ double-bond character) in pyridines.[11] The structure[12] of isoquinoline hydrochloride (**8**) shows the increase in length of the C–N bonds expected to accompany protonation of the nitrogen lone-pair electrons. Papaverine has been examined,[13] and its dimensions are as shown in structure **9**.



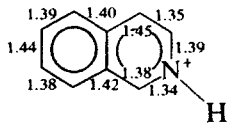
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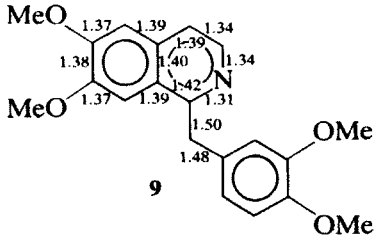
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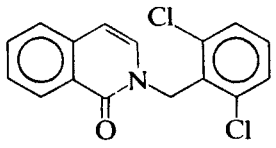


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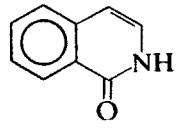


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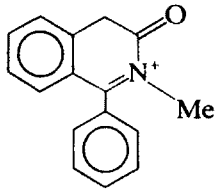
The bond lengths in 2-(2′,6′-dichlorobenzyl)-1-isoquinolone (**10**) are in fair agreement[14] with those calculated[15] by a semiempirical SCF MO π-approximation method for 1-isoquinolone (**11**) (Table I.1). In 2-methyl-1-



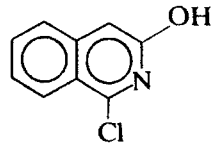
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12



13

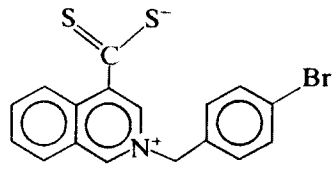
phenyl-3-isoquinolone (**12**) the N–C_3 bond length (1.447 A)[14] indicates an almost complete absence of conjugation between those two atoms; the suggested principal route for nitrogen–carbonyl conjugation is through the

benzenoid ring. The relevant bond lengths in 1-chloro-3-hydroxyisoquinoline (**13**) closely resemble those in 3-methylisoquinoline (**5**) and indicate that the compound exists in the lactim structure in the solid state.

TABLE I.1. BOND LENGTHS OF ISOQUINOLONES

Bond positions	Bond lengths (Å)				
	10[14]	**11**[15]	**12**[14]	**13**[14]	**3**[9]
C_1–N	1.390	1.376	1.379	1.304	1.300
N–C_3	1.383	1.412	1.447	1.366	1.366
C_3–C_4	1.334	1.348	1.433	1.366	1.360
C_4–C_{4a}	1.427	1.462	1.368	1.402	1.401
C_{4a}–C_5	1.403	1.403	1.412	1.416	1.434
C_5–C_6	1.373	1.393	1.338	1.350	1.374
C_6–C_7	1.382	1.400	1.432	1.416	1.379
C_7–C_8	1.379	1.393	1.350	1.354	1.349
C_8–C_{8a}	1.391	1.403	1.421	1.414	1.421
C_{8a}–C_1	1.466	1.466	1.379	1.405	1.405
C_{8a}–C_{4a}	1.413	1.403	1.426	1.436	1.414

A crystalline product from the reaction between 2-(4′-bromobenzyl)isoquinolinium bromide and carbon disulfide was obtained from dimethylformamide–acetonitrile solution, and its structure was shown[16] by X-ray crystallographic analysis to be 2-(4′-bromobenzyl)isoquinolinium-4-dithiocarboxylate (**14**); the molecular geometry and dimensions are described.



14

C. Dipole Moments

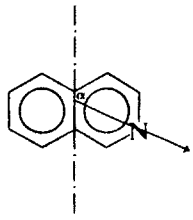
The dipole moment of isoquinoline is 2.49 D ± 0.01 D in benzene at 30.0°C.[4] Values of 2.60 D, 2.65 D, and 2.61 D were found[17] at 25°C for solutions in light petroleum, carbon tetrachloride, and benzene, respectively. Measurements in the vapor phase give values of 2.73 D[17] and 2.75 D,[18] compared with moments calculated[18] by the valence electrons self-consistent field (VESCF) method, of 2.41 D and 2.13 D, depending on the penetration terms adopted.

The dipole moments of several halogen-substituted isoquinolines have been measured[19] at 30°C in benzene (Table I.2), and using assumed[20]

TABLE I.2. DIPOLE MOMENTS OF HALOGENOISOQUINOLINES

Substituent	μ(D)	α(°)
None	2.53	—
1-Cl	3.35	108.5
3-Br	3.66	116.0
4-Br	2.70	105.0
5-F	2.10	123.5
5-Cl	2.35	114.5
5-Br	2.10	123.0
6-Br	1.24	98.0
7-Cl	1.92	109.0
8-Cl	3.15	98.0

moments for the C–F, C–Cl, and C–Br bonds, a mean value for the direction of the electric dipole moment in isoquinoline was derived, as shown in structure **15**. The dipole moment of isoquinoline *N*-oxide was measured[21]



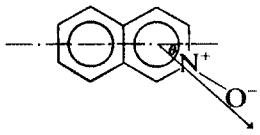
Mean $\alpha = 110°$

15

during an investigation into the double-bond character of N–O bonds in nitrogen heterocycles. The value of 4.47 D (cf. quinoline *N*-oxide, 4.07 D) compares favorably with that calculated[22]; the direction of the moment was predicted to be at an angle of 33°41′ with the *X*-axis, as indicated in structure **16**. Schmitz[23] measured the moment of 3,4-dihydroisoquinoline (**17**) by the Onsager method[24] and obtained values of μ_{20} 1.78 D, μ_{30} 1.83 D, and μ_{40} 1.87 D. A value of $\mu = 1.99$ D was measured[25] for 1-methyl-3,4-dihydroisoquinoline, and its direction was deduced from the dipole moment of 1-methyl-7-nitro-3,4-dihydroisoquinoline to act from C-4a through the nitrogen atom as shown in structure **18**.

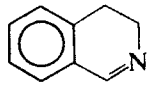
D. Ionization Constants

The lone-pair electrons of the nitrogen atom of isoquinoline are not delocalized into the π-aromatic system of this molecule but are present in

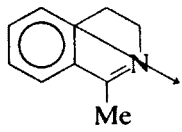


$\theta = 33°41'$

16



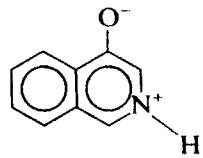
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18

an orbital that has a large proportion of *s*-character. Thus isoquinoline should presumably be a much stronger base than indole ($pK_a = -2.4$) but weaker than a typical aliphatic amine (e.g., trimethylamine, $pK_a = 9.7$). The pK_a value[26] of 5.40 (in water at 20°C) for isoquinoline is similar to that for pyridine ($pK_a = 5.23$)[27] but slightly higher than that for quinoline ($pK_a = 4.94$).[27] The ionization constant of isoquinoline has been determined[28] in a range of aqueous solvent mixtures, and the value for $\Delta pK/\Delta(1/D)$ (where D is the dielectric constant of the solvent mixture) was shown to increase through the series ethanol < 2-methoxyethanol < 1,2-dimethoxyethane < sulfolane < *N*-methylpyrrolidone < dimethylformamide < *N*-butylacetamide. This sequence is the same as that for quinoline but different from that for pyridine.

A nitro-group substituent is capable of exerting only a base-weakening effect because both $-I$- and $-M$-mechanisms act in unison; pK_a values for the nitroisoquinolines are 4-NO_2 1.35,[29] 5-NO_2 3.53,[30] 6-NO_2 3.47, 7-NO_2 3.61, and 8-NO_2 3.59. 4-Bromoisoquinoline[29] ($pK_a = 3.31$) is also a weaker base than the unsubstituted molecule because of the $-I$-effect of the halogen atom. Comparison[29] of the ionization constants of 4-nitro-, 4-bromo-, and 4-aminoisoquinoline as determined by a spectrophotometric method indicates that the Taft equation is followed with $\sigma = 0.95_{\sigma I} + 0.38_{\sigma R}$; an anomalous value of 4.70 for the 4-hydroxy compound is attributed to the contribution made by the zwitterion **19** (as much as 70%).



19

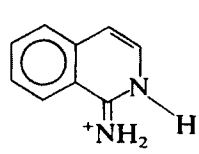
Protonation of aminoisoquinolines has been shown[26] to occur first at the ring nitrogen, and not at the substituent amino group. The first and second ionization constants of the aminoisoquinolines have been measured and are presented in Table I.3. It is possible to rationalize the first pK_a values using the concept of additional ionic resonance.[27] Thus amines with monocations from which additional ionic resonance is absent (4-, 5-, and 7-aminoisoquinolines) give ΔpK_a values of less than 1 unit. In contrast, 1-, 6-, and 8-aminoisoquinolines (cation resonance contributions **20**, **21**, and **22**,

TABLE I.3. IONIZATION CONSTANTS OF AMINOISOQUINOLINES

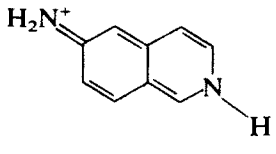
Substituent	First pK_a	Second pK_a
None	5.40[26]	—
1-NH_2	7.62[27]	−9.59[31]
3-NH_2	5.05	−4.20
4-NH_2	6.28	−2.29
5-NH_2	5.59	1.07
6-NH_2	7.17	−0.59
7-NH_2	6.20	1.13
8-NH_2	6.06[a]	0.18

[a] From ΔpK_a value quoted and the rationale in the discussion section, this value should read 7.06.

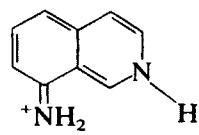
respectively) have ΔpK_a values considerably greater than 1 unit. In the case of 3-aminoisoquinoline it is suggested that the *ortho*-quinonoid ionic resonance form **23** is not sufficiently favored for increase of the stability of the cation relative to that of the base. The second pK_a of 1-aminoisoquinoline (−9.59) is similar to that of 2-aminopyridine[32] ($pK_a = -8.1$) and is probably due to the close proximity of the two positive charges on the molecule and some interaction with the perihydrogen atom. In the case of 3-aminoisoquinoline, where two close positive charges also exist, the second pK_a is lower than expected. The value for 4-aminoisoquinoline ($pK_a = -2.29$) is in general agreement with that for 3-aminopyridine[32] ($pK_a = -1.5$). The second ionization constants of 6- and 8-aminoisoquinolines are lower than those of the 5- and 7-isomers because of the more facile second protonation of the additional ionic resonance forms **21** and **22**.



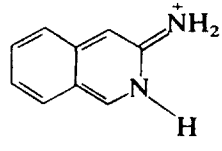
20



21



22



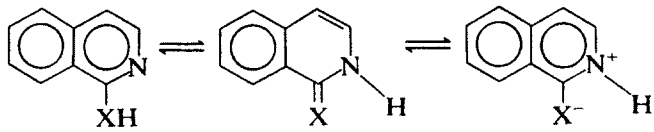
23

The ionization constants of hydroxy-[33–35] and mercaptoisoquinolines[36] and some of their *X*-Me derivatives are shown in Table I.4.

TABLE I.4. IONIZATION CONSTANTS OF HYDROXY- AND MERCAPTOISOQUINOLINES

Substituent	pK_a (Proton lost)	pK_a (Proton gained)	Ref.
1-OH	—	−1.2	33
N-Me	—	−1.8	33
O-Me	—	3.05	33
3-OH	9.62	2.18	34
4-OH	8.68	4.80	35
N-Me	—	4.93	35
5-OH	8.45	5.40	35
N-Me	—	6.90	35
6-OH	9.15	5.85	35
N-Me	—	6.02	35
7-OH	8.88	5.70	35
N-Me	—	7.09	35
8-OH	8.40	5.66	35
N-Me	—	5.81	35
1-SH	10.82	−1.9	36
N-Me	—	−2.13	36
S-Me	—	3.93	36
3-SH	8.58	0.39	36
S-Me	—	3.41	36

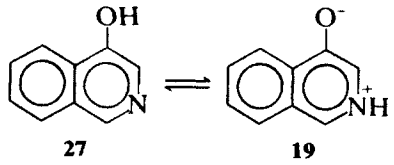
The close similarities between the proton-gained pK_a values for the *N*-unsubstituted and *N*-methyl derivatives of the 1-OH, 1-SH, 6-OH, and 8-OH isomers indicate that the neutral molecule exists predominantly in the forms containing an *N*-H (**25** and **26**). If tautomer **24** were the dominant



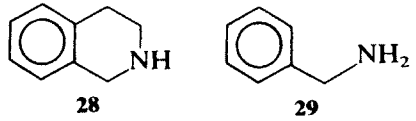
24 **25** **26**

form, the pK_a for the *X*-Me derivatives would be more closely aligned to those of the corresponding unsubstituted molecules. A greater difference between the base strengths of the *N*-methyl and *N*-unsubstituted compounds is found in isomers where no tautomeric stabilization can occur (5- and 7-hydroxy), except for the anomalous behavior of 4-hydroxyisoquinoline (**27**), in which stabilization of the neutral molecule is achieved by contribution from the zwitterionic form **19**. The 1-XH and 3-XH isomers, in which there is considerable stabilization of the neutral species by the amide tautomer **25**, are also weaker acids than the other isomers.

The base strength[37] of 1,2,3,4-tetrahydroisoquinoline (**28**) ($pK_a = 9.41$) is that expected for a cyclic alkyl derivative of benzylamine (**29**) ($pK_a = 9.34$).



27 19



28 29

III. SPECTROSCOPIC PROPERTIES

A. Infrared Absorption

A total assignment of the vibrational spectrum of isoquinoline has been reported,[38] and a comparison has been made with both quinoline and naphthalene. The frequency assignments of the 45 fundamental vibrations have been compared with those calculated by normal coordinate analysis and found to be in good agreement.

Of the substituted isoquinolines, only the hydroxyl and amino derivatives have been studied systematically. The hydroxyisoquinolines were examined[39] to measure tautomerism in the system. Stretching frequencies in the O–H, N–H, and double-bond regions are shown (Table I.5) for both solutions and solid state. There is no absorption in the O–H region ($\sim$3600 cm^{-1}) with either 1-hydroxyisoquinoline or homophthalimide, thus

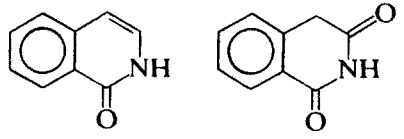
TABLE I.5. STRETCHING FREQUENCIES (cm^{-1}) OF HYDROXYISOQUINOLINES

	N–H		C=O	
Compound	Solution	Solid	Solution	Solid
1-Hydroxyisoquinoline	3411	3278 w, 3150 s	1658	1653 s
Homophthalimide	3383	—	1699	—
	O–H			
Substitution	Solution	Solid	Double-bond stretch	
4-OH	3603	2900–2500 m, br	1626 m,	1582 s
5-OH	3615	2950–2550 m, br	1623 m,	1588 s
6-OH	3610	2920–2620 m, br	1625 m,	1614 s
7-OH	3619	2900–2600 m, br	1628 m,	1589 s
8-OH	3611	2920–2550 m, br	1621 m,	1558 s

TABLE I.6. NITROGEN-HYDROGEN FORCE CONSTANTS FOR AMINOISOQUINOLINES

Substituent	ν_a (cm^{-1})	ν_s (cm^{-1})	K (10^5 dyne cm^{-1})
3-NH_2	3503	3405	6.61
4-NH_2	3477	3397	6.54
5-NH_2	3481	3399	6.55
6-NH_2	3500	3410	6.61
7-NH_2	3481	3401	6.56
8-NH_2	3484	3405	6.57

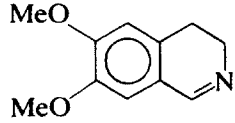
suggesting that both of these compounds must be present solely in the amide forms **30** and **31**, respectively, in both the solid state and in solution in carbontetrachloride. Compounds that could be in tautomeric equilibrium with vinylogous amide forms (6-OH and 8-OH) do not absorb in the amide C=O range, thus suggesting that this tautomer is at most a very minor contributor.



30 **31**

The aminoisoquinolines present a similar case, but a more quantitative measure of the interaction between the amino group and the ring nitrogen atom has been obtained[40] by determining the N–H force constant (K) (Table I.6). Whereas it seems reasonable to expect electromeric interaction to occur in those cases for which it is formally possible (the 3-, 6-, and 8-isomers), this is only realized for the 3- and 6-amino compounds.

Infrared (ir) spectroscopy has been used[41] together with ultraviolet (uv), nuclear magnetic resonance (nmr), and polarography to study the tautomerism of isoquinolinium salts. The effects of substituents in 3,4-dihydroisoquinolines have been systematically studied[42] by examining the region 1700 to 1500 cm^{-1}. The C=N stretching vibration was found to occur at 1622 cm^{-1} for the unsubstituted base and to be intensified and moved to higher wavenumber in the dimethoxy derivative **32**. Protonation or quaternization of the nitrogen atom causes the $C{=}N^+$ group to absorb near 1660 cm^{-1}. The effect of alkyl substituents at C-1 causes a slight shift (2 to 6 cm^{-1}) toward higher frequencies for the free bases; in the quaternary salts, however, a rather marked shift of 23 to 33 cm^{-1} toward lower frequencies is observed.



32

B. Ultraviolet Spectroscopy

The uv absorption spectrum of isoquinoline closely resembles that of both quinoline and naphthalene. The observed bands have been assigned[43] as α- 317 nm ($\varepsilon = 3100$), p- 266 (4030); β- 217 (37,000), and t- 471.5 (3170) by Clar convention. The $n \rightarrow \pi^*$ bands displayed by many azines (identified by their shift to lower wavelength on changing from hydrocarbon to hydroxylic solvent) are not observed, as they are presumably masked by the $\pi \rightarrow \pi^*$ bands. The wavelengths of bands derived from singlet–singlet transitions have been calculated by SCF MO methods using slightly different parameters and approximations; the results obtained are collected in Table I.7. *N*-Protonation[48] causes a bathochromic shift of all bands; the resulting spectrum is very similar to that of the *N*-quaternized derivative, except in some cases of quaternary iodides in ethanol where the formation of charge-transfer complexes has been observed.[49]

TABLE I.7. CALCULATED π–π^* BANDS FOR ISOQUINOLINE

	Calculated by method under reference						
Compound	Obs.[43]	Calc.[44]	Calc.[45]	Calc.[45]	Calc.[46]	Calc.[47]	Obs.[47]
Isoquinoline	217	217	220	224	227	229	(222)
	266	280	273	277	285	286	(285)
	317	305	309	313	300	319	(321)
	Obs.[48]						
Isoquinolinium	228		223	240			
	274		290	304			
	331		348	380			

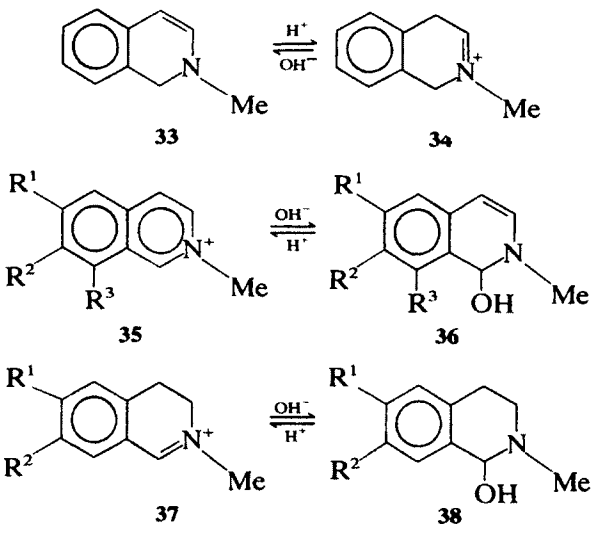
The introduction of methyl or halogen substituents produces a small bathochromic shift in the spectrum of isoquinoline; attempts to calculate this substituent effect have met with little success (Table I.8). The complete spectrum of each methylisoquinoline is sufficiently distinctive to be diagnostic;[50] the pattern remains unchanged when methyl is replaced by other alkyl groups. The effects of dialkyl substitution are more complex and differences between isomers much less distinct. Hydroxyl substituents cause[55] a small red shift in the spectrum, but the picture is further complicated by a pH dependence due to zwitterion formation. This dependence has been examined, and values for the equilibrium constant of each tautomerism have been calculated. A further red shift occurs[56] under strong-base conditions ($OH \rightarrow O^-$) and a blue shift on ether formation ($OH \rightarrow OMe$). Wavelengths corresponding to $\pi \rightarrow \pi^*$ transitions have been calculated[57] for the hydroxyisoquinolines using HMO theory, but again the

TABLE I.8. OBSERVED AND CALCULATED BANDS OF METHYLISOQUINOLINES AND HALOGEN ISOQUINOLINES

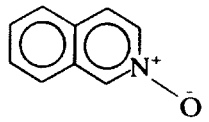
Substituent	Observed λ (nm)		Calculated λ (nm)		
1-Me	270, 320	Ref. 50	321	Ref. 53	
3-Me	267, 324		325		
4-Me	271, 321		326		
5-Me	272, 320		327		
6-Me	277, 321		320		
7-Me	279, 327		321		
8-Me	272, 322		325		
1-Cl	276, 324	Ref. 51	325		
3-Cl	274, 329		324		
4-Cl	277, 324		327		
5-Cl	276, 326		328		
6-Cl	273, 320		321		
7-Cl	268, 329		325		
8-Cl	276, 326		326		
1-F	265, 317	Ref. 52	323	288, 322	Ref. 54
3-F	270, 326		323	288, 325	
4-F	270, 320		325	290, 324	

correlation is not good. A study[58,59] of the effects of *ortho*-dimethoxy and methylenedioxy substituents on the uv spectra of isoquinolines and their partially reduced forms has led to data useful in assignment of substitution patterns in alkaloids, since relative intensity changes are dependent on the positions of substitution.

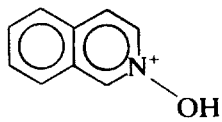
1,2-Dihydroisoquinolines (**33**) are often unstable but can[60–62] readily be detected by a strong absorption ($\varepsilon \approx 10{,}000$) in the region of 330 nm. Protonation at C-4, to form a 1,4-dihydroisoquinolinium salt (**34**), can be



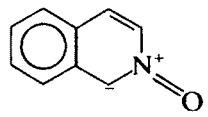
demonstrated by a transformation of the uv spectrum to that of a normal benzenoid type. 3,4-Dihydroisoquinolines and their salts each exhibit two main bands, the former at 210 nm and 260 nm and the latter at 220 nm and 290 nm. The pH dependence of the equilibria between quaternary salts of both aromatic and 3,4-dihydroisoquinolines (**35** and **37**) and their pseudobases (**36** and **38**) has been studied[41] by uv spectroscopy to analyze the mixtures obtained. Isoquinoline *N*-oxide (**39**) exhibits[63] an absorption spectrum of 218 nm ($\varepsilon = 23{,}300$), 250 nm ($\varepsilon = 31{,}000$), and 294 nm ($\varepsilon = 8600$), and its conjugate acid **40** shows bands at 212 nm ($\varepsilon = 20{,}500$), 234 nm ($\varepsilon = 47{,}400$), 280 nm ($\varepsilon = 2700$), and 330 nm ($\varepsilon = 3600$). The considerable change in going to acid solution suggests that significant contribution to the structure of the *N*-oxide must be made by other forms, such as **41**.



39



40



41

C. Nuclear Magnetic Resonance

Proton magnetic resonance (pmr) spectroscopy has proved to be a valuable tool in structure investigations of substituted isoquinolines. From knowledge of the spectra of benzene, naphthalene, and pyridine, qualitative predictions of the pmr parameters of isoquinoline can be made. Hydrogen-1 should be at lowest field and H-3 downfield of H-4; H-6, and H-7 should be upfield of H-5, and H-8 and not too different from H-4; H-8 might be expected to be downfield of H-5. The coupling constants should be in the order $J_{5,6} \approx J_{7,8} > J_{6,7} > J_{3,4}$. A high-resolution spectrum[64] (Table I.9) of isoquinoline in CCl_4, with ^{14}N decoupling, confirms these expectations and reveals several interesting features. The values of $J_{3,5}$ and $J_{3,7}$ agree fairly well with those for analogous couplings in naphthalene, and the relative signs of the interring couplings that have been determined show the expected bond alternation, that is, negative across an even number of bonds and positive for an odd number. The spectra of 1-methyl-, 3-methyl-, 4-bromo-, and 5-aminoisoquinolines have been similarly examined and discussed.

On changing from the base to either the quaternary salt or protonated species, an increase of 1.0 Hz in the coupling constant $J_{3,4}$ occurs,[65] and the chemical shifts of the C-1, C-3, and C-4 protons move downfield by 0.7 ppm, 0.2 ppm, and 0.8 ppm, respectively. A decrease in the chemical shifts of H-1 and H-3 was found[66] in the spectrum of 4-hydroxyisoquinoline with increasing pH, which follows a corresponding increase in π-electron density at these positions. Attempts have been made to correlate proton

TABLE I.9. HIGH-RESOLUTION PMR OF ISOQUINOLINE

Position	1	3	4	5	6	7	8
Chemical shift (δ ppm)	9.114	8.448	7.501	7.697	7.563	7.582	7.853

	Coupling constants [J (Hz)]					
Position	1	3	4	5	6	7
3	0.0	—	—	—	—	—
4	1.0	+5.75	—	—	—	—
5	0.87	0.1	−0.36	—	—	—
6	0.0	0.0	0.0	8.29	—	—
7	0.0	0.3	−0.07	1.17	6.92	—
8	−0.29	0.05	+0.08	0.80	1.21	8.27

chemical shifts with π-electron densities in azanaphthalenes, but no quantitative relationship has been established.[67]

The substituent interactions in some nitroisoquinolines (Table I.10) are[68] qualitatively similar to those obtained[69] for nitroquinolines. The shifts to lower field are consistently greater by 0.1 to 0.3 ppm, thus suggesting a more effective withdrawal of electrons from the isoquinoline than from the quinoline molecule.

The isoquinoline molecule is ideally suited to structure investigation by pmr in the presence of lanthanide shift reagents (LSR). Unequivocal assignment of substitution patterns of some mono- and disubstituted molecules have been reported[70] after using Eu(*fod*)$_3$ to "spread" the spectrum. The isoquinoline nitrogen atom coordinates readily, and the largest effects are found at the α-positions; the values observed using Eu(*dom*)$_3$ in CCl_4 have been measured (Table I.11).[71] The shift can be successfully explained[72,73] using a pseudocontact model, and a *N*–Eu distance of 3.2 Å has been proposed.[73] The ^{1}H shift ratios for the seven protons of isoquinoline have been calculated[74] according to the assumption that the LSR adducts exist in solution as an ensemble of many interconverting geometric isomers. The values obtained (1.000, 1.000, 0.439, 0.248, 0.154, 0.144, and 0.252) are

TABLE I.10. CHEMICAL SHIFTS IN NITROISOQUINOLINES

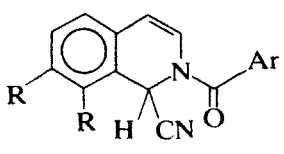
Substituent	Chemical shift (δ ppm)						
	H-1	H-3	H-4	H-5	H-6	H-7	H-8
5-Nitro-	9.39	8.75	8.46	—	8.59	7.72	8.36
7-Nitro-	9.62	8.88	7.83	8.13	8.57	—	9.02
8-Nitro-	10.40	8.74	7.80	8.15	7.77	8.35	—

TABLE I.11. EFFECT OF Eu(*dpm*)$_3$ ON PMR OF ISOQUINOLINE

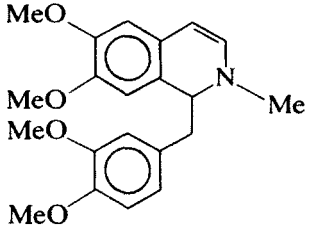
Molecular ratio (Eu: isoquinoline)	H-1	H-3	H-4	H-5	H-6	H-7	H-8
0.1	3.2	3.6	1.0	0.9	0.3	0.3	0.9
0.3	8.6	9.6	3.3	2.1	1.1	1.1	2.1
0.5	14.2	15.7	5.3	3.4	1.9	1.9	3.4
(1.0)	30	33	11	8	4	4	8
Relative movements	0.91	1.00	0.33	0.24	0.12	0.12	0.24

similar to those observed experimentally. A series giving the H-1 shift ratios for the Ln(*dpm*)$_3$ range for Pr–Yb was also reported.

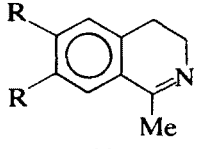
The chemical shifts of H-1 and H-3 in isoquinoline *N*-oxide are 8.77 δ and 8.14 δ, respectively, and coupling constants of $J_{3,4} = 7.0$ and $J_{1,3} = 1.0$ Hz were reported.[75] The values of $J_{3,4}$ in several 1,2-disubstituted-1,2-dihydroisoquinolines are typical of *cis*-styrenes and lie[76] in the range 7.7 ± 0.5 Hz and are largely independent of the nature of the substituent; this has been used to correct erroneous structural assignments to reaction products. Long-range coupling of nearly 1 Hz between H-1 and H-3 of isoquinoline Reissert compounds **42**[77] suggests that the five atoms involved are adopting an almost planar conformation. This requires the hydrogen atom at C-1 to be quasiequatorial, similar to that proposed[78] for 1,2-dihydro-*N*-methylpapaverine (**43**). Long-range coupling has also been observed[79] between the methyl protons and those at C-3 in the 3,4-dihydroisoquinolines **44** (R = H, OMe, and $-OCH_2O-$), and corresponding methiodides. Proton



42

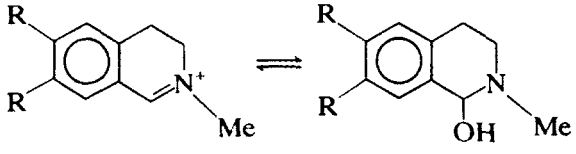


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44

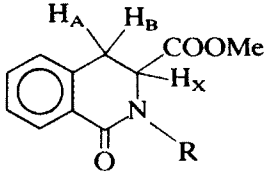
magnetic resonance has been used[62] to investigate the position of equilibrium of the tautomerism between 3,4-dihydroisoquinolinium compounds **37** and their pseudobases **38** at different pH values.



37 **38**

Studies of the temperature and solvent dependence of the vicinal coupling

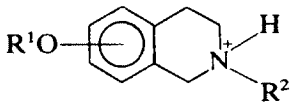
constants, J_{AX} and J_{BX}, of *N*-H and *N*-methyl-3-carbomethoxy-3,4-dihydroisocarbostyril (**45**) have helped to assign the preferred conformations



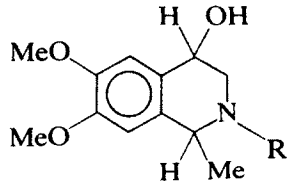
45

of these compounds.[80] When R = Me, the coupling constants (J_{AX} = 6.2 and J_{BX} = 2.4 Hz) remained constant under varying conditions, thus suggesting a conformational rigidity with a quasiaxial orientation of the ester function. When R = H, a greater flexibility was present with an increasing contribution from the quasi-equatorial ester conformer at higher temperatures and lower solvent polarity.

The *N*-methyl- and *N*-unsubstituted-1,2,3,4-tetrahydroisoquinoline hydrochlorides have very similar pmr spectra, with the C-1 protons appearing as singlets at 4.18 δ and 4.31 δ, respectively.[81] The 5-, 6-, 7-, and 8- hydroxy-, and methoxy-1,2,3,4-tetrahydroisoquinoline salts **46** have been studied, and the position of substitution can be determined from the complexity of the patterns due to the aromatic protons and the shift differences for the C-4 and C-1 protons.[81]



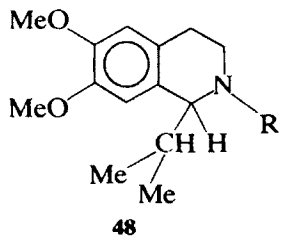
46



47

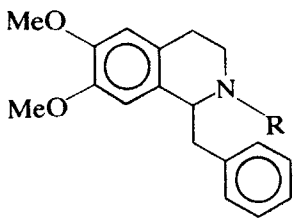
Structures of the two diastereomers of the tetrahydroisoquinolines **47** were assigned[82] on the basis of the pmr spectra of these diastereomers and, in particular, of the chemical shifts of H-1 in the *N*-methyl derivatives. In both forms the hydroxyl group takes up a quasiequatorial position, and the H-1 shifts are 3.39 δ (quasiaxial) and 3.68 δ (quasiequatorial).

Substituents at C-1 of tetrahydroisoquinolines have been shown to experience hindered rotation. The chemical shifts of the two methyl groups in the 1-isopropyl derivative **48** differ[83] by 0.37 ppm when R = H and by 0.12 ppm

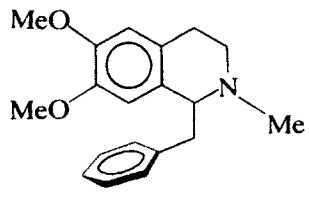


48

when R = methyl or ethyl. The case of hindered rotation in 1-benzyltetrahydroisoquinolines has received much attention since it was first reported[84] in 1965. Whereas the chemical shifts of H-5 and H-8 of **49** (R = H) both occur at 6.61 δ, the same protons appear at 6.57 δ and 5.99 δ respectively, in the *N*-methyl derivative. It is argued that this upfield shift of H-8 occurs as a result of shielding by ring *C*, now taking up a preferred conformation underneath ring *A*, as shown in structure **50**. Similarly, the

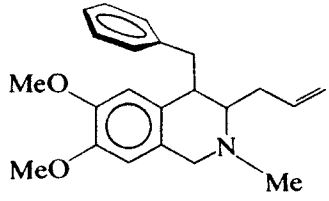


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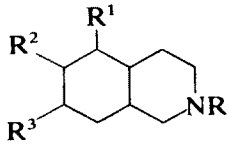


50

methoxyl groups of **49** (R = H) absorb at 3.84 δ and 3.78 δ but at 3.82 δ and 3.52 δ in the *N*-methyl compound; the C-7 substituent is moved upfield by 0.26 ppm by the ring-shielding effect. A correlation between the size of the *N* substituent and the degree of twist of ring *C* has been reported.[85] A similar effect is found with 1,2-dihydro 2-methylpapaverine (**43**) and with the 4-benzyl derivative (**51**).[61]



51



52 R = H or Me
R^{1-3} = H or OH or Cl

Both *cis*- and *trans*-decahydroisoquinolines (**52**) have been studied,[86,87] and their geometries have been assigned by analysis of the pmr spectra using[88] a modified Karplus relationship.

The ^{13}C nuclear magnetic resonance (nmr) of isoquinoline has been reported (Table I.12).[89] There is a marked similarity in chemical shifts between the corresponding positions in pyridine and isoquinoline, thus suggesting that the nitrogen has a characteristic effect on a six-membered aromatic ring even in a polycyclic system. The benzenoid ring has a secondary effect, as illustrated by the 9.3-ppm separation between peaks arising from ^{13}C atoms α to the nitrogen atom in isoquinoline. Carbon-13 shifts reflect important electronic features, and a moderate correlation is obtained with total $(\pi + \sigma)$ electron densities as calculated by a CNDO/2 method. Nuclear magnetic resonance ^{13}C spin–spin coupling constants can

TABLE I.12. THE ^{13}C NMR OF ISOQUINOLINE AND PYRIDINE

	Chemical Shift (ppm Relative to Benzene)								
	C-1	C-3	C-4	C-4a	C-5	C-6	C-7	C-8	C-8a
Isoquinoline	−24.6	−15.3	7.7	−7.5	1.7	−2.0	1.0	0.6	−0.6

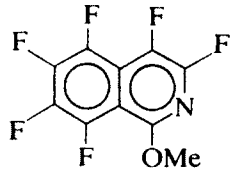
	α	β	γ
Pyridine	−21.7	4.5	−7.4

be derived using additivity rules,[90] and the values so obtained[91] for C-1, C-3, and C-4 of isoquinoline (180.5 Hz, 180.5 Hz, and 162.0 Hz, respectively) compare favorably with those observed (176.0 Hz, 176.0 Hz, and 163.0 Hz). The ^{13}C chemical shifts in isoquinoline show[92] a pH dependence; in passing from base to acid conditions the changes in shift observed were C-1 (+5 Hz), C-3 (+10 Hz), C-4 (−5 Hz), C-4a (−3 Hz), C-5 (−2 Hz), C-6 (−6 Hz), C-7 (−4 Hz or −3 Hz), C-8 (−3 Hz or −4 Hz), and C-8a (+1.5 Hz). From the points of inflection of the pH–δ curves, a mean value for the pK_a of isoquinoline of 4.95 was obtained.

The change in ^{13}C chemical shifts caused by coordination with lanthanide compounds is more complex than that observed in the proton spectra. The inclusion of a Fermi contact contribution is necessary[73] to obtain correlation of ^{13}C shifts caused by 1:1 Eu(*dpm*)$_3$ complexing. The degree of contact-term contribution depends[72] on the lanthanide element involved and is greater for praseodymium than for europium.

The ^{14}N chemical shift for isoquinoline in diethylether solution was measured[93] as 64 ± 4 ppm relative to nitrate ion. A later study[94] reported the ^{14}N signal as a doublet ($J_{N,H}$ = 68 Hz) at 68 ppm and a similar doublet at 188 ppm for the hydrochloride (cf. pyridine δ = 68 and pyridine hydrochloride δ = 181 ppm). A correlation is proposed[95] between the π-electron density at the nitrogen atom and the ^{14}N chemical shift in nitrogen heterocycles.

Fluorine-19 nmr is a useful tool in establishing the structure of substitution products in polyfluoro compounds. A very low field peak (δ = 61 Hz relative to CCl_3F) observed[96] in the spectrum of heptafluoroisoquinoline does not appear in the case of the 1-methoxyderivative **53** and must thus



53

arise from the C_1-fluoro atom, whereas a peak at 96.5 Hz is assigned to C_3–F; peri coupling of the order $J_{1,8} = 60$ to 65 Hz and $J_{4,5} = 50$ Hz is found in these compounds and several other derivatives. The ^{19}F chemical shifts of 6-fluoro- and 7-fluoro-2-methyl-1,2,3,4-tetrahydroisoquinoline and their methosalts have been measured.[97]

D. Electron Spin Resonance

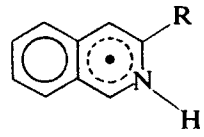
The radical anion of isoquinoline, prepared in 1,2-dimethoxyethane by reduction with sodium, has been examined[98] by electron spin resonance (esr). The spectrum, like that of quinoline, is complex because of coupling of the unpaired electron with ^{14}N and with seven nonequivalent protons. In the case of isoquinoline, some simplification of the spectrum occurs as a result of the accidental degeneracy of two coupling constants. Only the coupling due to nitrogen (2.28 G) can be deduced by analysis of the spectrum. The proton hyperfine splitting constants (Table I.13) are assigned on the basis of the a_H values missing in the spectra of the various methyl-substituted derivatives.

TABLE I.13. HYPERFINE SPLITTING CONSTANTS FOR ISOQUINOLINE

	Experimental		
Position	Ref. 98	Ref. 100	Hückel
C-1	7.16	5.38	6.15
N	2.28	1.92	3.82
C-3	0.11	0.37	0.59
C-4	4.20	4.01	4.20
C-5	2.53	3.95	3.90
C-6	4.20	3.26	2.40
C-7	0.11	0.04	1.20
C-8	5.16	6.26	7.35

The overall splittings, methyl-proton coupling constants and other coupling constants of the methylisoquinolines, are quoted.[98,99] The isoquinoline radical ion has also been examined[100] in hexamethylphosphoramide (HMPA) and the values obtained for the splitting constants compared with those predicted by a Hückel approach (Table I.13). A striking similarity was noted between the uv spectra of the radical ions produced from naphthalene, quinoline, and isoquinoline, but with the absorption maxima of the aza compounds moved to shorter wavelength. The radicals produced when isoquinoline or 3-methylisoquinoline are irradiated at low temperature are formed[101] by a monophotonic process. Spin densities of radicals **54** and their theoretical second moments (M_2) have been calculated and the values

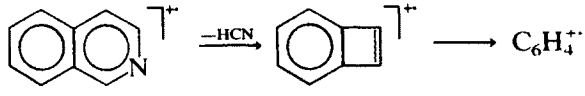
obtained (**54**; R = H, $M_2 = 68$ and **54**; R = Me, $M_2 = 70$) compare with the values of 73 and 75, respectively derived from esr measurements.



54

E. Mass Spectrometry

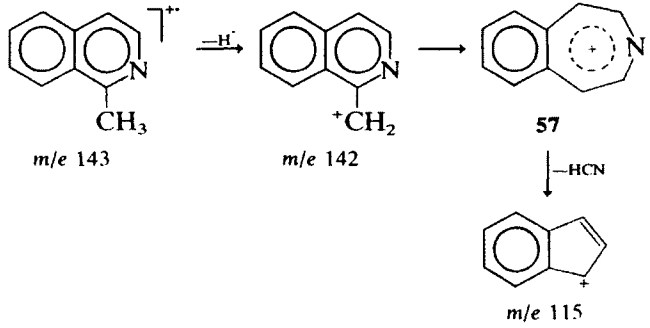
The mass spectrum of isoquinoline exhibits[102] a stable molecular ion followed initially by a loss of HCN (**55** → **56**); ^{13}C studies have not been



m/e 129 *m/e* 102 *m/e* 76

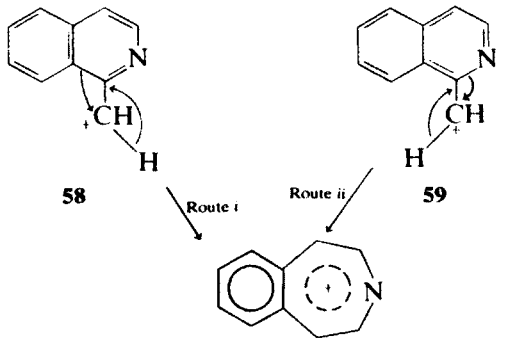
55 **56**

undertaken to determine whether C-1 or C-3 is preferentially lost. A methyl substituent, especially at C-1 or C-3, reduces the importance of this process[103] and introduces a new mode of fragmentation through the formation of an azatropylium ion such as **57** (Eq. 1). Two possible mechanisms

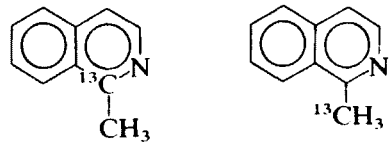


m/e 143 *m/e* 142 **57** *m/e* 115 (1)

(Scheme 1) for the ring expansion involve either a phenyl-to-carbon migration (route *i*) or a nitrogen-to-carbon migration (route *ii*). To study the relative contributions of these two processes, the fragmentations of 1-methyl- $^{13}C_1$-isoquinoline (**60**) and 1-^{13}C-methylisoquinoline (**61**) were examined.[104] The azatropylium ion (**62**) would be formed from **60** by route *ii* and from **61** by route *i*; conversely, ion **63** would arise by the alternative mechanisms. From an examination of the ratio of the peaks *m/e* 115: *m/e* 116 it was concluded that both pathways were important contributors, with a small preference toward route *i*. Isoquinolines with an ethyl group at



Scheme 1

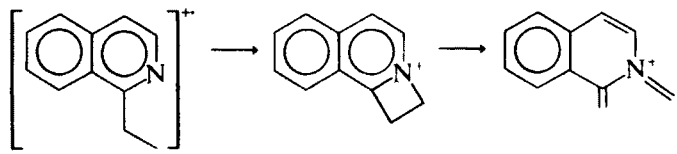




m/e 116 only

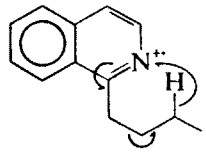
m/e 116
m/e 115 } 1:1

either C-1 or C-3 fragment through the initial loss of a hydrogen radical (**64** → **65** → **66**), whereas, with a longer alkyl chain, a McLafferty-type

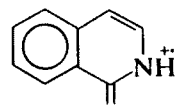


rearrangement (e.g., **67** → **68**) dominates.[103] By the use of appropriate D-labeled compounds, site-specific γ-H transfer has been demonstrated.

Thermal decompositions of *N*-methylisoquinolinium salts occur in a mass spectrometer[105] such that the resultant spectrum is that of the free base superimposed on the methyl derivative (e.g., methyl iodide from methiodides). The dominance of this reaction can be reduced by employing



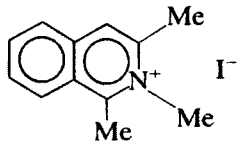
67



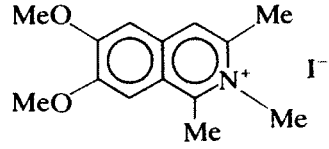
m/e 143

68

the minimum source temperature necessary to produce a spectrum; for example, the spectra of the two methiodides **69** and **70** showed base peaks



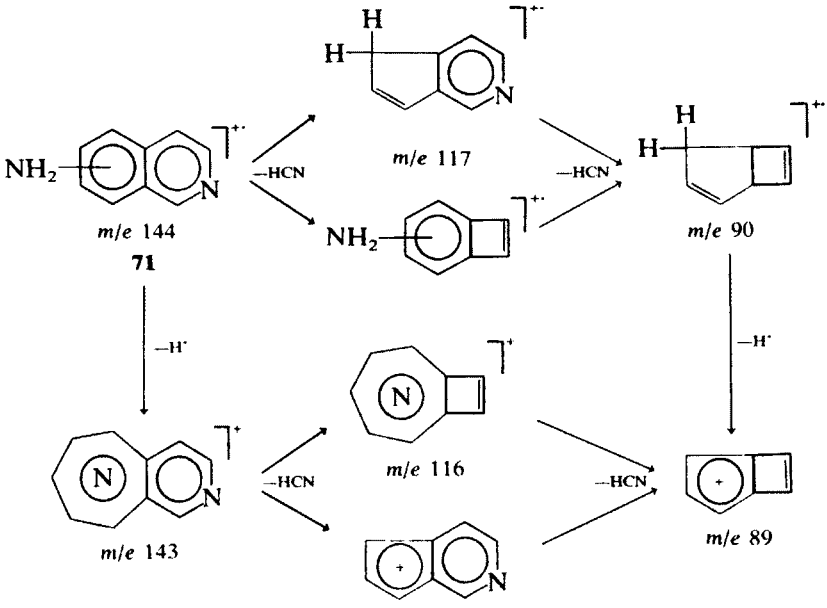
69



70

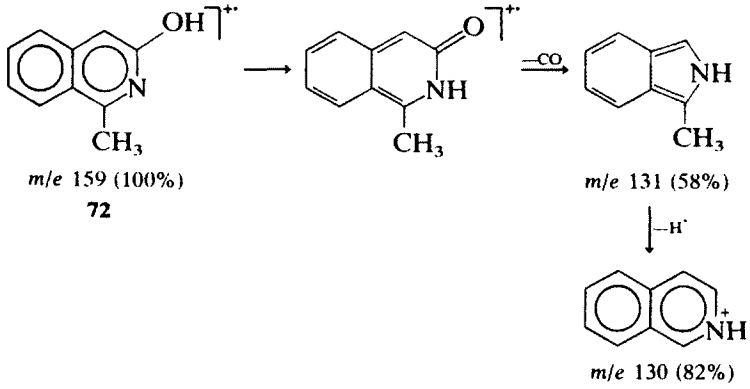
at $M^+ - 1$ with $M^+ - 15$ of 7% and 29%, respectively.[61] The spectra of methoperchlorates are further complicated by thermally induced oxidation and chlorination reactions.[105]

The most abundant ion in the mass spectra of the aminoisoquinolines is that of the molecular ion **71**.[106] Two consecutive losses of HCN occur, and two parallel fragmentations have been proposed (Scheme 2). Evidence to support these fragmentations is obtained from an interpretation of the spectrum of 5-^{15}N-aminoisoquinoline.



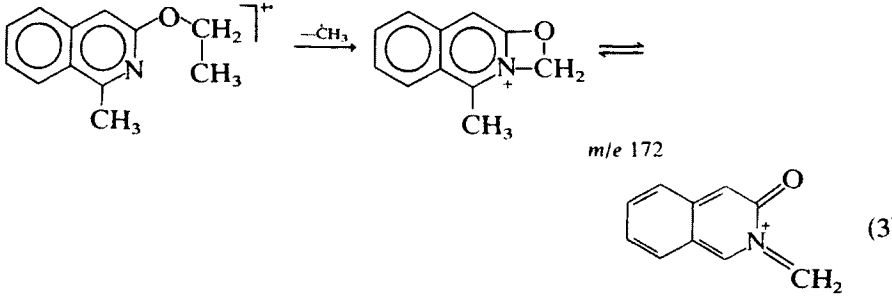
Scheme 2

Little work has been reported on the fragmentation of simple hydroxyisoquinolines. The molecular ion of 1-methyl-3-hydroxyisoquinoline (**72**) breaks down by the expected loss of CO, followed by H$^{\bullet}$ (Eq. 2).[107] The



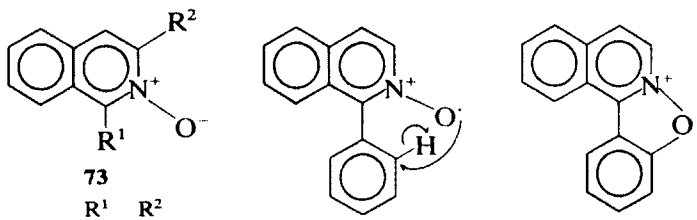
(2)

spectrum of the ethyl ether, however, shows a strong M^{+}-15 peak, and interaction with the nitrogen atom is proposed (Eq. 3).



(3)

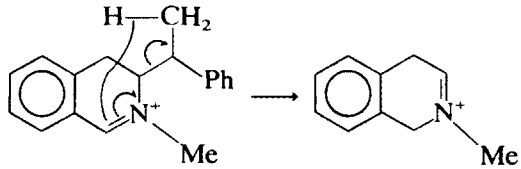
The loss of an oxygen atom from the molecular ions of both quinoline and isoquinoline *N*-oxides has been shown[108] to be due to thermal, rather than electron-impact, fragmentation. A competing loss of HCN from isoquinoline *N*-oxide (**73a**) is explained[109] by an initial oxygen transfer to C-1. Methyl substituents adjacent to the *N*-oxide linkage alter the fragmentation pathway; the major fragment ions from **73b** and **73c** result from the expulsion of



	R^1	R^2
73a,	H	H
73b,	Me	H
73c,	H	Me

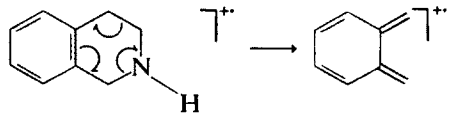
OH from the respective molecular ions.[109] A dominant loss of H· from the molecular ion of 1-phenylisoquinoline *N*-oxide (**74**) must be from the phenyl group, and the formation of **75** has been proposed.

The initial fragmentation of 1,2-dihydroisoquinolines involves the loss of an atom or group from C-1 to form the aromatic species. With 1,2-dihydroisoquinoline itself, a hydrogen radical is lost[110] to give an intense $M^+ - 1$ ion at *m/e* 130. When there is a substituent at C-1 that would give rise to a stable radical (e.g., allyl or benzyl), the loss of this group is the major fragmentation.[61] In each case the remainder of the spectrum is that expected from fragmentations of the aromatic species. A similar drive toward aromaticity dominates the breakdown of 3,4-dihydroisoquinoline; a McLafferty rearrangement, however, led to the base peak corresponding to **77** from the 3-substituted compound **76**, although a further loss of two hydrogens gave the aromatic structure (12%).[61]

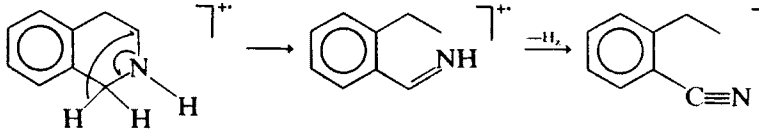


76 **77**

Tetrahydroisoquinoline undergoes two major fragmentations;[111] the first is the loss of H·, probably from C-1 to give a stable iminium ion, and the second is a retro Diels–Alder reaction (Eq. 4). The thermal decomposition of 1,2,3,4-tetrahydroisoquinoline[112] yields *o*-ethylbenzonitrile as the major product; the one-step loss of H_2 (metastable) occurring under elec-

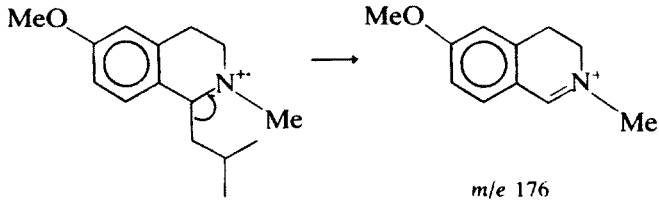


(4)



(5)

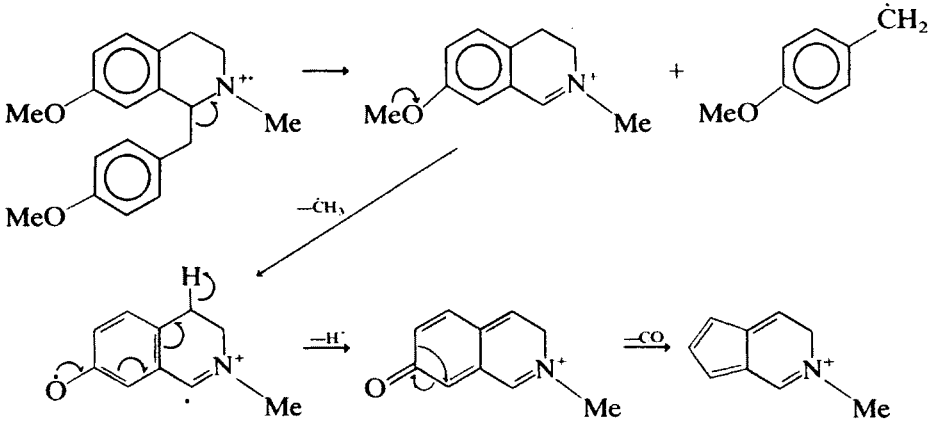
tron impact could be explained by a simple rearrangement leading to a parallel reaction (Eq. 5). Many alkaloids containing the 1,2,3,4-tetrahydroisoquinoline nucleus have been examined. The dominant feature is the loss of a substituent from C-1 (or C-3) to form an iminium cation that is usually the base peak. Thus the 1-isobutyl derivative shows[113] a weak M^+ (**78**), and the base peak corresponds to the ion **79**. 1-Benzyl-1,2,3,4-tetrahydroisoquinoline derivatives occur abundantly, often with oxygen



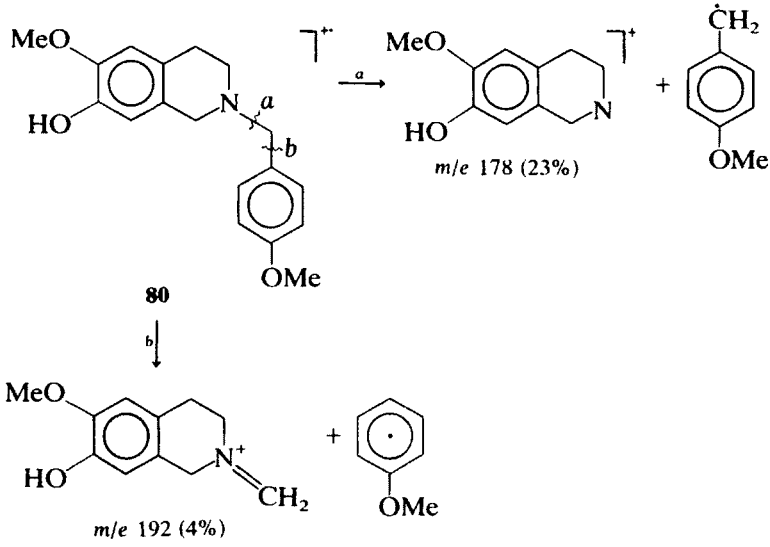
78

m/e 176

79



Scheme 3



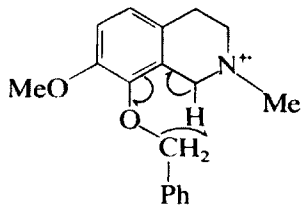
m/e 178 (23%)

m/e 192 (4%)

Scheme 4

functions on both the benzyl and isoquinoline benzenoid rings. The fragmentations of this large family of compounds follow a common pattern, as illustrated by the simple example in Scheme 3.[114] When the benzyl group is attached to the nitrogen atom, as in the alkaloid Sendaverine (**80**), the fragmentation is quite different;[115] the molecular ion is of greater intensity and two competing breakdowns occur (Scheme 4).

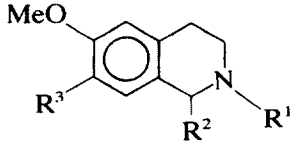
An interesting proximity effect was noted in the fragmentation of 8-benzyloxytetrahydroisoquinoline (**81**), in which a loss of toluene was shown[116] to occur, and a cyclic transition state was proposed.



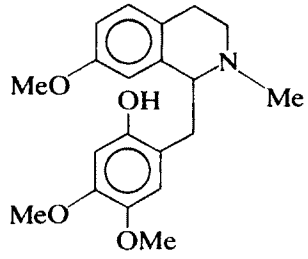
81

F. Optical Rotatory Spectroscopy

Optical rotatory power is the only generally accessible physical property by which enantiomers can be assigned relative or absolute configurations. This is of particular interest for study of the many optically active tetrahydroisoquinolines found as natural products. Optical rotatory dispersion (ord) curves of some 1-substituted-1,2,3,4-tetrahydroisoquinolines (**82**) have been



82

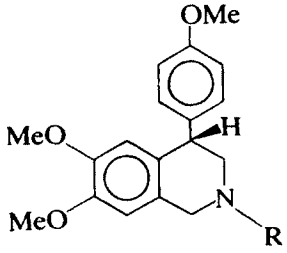


83

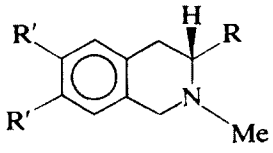
recorded.[117] In these compounds the aromatic chromophore is attached to an asymmetric center and, even with simple alkyl substituents at C-1, strong Cotton effects occur at about 270 to 290 nm. The amplitudes for compounds with 1-benzyl substituents are considerably greater than for those with small 1-alkyl substituents. The 1-benzyl-1,2,3,4-tetrahydroisoquinolines also exhibit a second Cotton effect at about 240 nm.[117,118]. The absolute configurations of these compounds are known, and all members of the *S* series have two positive Cotton effects, whereas the enantiomeric *R* compounds have double-negative curves. The uv and ord spectra of 1-

benzyltetrahydroisoquinolines remain unchanged[119] on quaternization or protonation, except when such a change causes alteration in the shape, and hence the dipole moment, of the molecule; for example, in **83**, hindered rotation in the salt form causes a marked change in the ord curve on protonation of the base. The circular dichroism (cd) curves of 1-phenyl-1,2,3,4-tetrahydroisoquinolines give[120] three Cotton effects at 200 to 300 nm; the effects are all of the same sign and are positive for the *S*-enantiomer. The corresponding methiodides give a cd curve similar to that of the base at 200 to 255 nm but differ at higher wavelengths.

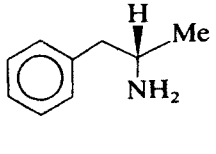
The absolute configurations of 4-phenyl-1,2,3,4-tetrahydroisoquinolines have been established by ord and cd comparisons with the known isomer **84**,[121a] and confirmed by application of the aromatic chirality method.[121b] All 4-(*S*) compounds exhibit a negative first Cotton effect at 270 to 290 nm. In general, the cd curves are better resolved than the ord spectra; the latter also show a strong background rotation as a result of the $n \rightarrow \sigma^*$ transition of the nonbonding electron pair of the nitrogen atom that disappears in acidic media.[121c] *S*-(+)-2,3-Dimethyl-1,2,3,4-tetrahydroisoquinoline **85** (R = Me; R′ = H), derived from the known *S*-amphetamine (**86**), and (+)-3-allyl-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline **85** (R = allyl; R′ = OMe) both exhibit positive Cotton effects at about 280 nm[122] from which the absolute configuration of the latter compound could be assigned.



84

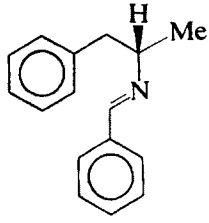


85

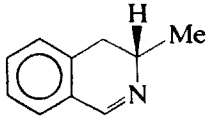


86

S-3-Methyl- and *S*-1,3-dimethyl-3,4-dihydroisoquinolines gave[123] positive Cotton effects at about 300 nm. Ultraviolet spectra of **87** and **88** are



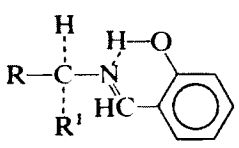
87



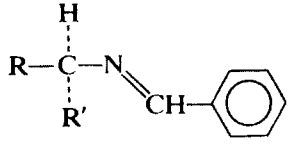
88

identical, with a shoulder at about 280 nm, but this band is optically active only in the case of the ring-closed structure. A similar effect due to ring formation is shown[124] by a Cotton effect at 300 nm for the salicylaldehyde

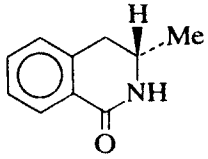
Schiff's base **89**, which is not present in the corresponding *N*-benzal derivative **90**. A positive Cotton effect was observed[125] for *S*-(+)-3-methyl-3,4-dihydro-1-isoquinolone (**91**), which corresponds to the uv absorption expected for this chromophore.



89



90



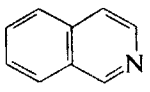
91

IV. REACTIONS

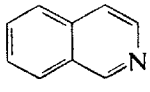
A. Substitution

(a) *Theoretical Considerations*

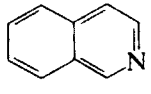
Of the nine canonical forms **92–100** that can be written for isoquinoline, the uncharged contributors **92**, **93**, and **94** are expected to be the most important. This is confirmed by X-ray crystallographic measurements (Section II.B). The most important charged forms should be **95** and **96**, in which the π-aromatic system of the benzenoid ring is maintained. Since both of



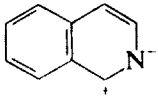
92



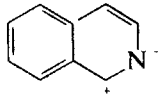
93



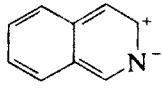
94



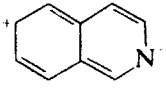
95



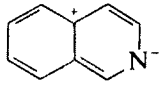
96



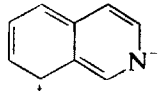
97



98



99



100

these forms bear the positive charge at C-1, this position would presumably be the most electron deficient. π-Electron densities deduced from nmr chemical shifts (Section III.C) and the observed exclusive reaction of nucleophiles at C-1 are in accord with this prediction. The anticipated sites of electrophilic attack (4, 5, and 7) do not agree with those found experimentally, when the usual orientation is C-5, followed by C-8.

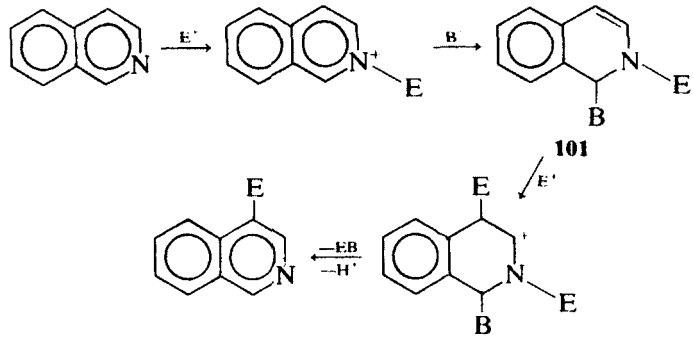
Many attempts have been made to apply the Hückel molecular orbital approach as a more quantitative treatment to predict relative reactivities in heterocyclic compounds. Calculations of the π-electron densities in isoquinoline give rise to a wide range of results dependent on the values of parameters used and the approximations made; some values are presented in Table I.14. The uncertainty of the calculation of these quantities complicates any discussion of their value as reactivity indices. There is general agreement that the position of lowest π-electron density is at C-1, which should correspond to the preferred site for nucleophilic reaction. It has been suggested[131] that the combined $(\pi + \sigma)$ electron densities might be a better measure of comparative reactivity; however, although the results obtained from such calculations show an excellent correlation with pmr chemical shifts, the predicted sites for electrophilic reaction ($4 > 5 > 7 > 8$) do not agree with experimental results.

Reactions carried out under strongly acid conditions may involve a fast reaction of the low concentration of base or a slow reaction of the more abundant isoquinolinium cation. In the former the position of attack would be controlled by electron density distribution, but in the latter a comparison of localization energies might presumably be more meaningful.[132-134] An early approach along these lines[135] led to a prediction for the order of nitration of $5 > 8 > 7 > 4 > 6 \approx 3 \gg 1$. The various reactivity indices for electrophilic, nucleophilic, and radical attack (q, F, and S, respectively), were calculated[127] for both isoquinoline and its conjugate acid. The indices for the

TABLE I.14. CALCULATED π-ELECTRON DENSITIES IN ISOQUINOLINE

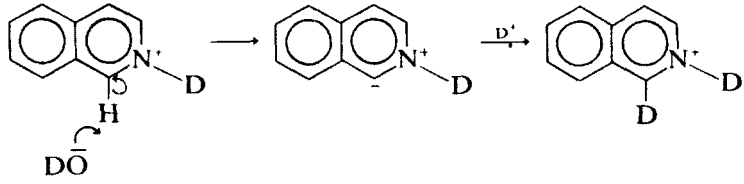
	Reference					
Position	126	127	128	129	18	130
C-1	0.767	0.8955	0.940	0.956	0.994	0.8261
N	1.594	1.1984	1.100	1.096	1.032	1.3992
C-3	0.942	0.9466	0.960	0.971	1.002	0.7022
C-4	0.938	1.0086	1.012	0.998	0.999	1.0609
C-5	0.996	1.0031	1.003	0.999	0.993	0.9425
C-6	0.940	0.9839	0.993	0.995	0.986	1.0776
C-7	0.984	1.0001	1.002	0.998	0.988	0.9251
C-8	0.948	0.9841	0.996	0.996	0.989	1.0378
C-4a	0.919	—	0.986	0.991	1.003	0.9593
C-8a	0.973	—	1.009	0.999	1.014	1.0693

protonated form proved to be linearly correlated with those of the free base and do not display a different reactivity pattern, thus suggesting that different mechanisms of substitution must be involved to result in the observed orientations. Under conditions of lower acidity, a preferred attack at C-4 can be explained[136] by the initial formation of a 1,2-dihydroisoquinoline system **101** (Scheme 5). The π-electron densities for this intermediate have been calculated, and a strong preference for electrophilic attack at C-4 is predicted.



Scheme 5

A more quantitative comparison of the susceptibilities of sites to electrophilic substitution was obtained by the technique of acid-catalyzed deuterium exchange.[137] The rates of exchange in D_2SO_4–D_2O solutions were followed using pmr spectroscopy, and at 180°C it was found that only the protons at C-5 and C-8 were affected, with C-5 at a higher rate than C-8. At 245°C, however, under high acid strengths, these reactions were joined by a slower exchange at C-7. The dominant reactions under weaker acid conditions were at C-4 and C-1. The mechanism for exchange at C-1 was suggested to involve a deprotonation of the conjugate acid by OD^- (Eq. 6) or D_2O, whereas the exchange at C-4 is similar to that proposed for



(6)

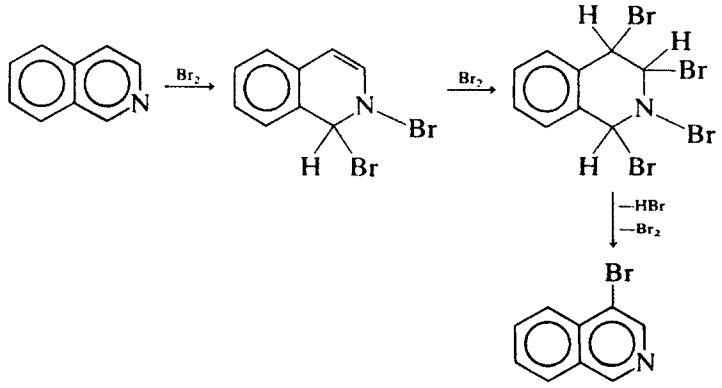
electrophilic reaction under weakly acidic conditions (Scheme 5). Isoquinoline *N*-oxide undergoes acid-catalyzed deuterium exchange, also at C-5 and C-8, at a higher rate than for isoquinoline. The same technique has been applied to 1-isoquinolinol,[138] and the order of exchange in 61% D_2SO_4 was found to be $4 > 5 \geqslant 7 > 8 > 3$.

The exclusive attack of nucleophiles and radicals at C-1 in both isoquinoline and its quaternized form is successfully predicted from the appropriate localization energies; this forms the basis of the most successful

approach[127] to relative site reactivities in isoquinolines, although other reactivity indices are sometimes employed with certain specific reasons, for example, the use of superdelocalizability in the case of the oxidative cyanation of isoquinoline *N*-oxide.[139]

(b) *Electrophilic Substitution*

Nitration of isoquinoline with mixed acid at O°C provides 90.4% of 5-nitroisoquinoline and 9.6% of the 8-isomer; however, at 100°C the proportions are 84.8% and 15.2%, respectively.[135,140,141] Bromination and sulfonation of isoquinoline in strongly acidic solution yield the 5-substituted compound. At high temperatures bromination of isoquinoline occurs at C-1 in very low yield.[142] Bromination under other conditions[143] gives good yields of 4-bromoisoquinoline. This reaction has been interpreted by Palmer,[144] as shown in Eq. 7. The reaction can be carried out by using hot sulfur

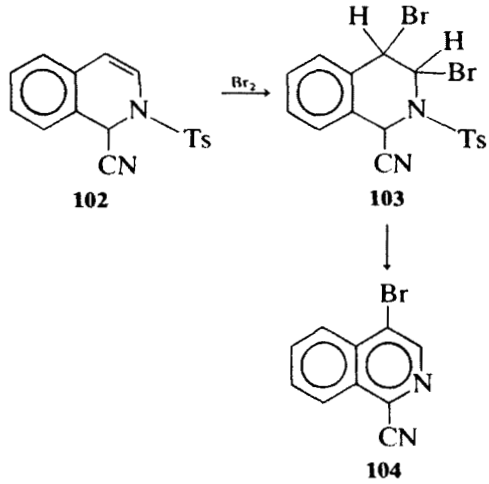


(7)

monochloride as solvent[145] or by heating the dry hydrobromide salt with bromine. A recent modification[146] enables 4-bromoisoquinoline to be obtained in yields of 70 to 80% easily by adding bromine to a slurry of isoquinoline hydrochloride in nitrobenzene. 1-Ethyl- and 1-phenylisoquinoline can also be brominated at C-4[143,147] When the Reissert compound **102** is treated with bromine,[148] the cis adduct **103** is produced, which is converted into **104** when heated under reflux with morpholine.

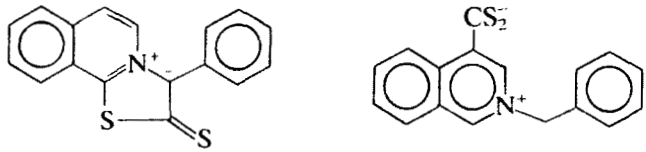
Isoquinoline can be nitrated at C-4 (14% yield) by using nitric acid in acetic anhydride at 100°C.[149] Nitration of 3-methylisoquinoline gives[150,151] the 5-nitro derivative as the major product, together with small amounts of 3-methyl-8-nitroisoquinoline. Isoquinoline-*N*-oxide is nitrated exclusively in the C-5 position, but bromination occurs at C-4.[152]

A curious reaction occurs[153] when isoquinoline is treated with sulfuryl chloride and potassium cyanide; 1-cyano-4-chloroisoquinoline can be isolated in 15% yield, and 66% of the isoquinoline is recovered. When



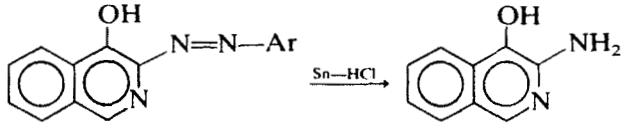
102 **103** **104**

N-benzylisoquinolinium salts are reacted with carbon disulfide and alkali,[154] the two major products are **105** and **106**.



105 **106**

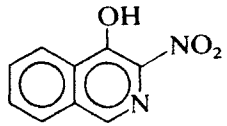
Strongly activating groups attached to the isoquinoline ring can alter the position of substitution considerably. Thus 4-hydroxyisoquinoline couples at C-3 with diazonium salts.[155] These azo compounds (**107**) can be reduced by tin and hydrochloric acid to 3-amino-4-hydroxyisoquinoline (**108**). Nitration



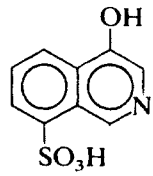
107 **108**

of 4-hydroxyisoquinoline, using potassium nitrate in sulfuric acid occurs also at C-3 to give **109**. These observations are in keeping with the results of deuterium exchange (1*N* NaOD at 145°C), when it was found[156] that C-3 is the most active position, followed by C-1. However, sulfonation of 4-hydroxyisoquinoline with 20% oleum at 200°C gave[157] the 8-substituted sulfonic acid **110**, but if 4-hydroxyisoquinoline is treated[158] with aqueous sodium sulfite at 90°C in the presence of manganese dioxide, a 60% yield of 4-hydroxyisoquinoline-3-sulfonic acid can be isolated.

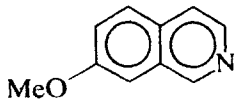
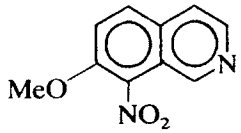
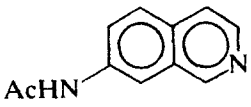
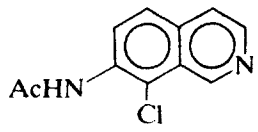
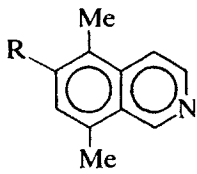
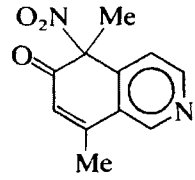
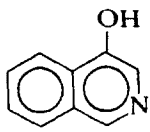
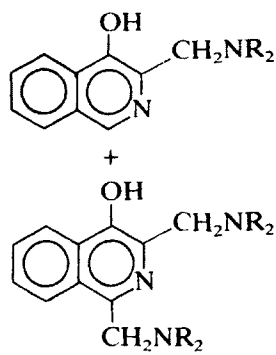
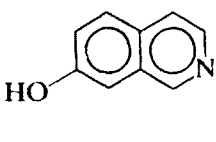
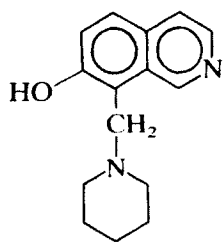
Electrophilic substitution reactions on simple isoquinoline derivatives are

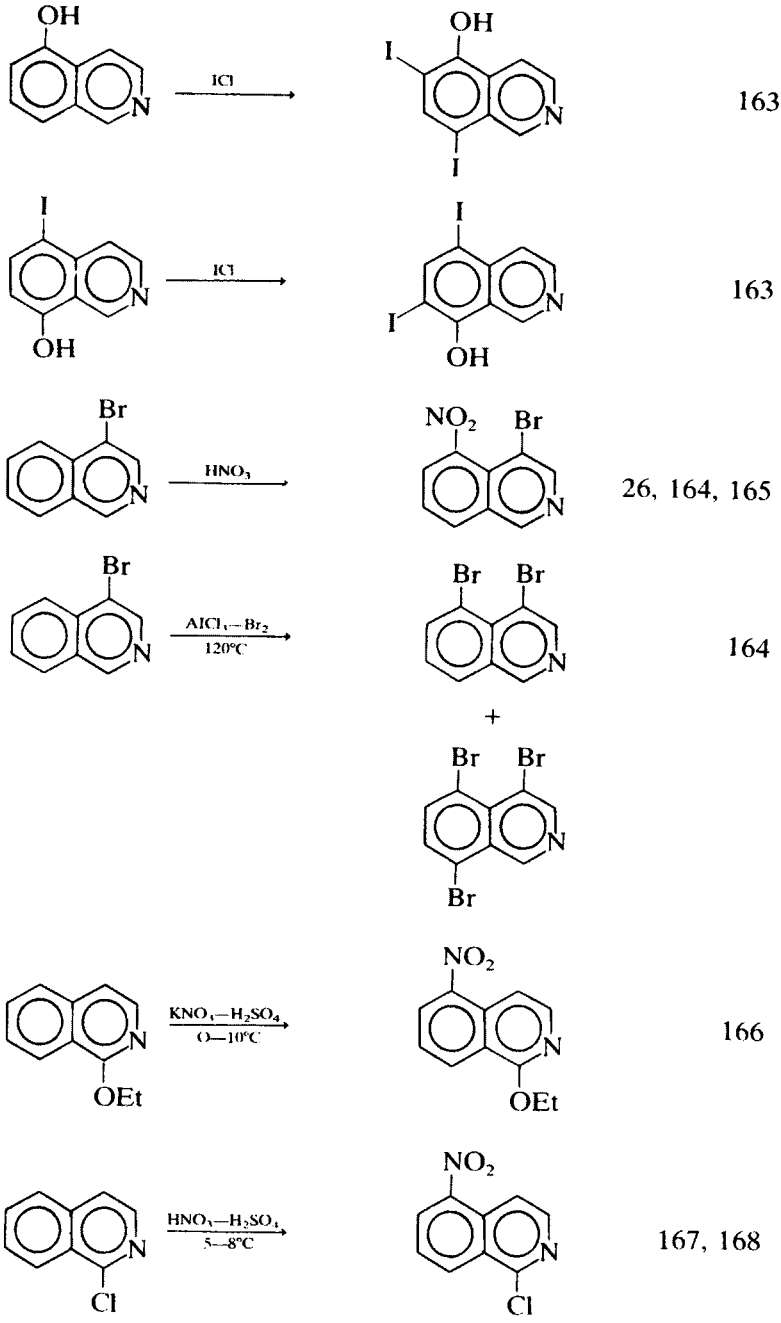


109

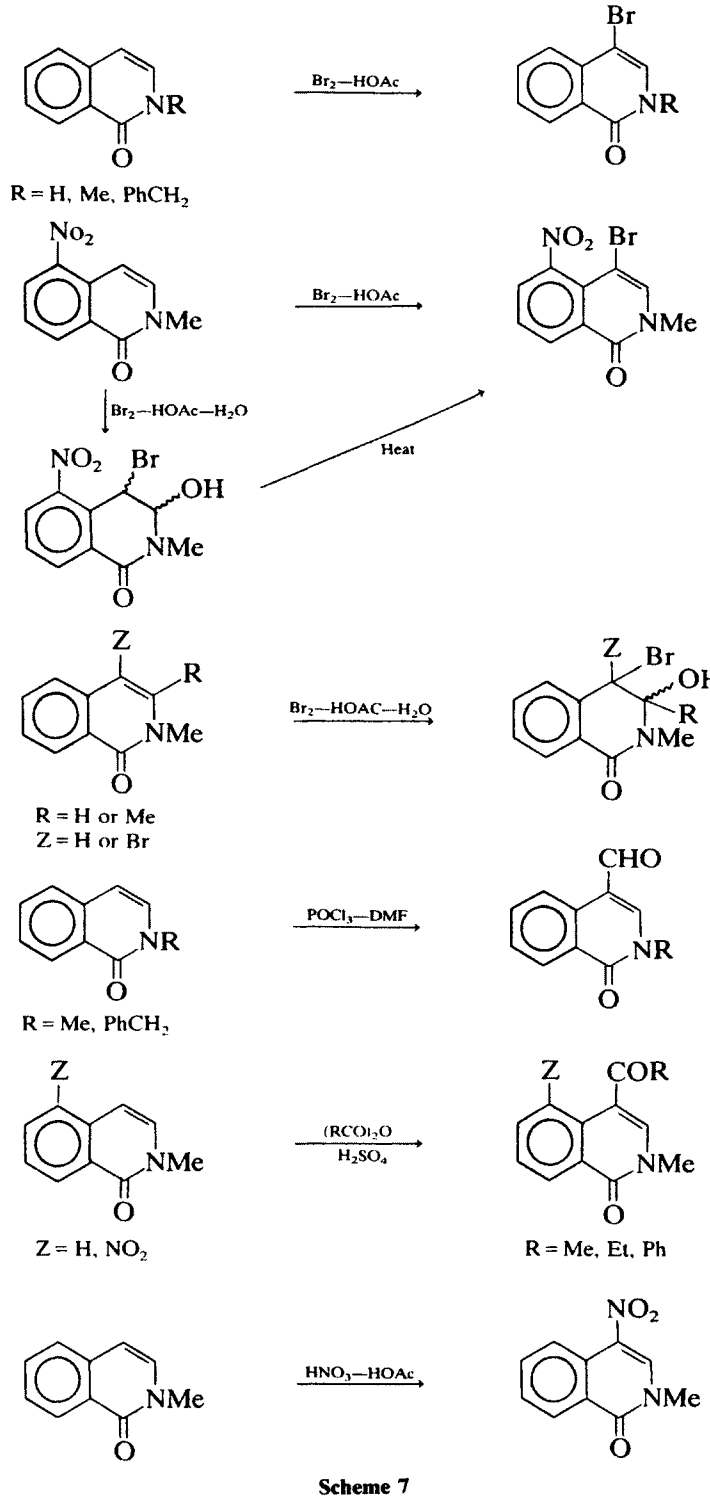


110

Substrate	Product	Ref.
		159a
		159b
 R = OH, OMe		160
		161
		162


OH
ICl
OH
I
I
163
I
ICl
I
OH
I
OH
163
Br
HNO3
NO2
Br
26, 164, 165
Br
AlCl3—Br2
120°C
Br
Br
164
+
Br
Br
Br
NO2
KNO3—H2SO4
0—10°C
OEt
NO2
166
OEt
HNO3—H2SO4
5—8°C
NO2
167, 168
Cl
Cl

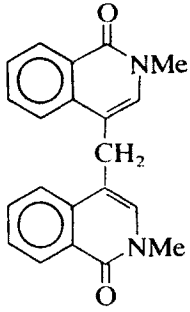
Scheme 6


Br
NR
O
Br2—HOAc
R = H, Me, PhCH2
NO2
NMe
Br2—HOAc—H2O
Heat
OH
Z
R
Br2—HOAC—H2O
R = H or Me
Z = H or Br
CHO
POCl3—DMF
R = Me, PhCH2
COR
(RCO)2O
H2SO4
Z = H, NO2
R = Me, Et, Ph
HNO3—HOAc

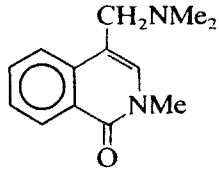
Scheme 7

not common, but some examples are shown in Scheme 6. Electrophilic substitution in 3,4-dihydroisoquinolines occurs at C-5 and/or C-7, whereas 1,2,3,4-tetrahydroisoquinolines are nitrated at C-7.

A study has been made by Horning et al.[169,170] of electrophilic substitution reactions in isocarbostyrils, and this work is summarized in Scheme 7. Similar reactions have been described by Tomisana et al.[171,172] when both 4- and 7-acylated products were found. The Mannich reaction with 2-methylisocarbostyril gives[173] mainly the dimer **111**, but **112** is also formed in 15% yield.



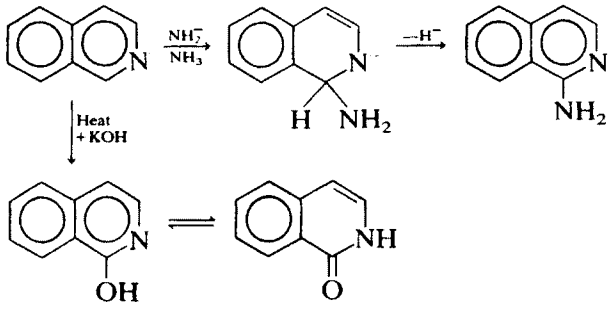
111



112

(c) *Reactions with Nucleophiles*

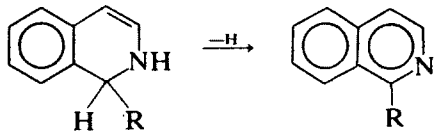
By analogy with the chemistry of pyridine, C-1 and C-3 of isoquinoline would presumably be susceptible to attack by nucleophilic reagents. In practice, C-1 is substantially more reactive than C-3.[1] Sodium amide, for example, reacts with isoquinoline[48,174,175] to yield 1-aminoisoquinoline (Scheme 8). Similarly, hot potassium hydroxide converts isoquinoline



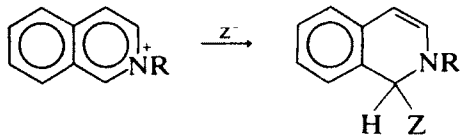
Scheme 8

into isocarbostyril (1-hydroxyisoquinoline). Grignard reagents and organolithium compounds react with isoquinoline to form 1-alkyl-1,2-

dihydroisoquinolines, which usually undergo rapid aerial oxidation to the aromatic derivatives (Eq. 8). Nucleophiles add even more readily to isoquinolinium salts, and the intermediate 1,2-dihydroisoquinoline may be sufficiently stable to be isolated (Eq. 9).



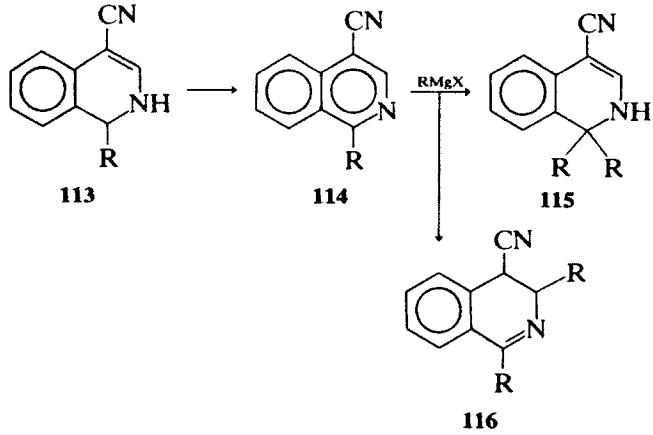
(8)



(9)

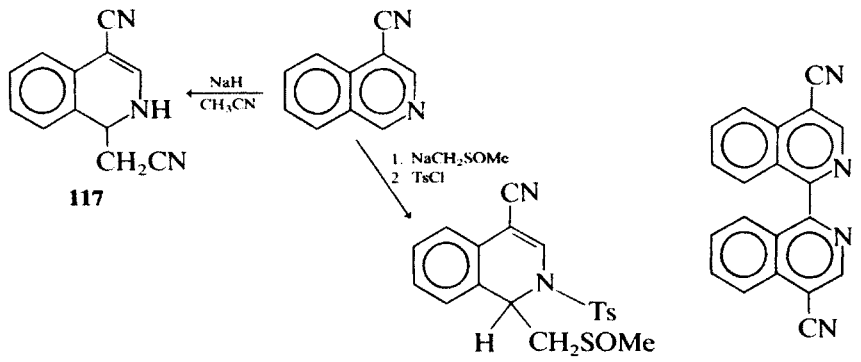
Z = OH, OMe, CN, alkyl, CH_2NO_2, CH_2COMe, etc.

4-Cyanoisoquinoline reacts with Grignard reagents at C-1 to form the 1,2-dihydroisoquinoline **113**, which can then undergo oxidation to **114**.[176,177] Further reaction with the same Grignard reagent is reported[177] to give a mixture of **115** and **116**. Similarly, addition of a second alkyl group

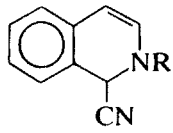


to C-1 of **114** (R = alkyl) has been observed to occur[176] in moderate yield without attack by the Grignard reagent at the cyano group. It is possible to react other nucleophiles at C-1 of 4-cyanoisoquinoline[176] to give the derivatives **117** and **118**. Whereas 4-cyanoisoquinoline reacts[178] with cyanide ions in dimethylsulfoxide to yield **119**, 4-cyanoisoquinoline *N*-oxide is converted by the same reagent into 1,4-dicyanoisoquinoline.

Isoquinoline-4-carboxylic acid and 3-methylisoquinoline are both aminated at C-1.[179] 1-Methylisoquinoline can[180] be prepared in quantitative yield by the reaction between isoquinoline and dimsyl sodium. 2-Acyl and



2-arylsulfonyl quaternary salts react easily with a variety of nucleophiles at C-1. When cyanide ion is used, the products **120** are the Reissert compounds (Section IV.E).

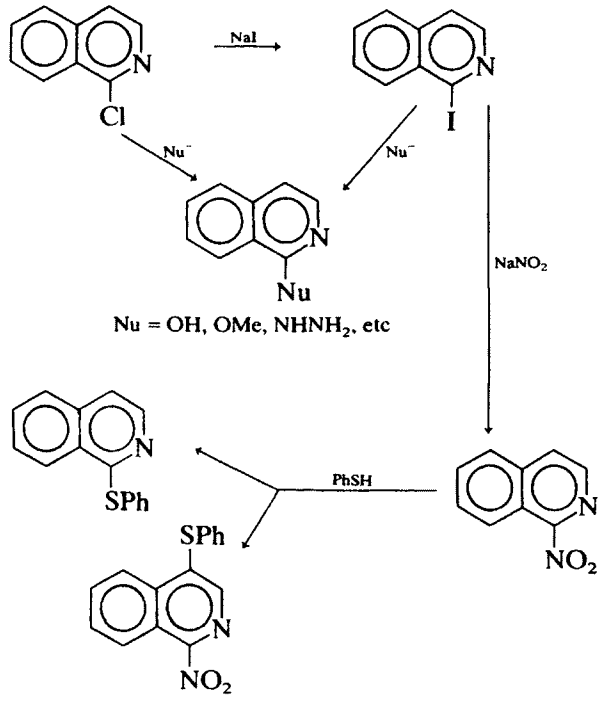


120

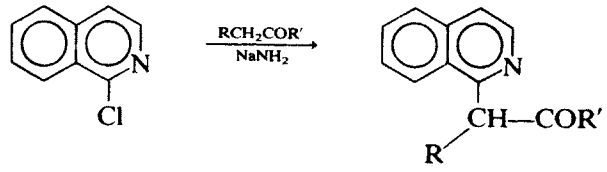
R = COPh or SO_2Ar

The nucleophilic displacement of substituents such as hydroxyl or halogen attached to C-1 or C-3 is a commonly observed reaction and is unexceptional. 1-Chloroisoquinoline, which is easily prepared from isocarbostyril, is a source of other 1-substituted isoquinolines (Scheme 9).[181] A useful recent method[182] for preparing 1-substituted isoquinolines involves treating 1-methanesulfonylisoquinolines with various nucleophiles (OEt^-, PhS^-, $\bar{C}H_2COR$, etc.) in the presence of sodium amide. A similar sequence has been applied[183] to 1-chloroisoquinoline to yield **121**. However, yields are low (3 to 25%). In 1,3-dichloroisoquinoline the C_1 substituent can be selectively replaced by nucleophiles,[184] for example **122** → **123** or **124**.

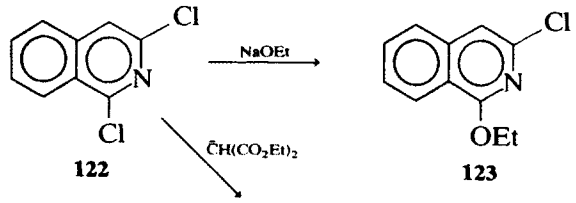
4-Bromoisoquinoline reacts with ammonia at elevated temperatures to give 4-aminoisoquinoline in low yield. A better conversion can be effected by using cupric nitrate in liquid ammonia. 4-Hydroxyisoquinoline is produced when 4-bromoisoquinoline is heated with sodium hydroxide in the presence of cupric sulfate.[185] The 4-bromo compound may also be converted into 4-cyanoisoquinoline with cuprous cyanide.[143] Under certain conditions of base treatment,[186] 3,4-isoquinolyne may be generated from 4-bromoisoquinoline. The reaction of the isoquinolines **125** with potassium amide in liquid ammonia has been studied.[187] The products are **126** and **127** in amounts varying with the nature of the halogen. A normal Chichibabin type of reaction and an abnormal addition–elimination process were involved. Evidence for a tetrahedral complex at C-1 came from pmr studies with 4-chloroisoquinoline.



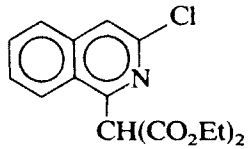
Scheme 9



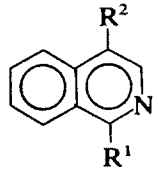
121



122 **123**



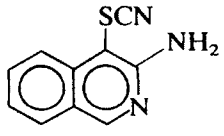
124



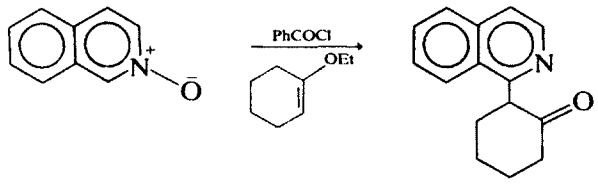
125, $R^1 = H$; $R^2 = F$, Cl, Br, or I
126, $R^1 = NH_2$; $R^2 = F$, Cl, Br, or I
127, $R^1 = NH_2$; $R^2 = H$

When 5-, 6-, 7- or 8-chloroisoquinoline is treated with ammonia, nucleophilic displacement of the halogen occurs to give the corresponding aminoisoquinoline. A high yield of 6-aminoisoquinoline has been reported[188] with heating of 6-hydroxyisoquinoline under pressure with ammonia solution. An alternative procedure involves[160] fusion of the phenol with zinc chloride and tetramine. 8-Nitro-7-hydroxyisoquinoline is converted[189] by ammonia into 8-nitro-7-aminoisoquinoline. The replacement of the sulfonic acid group at C-5 of isoquinoline by hydroxyl is unexceptional,[140,190,191] although it has been reported[167,192] that when isoquinoline-5-sulfonic acid is fused with NaOH, the product is 5-hydroxyisocarbostyril.

The reaction of 3-aminoisoquinoline with bromine and potassium thiocyanate[193] to yield **128** presumably involves electrophilic substitution at C-4 by bromine, followed by nucleophilic displacement by CNS^- ions. Isoquinoline *N*-oxide is also susceptible to nucleophilic attack at C-1 by, for example, Grignard reagents, and by enol ethers to give **129**.[194]



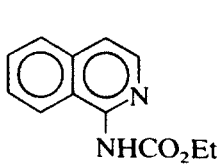
128



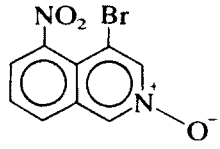
129

Reaction with potassium cyanide and potassium ferricyanide gives 1-cyanoisoquinoline *N*-oxide in 85% yield.[139] Cyanogen bromide reacts with isoquinoline *N*-oxide[195] to give a mixture of, predominantly **130**, together with some 4-substituted isoquinoline. Whereas nucleophilic attack on isoquinoline *N*-oxide normally occurs at C-1, the derivative **131** reacts very readily with secondary amines[165] to give **132**.

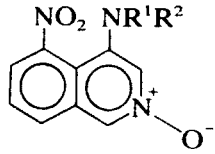
4-Hydroxy, and especially 4-acetoxy-1,2,3,4-tetrahydroisoquinolines,[196]



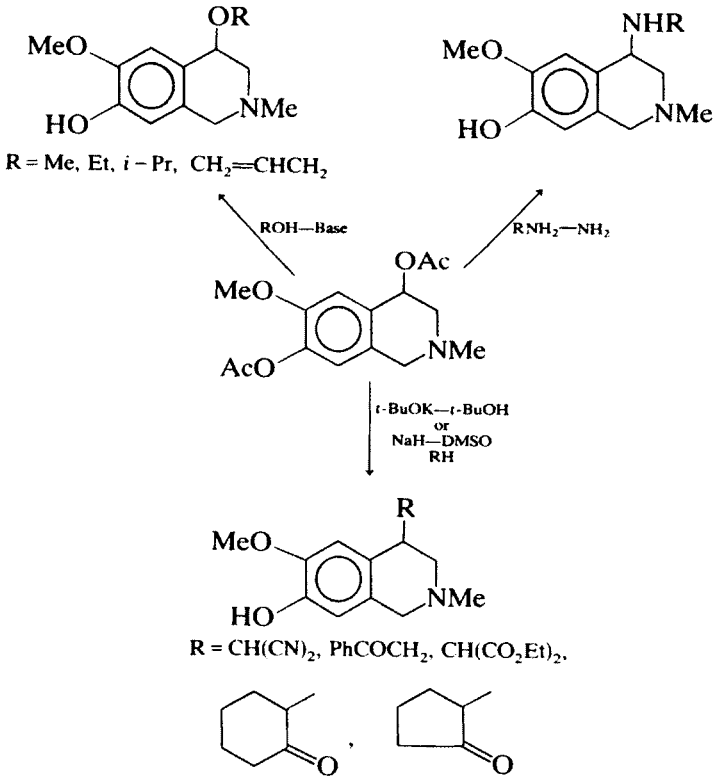
130



131



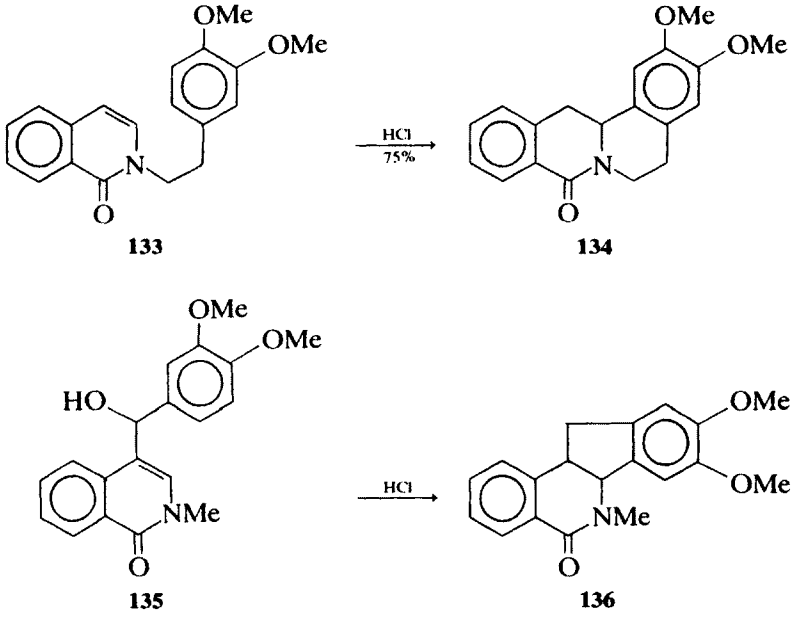
132



Scheme 10

are very susceptible to nucleophilic displacement at C-4,[197-199] thus providing a useful synthetic procedure for various 4-substituted isoquinoline derivatives (Scheme 10).

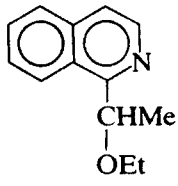
Some isocarbostyrils have been shown[200,201] to undergo nucleophilic attack at C-3, especially in an intramolecular cyclization reaction, such as **133** → **134** and **135** → **136**.



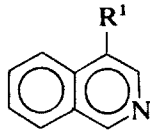
133 **134** **135** **136**

(d) *Radical Reactions*

Radical alkylation[202] of nitrogen heteroaromatic compounds is of synthetic value when the reaction is carried out in an acid medium (nitrogen is protonated), but yields and selectivity of position of attack are poor when the free base is used. In the case of isoquinoline, radical attack occurs invariably at C-1 in both the base and the isoquinolinium salt, in agreement with atom localization energies.[134] However, alkylation of the base with the use of lead tetraacetate or peroxides[203] gives poor yields of 1-methylisoquinoline, and benzylation occurs in low yields when dibenzyl mercury is used,[204] although yields are higher in acetic acid solution. It has been reported[205,206] that phenylation of a series of heterocycles using dibenzoyl peroxide gives results that are not in agreement with theoretical calculations for the free valencies of the heterocycles and their conjugate acids; however, isoquinoline is still substituted at C-1. A very useful method for generating radicals[207] involves treating a carboxylic acid with potassium persulfate in the presence of silver ions. Under these conditions 1-ethylisoquinoline was obtained in 33% yield and the 1-cyclohexyl derivative in 84%.



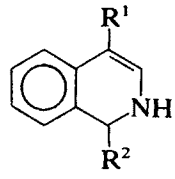
137



138

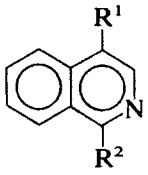
$R^1 = CN, CO_2Me$

$\xrightarrow{R^2OH,\ h\nu}$



139

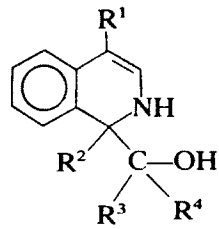
R^1	R^2	Yield (%)
CN	OMe	69
CN	OEt	36
CN	OPr	29
CO_2Me	OMe	27



140

R^1	R^2
CN	Me
CN	$PhCH_2$
CO_2Me	CH_2OAc

$\xrightarrow[h\nu]{R^3R^4CHOH}$



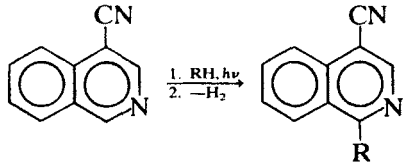
141

Irradiation of isoquinoline in ether solution results[208] in a 5% yield of **137**. When the 4-substituted isoquinolines **138** were photolyzed in the presence of various alcohols,[209] addition occurred to yield **139**. When the C-1 position is occupied by an alkyl group as in **140**, photoaddition can still occur[209] to yield **141**. A further sequence of addition reactions[209] was studied in which the intermediate 1,2-dihydroisoquinoline was dehydrogenated to the aromatic structure with chloranil (Eq. 10).

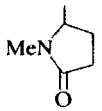
B. Reduction and Oxidation

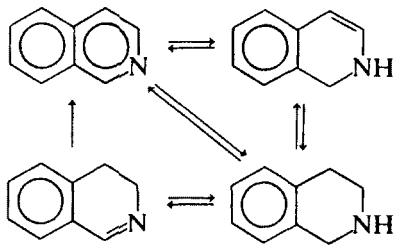
(a) *Introduction*

The various oxidation states of the heteroring in isoquinoline derivatives are summarized in Schemes 11 and 12, together with an indication of the possible modes of interconversion using oxidation or reduction reactions.



(10)

R	Yield (%)
Me—CH(OEt)—	48
Me—CH(OCOMe)—	9
—CH_2NMeCHO	15
	12
	27

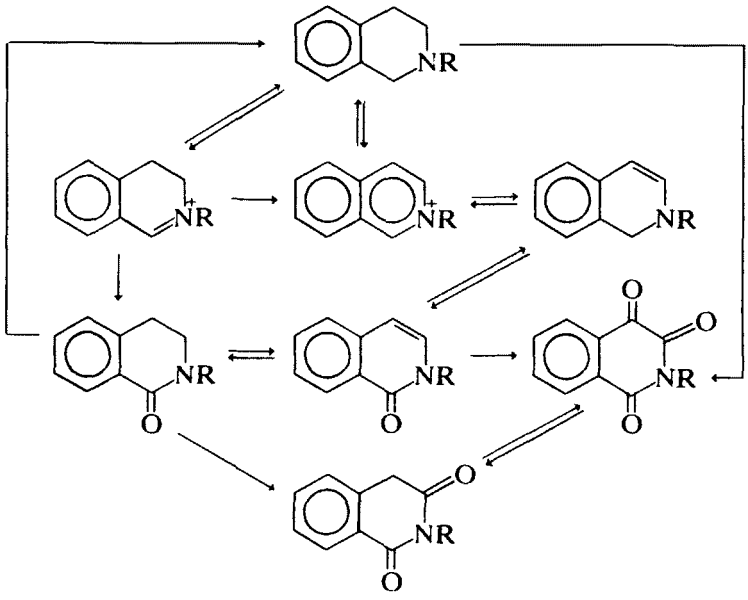


Scheme 11

(b) *Reduction*

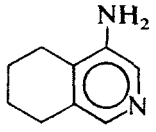
(*i*) CATALYTIC. Isoquinolines can be hydrogenated to 1,2,3,4-tetrahydroisoquinolines over platinum in neutral solution,[210,211] although this procedure is not always successful.[212] In acid solution (acetic acid plus trace sulfuric acid) isoquinoline is reduced to a mixture of *cis*- and *trans*-decahydroisoquinolines.[213,214] When a solution of isoquinoline in concentrated hydrochloric acid is subjected to prolonged hydrogenation over platinum oxide at room temperature and 50 psi (pounds per square inch), a 95% yield of 5,6,7,8-tetrahydroisoquinoline results.[215] The preparation and reactions of these and octahydroisoquinoline derivatives are discussed in Section V.

Substituted isoquinolines can also be hydrogenated to the 1,2,3,4-tetrahydro state over Raney nickel[162,216] or copper chromite.[217,218] Certain

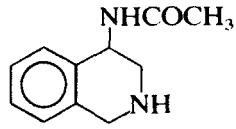


Scheme 12

groups attached to the isoquinoline nucleus may be reduced without affecting the ring. Thus a nitro group at C-4 or C-5 to C-8 may be reduced to an amino group, and halogens at C-1 or C-3 can be hydrogenolyzed. Reductive cleavage of benzyloxy groups is a standard procedure for the preparation of phenolic isoquinolines. A vinyl group or a ketone carbonyl group attached to the ring at C-1 can be selectively reduced to ethyl or carbinol, respectively.[219,220] Certain substituents can profoundly affect the course of reduction of the isoquinoline nucleus. Thus 4-aminoisoquinoline is reduced over platinum oxide in acetic acid or over Raney nickel in ethanol to **142**,[221] but 4-acetylaminoisoquinoline, under the same conditions, yields **143**.



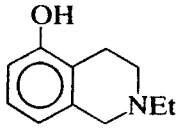
142



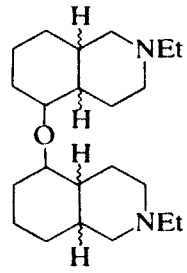
143

Catalytic hydrogenation of quaternary isoquinolinium salts to *N*-alkyl-1,2,3,4-tetrahydroisoquinolines is known,[222–224] although chemical reduction is now the preferred method. It is possible to hydrogenate a *N*-benzylisoquinolinium salt with retention of the benzyl group.[225] 1,2-Dihydroisoquinolines are formed in the hydrogenation of isoquinoline under certain conditions,[226,227] although certain aspects of this work have been corrected.[228,229] Further hydrogenation leads to 1,2,3,4-tetrahydroisoquinolines. 5-Hydroxy-2-ethylisoquinolinium bromide is reduced quantitatively to the expected 1,2,3,4-tetrahydroisoquinoline (**144**) over platinum

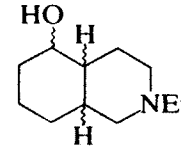
oxide at 40 to 50 psi in ethanol,[230] but in acetic acid solution the only product is **145**. However, hydrogenation of the 5-hydroxy-2-ethylisoquinolinium *p*-toluenesulfonate at high pressures and temperatures[211] yields the octahydro compound **146**. The conditions for the highest overall yield and for the highest cis:trans ratio were found. The work of Georgian et al.[191] who reported the production of **146** by hydrogenation of 5-hydroxyisoquinoline over Raney nickel and use of ethanol as a solvent, has been stated[231] to be difficult to repeat. 5-Nitro-2-ethylisoquinolinium *p*-toluenesulfonate has also been hydrogenated[231] to the octahydroamino derivative, and again conditions for highest yield and highest cis:trans isomer ratio were determined.



144



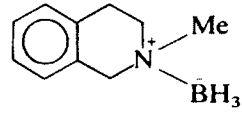
145



146

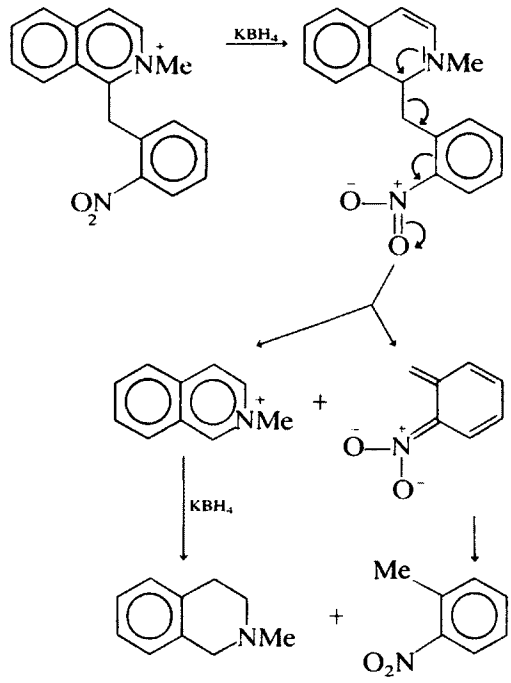
3,4-Dihydroisoquinolines are easily hydrogenated to 1,2,3,4-tetrahydroisoquinolines using platinum,[232–234] palladium[234,235] or nickel[216] catalysts. *N*-Alkyl-3,4-dihydroisoquinolinium salts can also be hydrogenated,[236] but chemical reduction is preferred.

(ii) CHEMICAL. Isoquinolines can be reduced to 1,2,3,4-tetrahydroisoquinolines by tin and hydrochloric acid[237] or by sodium and alcohol.[238] Isoquinolinium salts can be converted into 2-alkyl-1,2,3,4-tetrahydroisoquinolines by tin and hydrochloric acid[232,238] and by sodium borohydride in aqueous alcohol solution.[239–241] In some cases an *N*-borane complex (**147**) is formed[242,122] which can be converted into the tetrahydroiso-



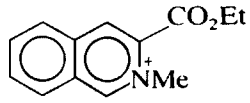
147

quinoline by acid treatment. If the isoquinolinium salt carries an *o*-nitrobenzyl group at C-1, a carbon–carbon bond cleavage reaction occurs in certain cases with potassium borohydride (Scheme 13).[243] If the reduction of an isoquinolinium salt with $NaBH_4$ is carried out in pyridine[78,244] or dimethylformamide[245] solution, reduction ceases at the intermediate stage and 1,2-dihydroisoquinolines can be isolated. Some isoquinolinium salts (e.g., **148** and **149**) are only partially reduced by $NaBH_4$, even in aqueous alcohol solution.[246,247]

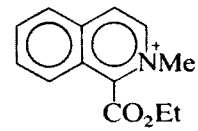


Scheme 13

N-Alkylisoquinolinium salts are reduced to 1,2-dihydroisoquinolines by lithium aluminum hydride in ether,[248] which will also convert[249]

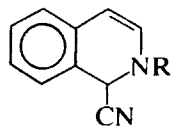


148



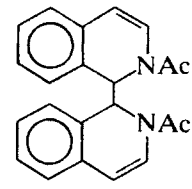
149

pseudocyanides **150** into the same dihydroderivatives. Isoquinoline *N*-oxide is also reduced to 1,2-dihydroisoquinoline.[250] Isoquinoline itself can be reduced to 1,2-dihydroisoquinoline by lithium aluminum hydride[250,251] and by sodium hydride.[252] 3-Methyl-6,7-methylenedioxyisoquinoline is similarly reduced by lithium aluminum hydride,[253] a reagent that can also cause slow reduction of these enamines to 1,2,3,4-tetrahydroisoquinolines.[254]



150

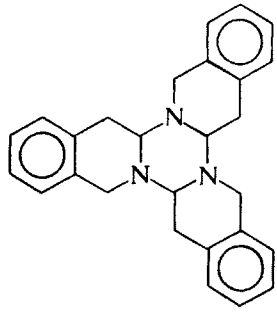
R = Me, Et, $PhCH_2$



151

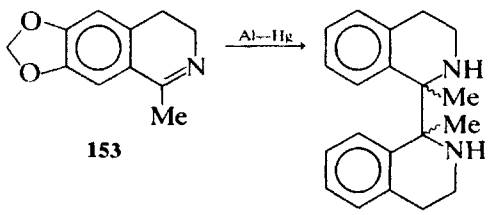
When isoquinoline is reduced with zinc in acetic anhydride,[255] the dimer **151** is formed, and reductive *N*-formylation of isoquinoline occurs on heating with formic acid and formamide.[256] *N*-Formyl-1,2,3,4-tetrahydroisoquinolines are also produced when 3,4-dihydroisoquinolines are similarly treated.[256,257]

When 1,3-dichloroisoquinoline is reduced with red phosphorus and hydrogen iodide, selective removal of the C_1 chlorine results.[258] Isoquinoline has been reduced with sodium in liquid ammonia,[259] and one of the products was formulated as the trimer **152**, formed from 1,2-dihydroisoquinoline via the imine tautomer.



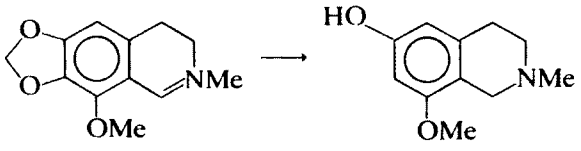
152

3,4-Dihydroisoquinolines can be reduced to the 1,2,3,4-tetrahydroisoquinoline by tin and hydrochloric acid,[2] but are stable to stannous chloride in ethanolic hydrogen chloride.[260] When reagents such as aluminum amalgam are used, dimeric products[261–263] can result (e.g., **153** → **154**). 3,4-Dihydroisoquinolinium salts are readily reduced to 2-alkyl-1,2,3,4-tetrahydroisoquinolines by tin, or zinc and hydrochloric acid[212] and by lithium aluminum hydride or sodium borohydride.[264]

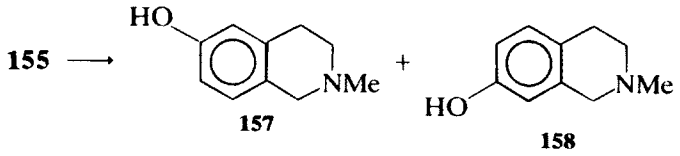


153 **154**

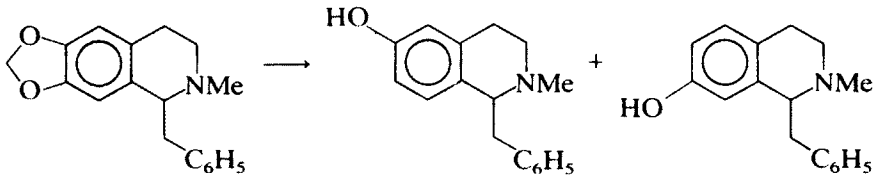
Some 1,2,3,4-tetrahydroisoquinolines have been reduced with sodium or lithium in liquid ammonia. Clayson[265] found that hydrocotarnine (**155**) is converted into **156** with sodium in isoamyl alcohol (Eq. 11); however, in liquid ammonia as solvent and in the presence of ammonium chloride, the products are **157** and **158** (Eq. 12). When **159** is similarly reduced[266] a mixture of **160** and **161** is produced (Eq. 13). Birch reduction of 2-methyl-6-methoxy-1,2,3,4-tetrahydroisoquinoline (**162**) yields the expected hexahydro compound **163**,[267] and similar treatment[268] of **164** gave **165**. In a



155 156 (11)

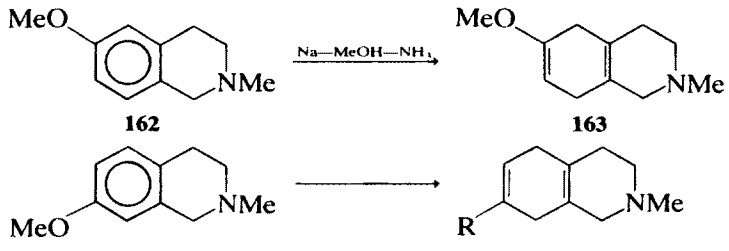


157 158 (12)



159 160 161 (13)

later study[269] 2-methyl-1,2,3,4-tetrahydroisoquinoline was reduced to **166** by using lithium in liquid ammonia in the presence of ethanol. An interest-



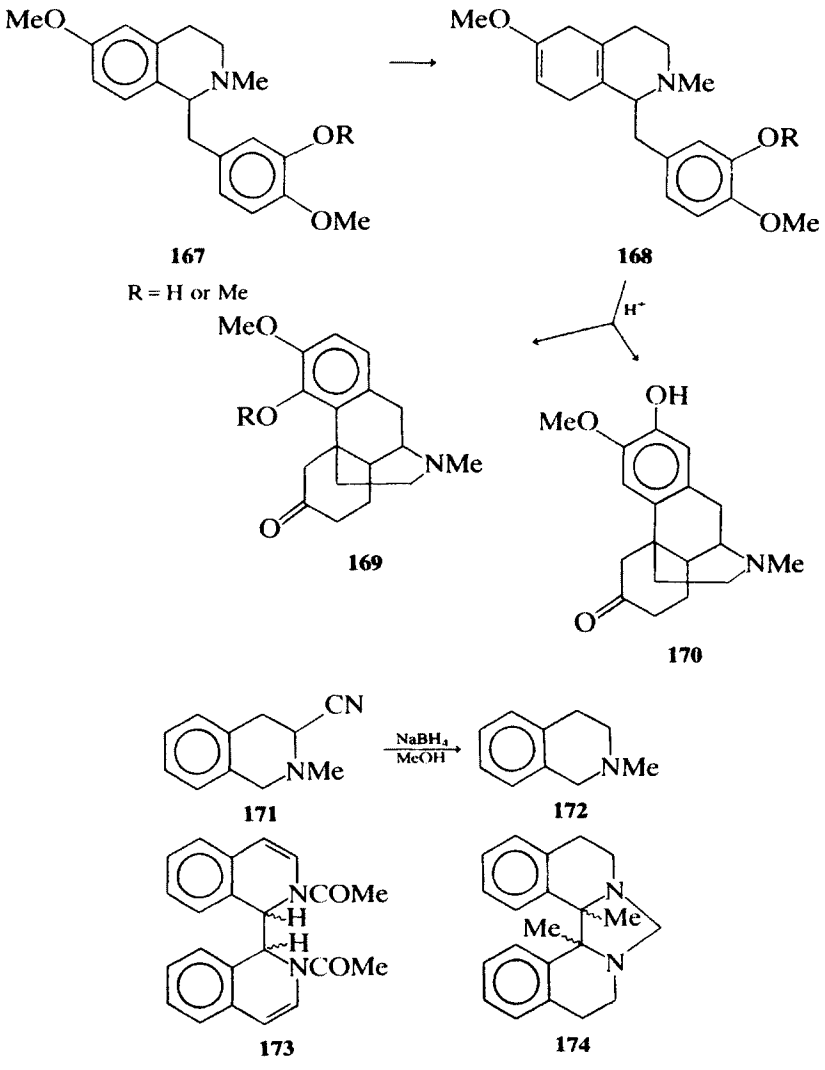
162 **163**

164 **165**, R = OMe
166, R = H

ing application of the Birch reduction led[270,271] to a new synthesis of the morphine skeleton **167** → **168** → **169** + **170**.

An interesting C–C bond cleavage occurs when 3-cyano-1,2,3,4-tetrahydroisoquinolines **171** are treated with sodium borohydride **171** → **172**.[272] The bimolecular reduction (Dimroth reaction) of isoquinoline derivatives with zinc and acetic anhydride has been studied.[262,263,273] With isoquinoline itself, a 58% yield of a 1 : 1 mixture of the racemic and meso forms of **173** is produced. When 1-methyl-3,4-dihydroisoquinoline is photolyzed in methanol,[274] the meso and racemic forms of **174** are formed.

Isocarbostyrils can be reduced with lithium aluminum hydride to 1,2-dihydroisoquinolines[248] and hydrogenated to dihydroisocarbostyrils using Raney nickel at 70 to 100 atm and 140 to 160°C.[275]

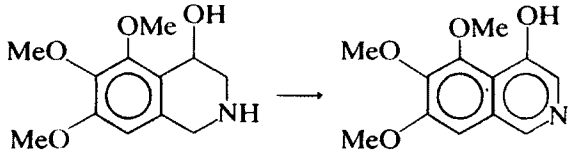


(c) *Oxidation*

1,2,3,4-Tetrahydroisoquinolines may be converted into 3,4-dihydroisoquinolines or into the fully aromatic derivatives by catalytic or chemical methods. Isoquinolines or *N*-substituted isoquinolinium salts may also be formed from 1,2- and 3,4-dihydroisoquinoline derivatives by similar methods.[1]

(i) CATALYTIC. Although catalytic dehydrogenation is widely used, the conditions are often severe, and failures or poor yields have been

reported. The reaction is particularly unreliable when it is applied to *N*-alkyl-1,2,3,4-tetrahydroisoquinolines. Much of the early work has been summarized by Gensler.[1] The catalyst may be palladium on charcoal,[276-286] palladium black,[185,234,283,287-294] palladium on asbestos,[295] Raney nickel,[167,296,297] silver,[298] palladium oxide,[298] or platinum.[299] A remarkable dehydrogenation involves[300] the conversion of 4-hydroxy-1,2,3,4-tetrahydroisoquinoline into 4-hydroxyisoquinoline with the use of palladium black at 180°C. This reaction has been used recently[301] in the synthesis of the oxoaporphine, imenine (Eq. 14).



(14)

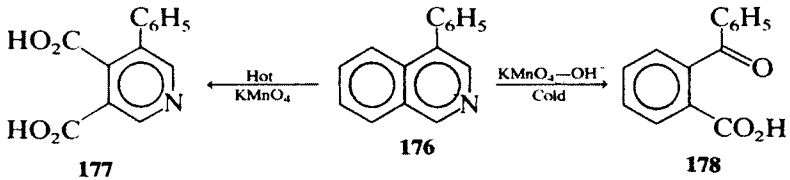
175

Whereas 3,4-dihydroisoquinolines carrying a nitro or a chloro substituent have been successfully dehydrogenated,[288,289] loss of fluorine has been observed[302] from monofluoro-1,2,3,4-tetrahydroisoquinolines unless special precautions were taken. Ethoxycarbonyl or acetyl functions at C-3[294,303] as well as phenoxymethyl[284] survive catalytic dehydrogenation.

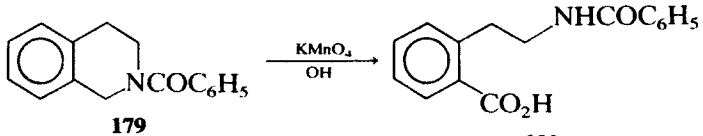
(ii) CHEMICAL

(1) *Formation of Fully Aromatic Structures.* Aromatic isoquinolines have been prepared from 1,2,3,4-tetrahydro- and 3,4-dihydroisoquinolines by using potassium permanganate,[304] nitric acid,[304,305] iodine and sodium acetate in ethanol,[305-312] mercuric acetate,[305,313-320] sulfur,[321-323] selenium,[324-326] or thionyl chloride.[327] The same reagents will oxidize *N*-alkyl-1,2,3,4-tetrahydroisoquinolines to fully aromatic or to 3,4-dihydroisoquinolinium salts. Certain 3,4-dihydroisoquinoline derivatives are resistant to further dehydrogenation with iodine[218,225,328] and with mercuric acetate.[316,329,330] In some cases total failure has been reported with the use of iodine,[331] mercuric acetate,[315,322] nitric acid,[237,332,333] or potassium permanganate.[185,237,332,333] With the latter reagent, ring degradation (**176** → **177** + **178** and **179** → **180**) becomes a significant alternative reaction.[334] Dehydrogenation of 1,2,3,4-tetrahydroisoquinoline itself with iodine results in a mixture of isoquinoline and 3,4-dihydroisoquinoline.[308]

The dehydrogenation of **181a** to the 3,4-dihydroisoquinoline **182a**[335] in 70% yield was the first example of the use of mercuric acetate in isoquinoline chemistry. The reagent has been used quite extensively, especially by Knabe,[336] with or without ethylenediaminetraacetic acid (EDTA). When simple 1,2,3,4-tetrahydroisoquinolines **181b** through **181g** are oxidized, the expected products, **182b** through **182g**, respectively, are formed in good yields.[336b,c,g] With **181h**, the tert-butyl group is lost with the formation of the fully aromatic quaternary salt. Even with the heavily substituted compound

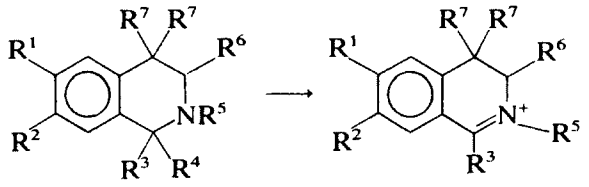


177 176 178

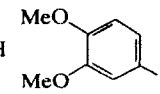


179 180

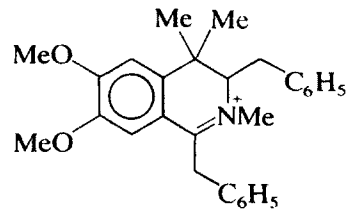
181i, the 3,4-dihydroisoquinolinium salt **182i** is produced,[336d] but dehydrogenation of **181j** with the mercuric acetate–EDTA complex gives a quaternary salt[336e] that was thought to be **183**, R = H or Me. This was later proved to be wrong,[336f] and it is now realized that a benzyl migration had occurred to give **184** (Section IV.F). Fremy's salt has been used to dehyd-



181 182

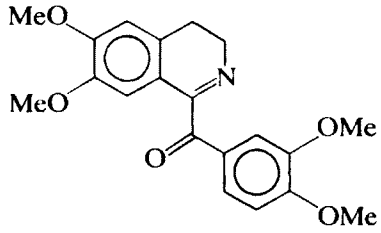
	R¹	R²	R³	R⁴	R⁵	R⁶	R⁷
a,	OMe	OMe	Me	H	H		H
b,	O—CH_2—O		Me	H	Me	H	H
c,	O—CH_2—O		Et	H	Me	H	H
d,	O—CH_2—O		*n*-Bu	H	Me	H	H
e,	OMe	OMe	$PhCH_2CH_2$	H	Me	H	H
f,	OMe	OMe	*t*-Bu	H	Me	H	H
g,	OMe	OMe	Ph	H	H	H	H
h,	OMe	OMe	*t*-Bu	H	H	H	H
i,	OMe	OMe	$PhCH_2$	H	Me	H	H
j,	OMe	OMe	$PhCH_2$	$PhCH_2$	Me	H	Me

183
R = H, Me



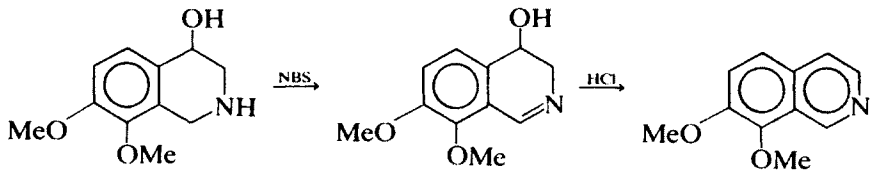
184

rogenate 1,2,3,4-tetrahydroisoquinolines.[337] For those substrates without a C_1-substituent good yields of the aromatic isoquinoline were observed, whereas the reaction stops at the 3,4-dihydroisoquinoline stage for those compounds that carry a methyl group at C-1. When tetrahydropapaverine is oxidized with Fremy's salt, the product is **185**. 1,2-Dihydroisoquinolines are readily oxidized to isoquinolines or isoquinolinium salts by air, silver nitrate, *N*-bromosuccinimide, and other oxidants.[248]



185

(2) *Formation of* 3,4-*Dihydroisoquinolines.* Such compounds, or the *N*-alkyl-3,4-dihydroisoquinolinium salts, may be obtained in high yield from 1,2,3,4-tetrahydroisoquinolines by reaction with *N*-bromosuccinimide.[338] For suitably substituted compounds, the preferred method for the formation of the fully aromatic isoquinoline involves[339] treating the 4-hydroxy-1,2,3,4-tetrahydroisoquinolines with *N*-bromosuccinimide, followed by dehydration, such as **186** → **187** → **188**. Sodium hypochlorite is reported[340] to convert

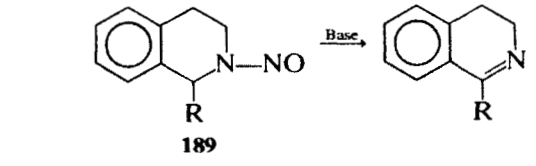


186 **187** **188**

1,2,3,4-tetrahydroisoquinolines into the 3,4-dihydro derivatives. Reaction of *N*-nitroso-1,2,3,4-tetrahydroisoquinolines **189** with base results[341] in the formation of 3,4-dihydroisoquinolines (Eq. 15), although in certain cases the formation of **191** as well as **192** becomes important.

When the amino acid derivative **193** is oxidized with periodic acid,[341–344] the product is **196**, and since the amount of oxidant consumed is exceptionally high, it was proposed that the reaction proceeded through the cation **194** and the quinone methide **195**.

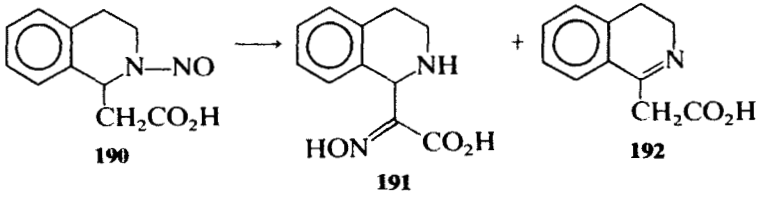
(3) *Formation of Oxygen-Containing Derivatives.* Pseudobases (Section IV.D) of isoquinolinium salts and 3,4-dihydroisoquinolinium salts can be oxidized with potassium ferricyanide to the corresponding amides[1,228,275,345] (although 3,4-dihydroisocarbostyrils are best prepared by hydrogenation[346] of isocarbostyrils). Oxidation of isocarbostyrils with chromium trioxide in



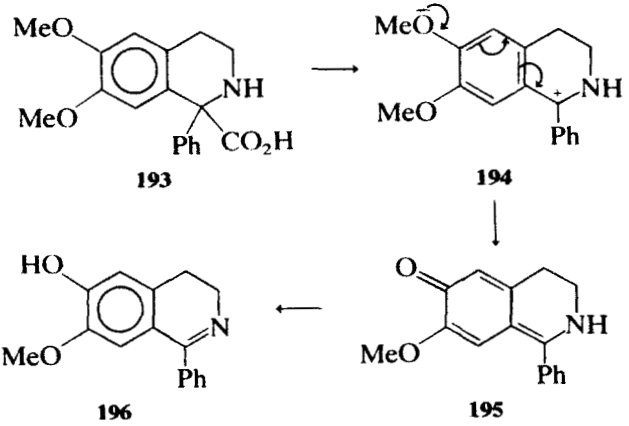
(15)

189

R = H, Me



190 **191** **192**

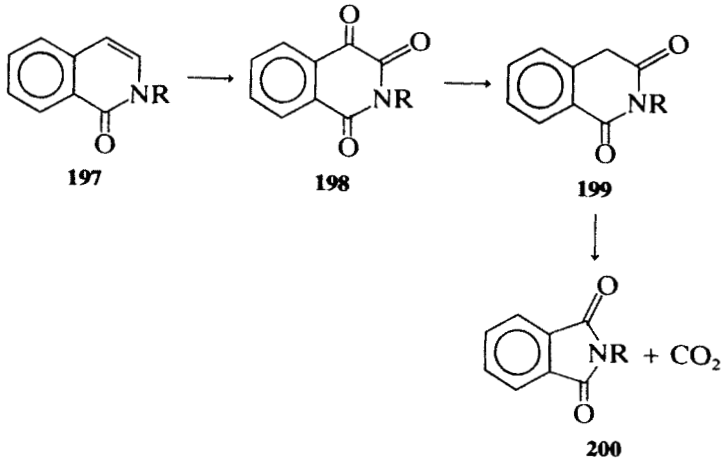


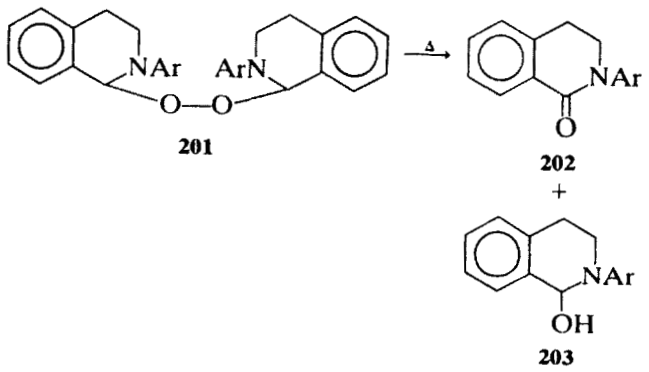
193 **194** **196** **195**

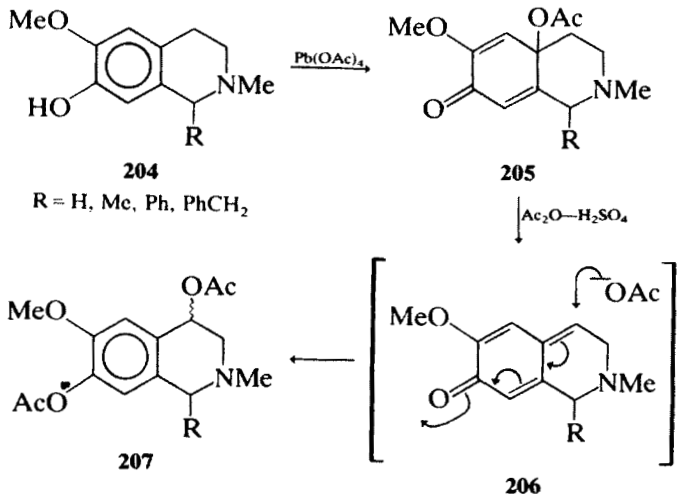
acetic acid[347,348] yields the phthalonimide derivatives, which may be reduced catalytically to homophthalimides, such as **197** → **198** → **199**. Phthalonimides can also be obtained by the oxidation of 1,2,3,4-tetrahydroisoquinolines.[349,350] When homophthalimides are oxidized with hydrogen peroxide in alkaline solution, phthalimides are formed; **199** → **200**. It has been established[351] that the carbon atom that is lost as carbon dioxide was originally C-3 of **199**.

N-Aryl-1,2,3,4-tetrahydroisoquinolines form peroxides **201** when treated with oxygen under photolytic conditions,[352,353] and these decompose thermally into **202** and **203**.

(4) *Oxidations not Involving the Heteroring.* A methyl group at C-1 or C-3 in an aromatic isoquinoline or at C-1 in a 3,4-dihydroisoquinoline is readily oxidized to an aldehyde with selenium dioxide or manganese dioxide.[354] It has been realized for some time[1] that the methylene group of a 1-benzylisoquinoline or 3,4-dihydroisoquinoline is readily oxidized, even in air, to a carbinol or to a ketonic carbonyl function.[355,356]

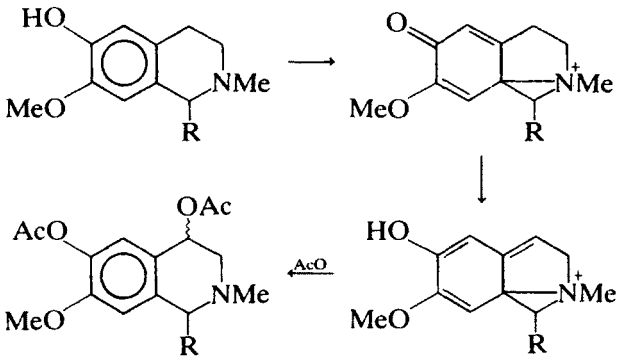

NR
O
197
198
199
NR + CO2
200


NAr
ArN
O—O
Δ
201
NAr
O
202
+
NAr
OH
203

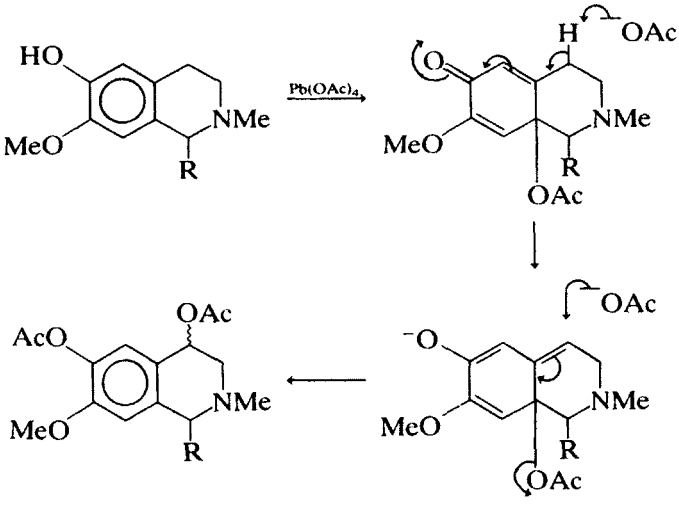

MeO
HO
NMe
R
Pb(OAc)4
OAc
O
204
R = H, Me, Ph, PhCH2
205
Ac2O—H2SO4
AcO
207
206

Scheme 14

The oxidation of 7-hydroxy-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinolines **204** with lead tetraacetate has been reported in an interesting study.[196] The *p*-quinol acetates **205** were isolated in modest yield. When these latter compounds were treated with acetic anhydride and sulfuric acid, 4,7-diacetates **207** were produced, and quinone methides **206** were considered to be intermediates in this type of transformation (Scheme 14). The isomeric 6-hydroxy-7-methoxytetrahydroisoquinolines are also oxidized by lead tetraacetate.[196] The mechanism proposed for this reaction is summarized in Scheme 15, but, on the available evidence, the present authors suggest that a pathway such as that shown in Scheme 16 is an acceptable alternative. Many phenolic tetrahydroisoquinolines have been oxidized by one-electron transfer reagents[357] or electrolytically[358] in attempts to simulate biosynthetic processes.



Scheme 15



Scheme 16

C. Ring Fission Reactions

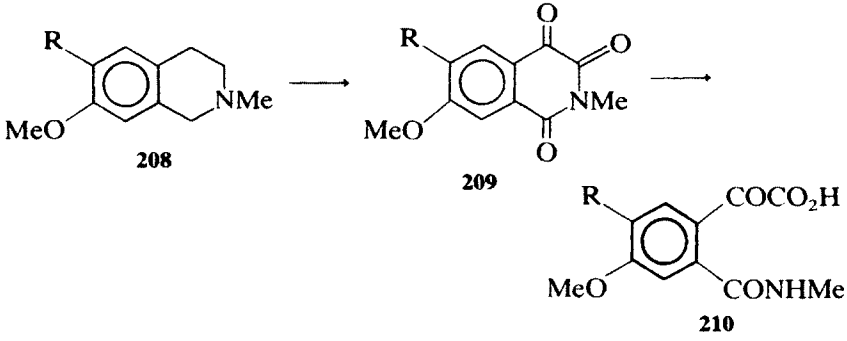
(a) *Oxidative Degradation*

Isoquinoline is oxidized by potassium permanganate to a mixture of phthalic acid and pyridine-3,4-dicarboxylic acid (cinchomeronic acid[2]), and the same mixture is produced in the reaction of isoquinoline with ozone.[359] Isoquinolines carrying electron-donating substituents in the benzenoid ring are oxidized to substituted phthalic acids,[360,361] and 3-substituted phthalic acids are also obtained from 5-nitro, 5-iodo,[362] or 5-carboxyisoquinolines.[363] 5-Aminoisoquinoline is oxidized by permanganate to cinchomeronic acid, and substituted cinchomeronic acids have been synthesized by oxidation of 5-aminoisoquinolines substituted in the heteroring.[364]

When isoquinolinium salts are oxidized in alkaline solution, the first step is formation of an isocarbostyril, which is further oxidized to phthalic acid derivatives.[361] The oxidative degradation of 4-phenylisoquinoline was mentioned in section IV.B(c)(ii)(1).

3,4-Dihydroisoquinolines are also degraded by potassium permanganate to phthalic acids,[365] whereas pyridine derivatives have been reported with nitric acid.[366]

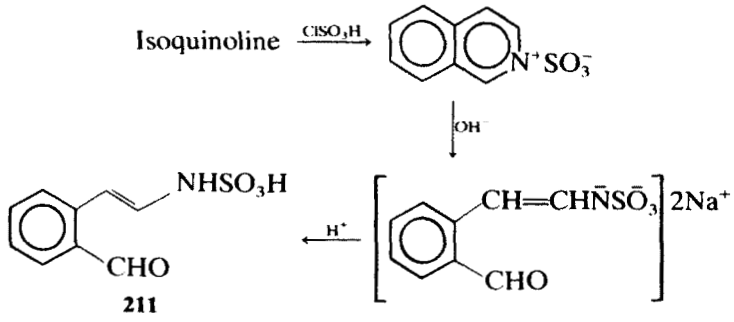
In the permanganate oxidation of 1,2,3,4-tetrahydroisoquinolines the products are once more phthalic acids, but in some cases the intermediate, phthalonimide, has been isolated[367] (Eq. 16; R = H). The same type of product (**209**, R = OMe) has been obtained by oxidation of **208** (R = OMe) with chromic acid.[349]



(16)

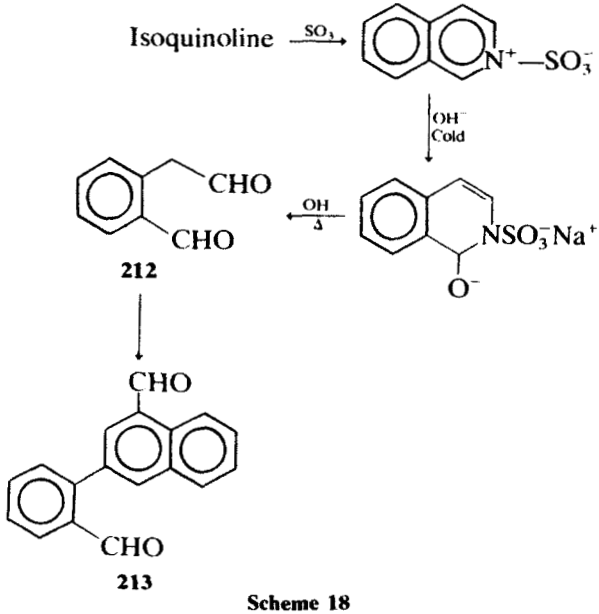
(b) *Nonoxidative Fission of Aromatic Isoquinolines*

Isoquinoline reacts with chlorosulfonic acid in chloroform[368] to give **211** (Scheme 17), which is reported to be stable at room temperature but reverts to isoquinoline in boiling water. However, isoquinoline reacts with sulfur



Scheme 17

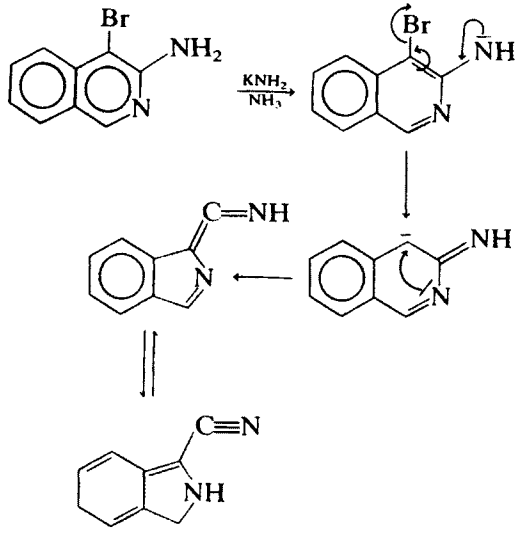
trioxide[368–371] to give the nitrogen-free dialdehyde **212**, which dimerizes to **213** (Scheme 18). Ring-opening reactions have also been reported[372] to



Scheme 18

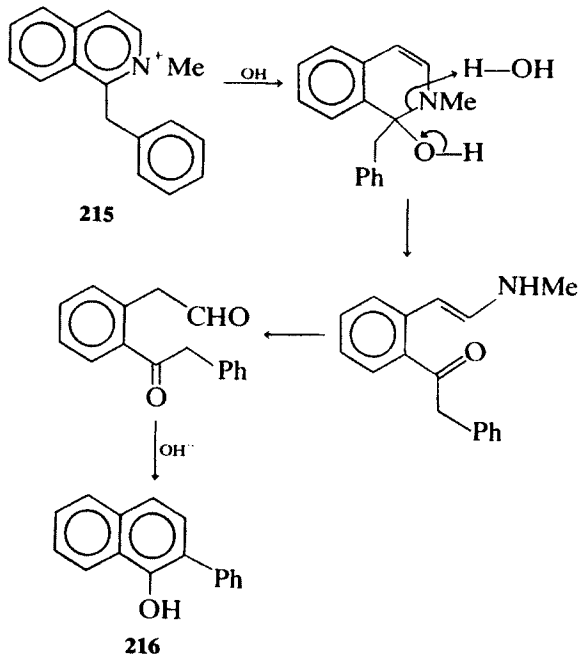
occur when certain bromoaminoisoquinolines are reacted with potassium amide in liquid ammonia. 1-Amino-3-bromoisoquinoline and 3-amino-1-bromoisoquinoline form *o*-cyanobenzyl cyanide, but 4-amino-3-bromoisoquinoline is converted into *o*-cyanobenzyl isocyanide. An unusual reaction occurs with 4-bromo-3-aminoisoquinoline, which yields the isoindole derivative **214** under similar conditions (Scheme 19).

When 1-benzylisoquinolinium salts **215** are treated with strong base, a nitrogen-free product (**216**) is obtained (Scheme 20).[373] A similar type of reaction occurs[374] with the nitromethane adducts of isoquinolinium salts (**217** → **218**) (Scheme 21).



214

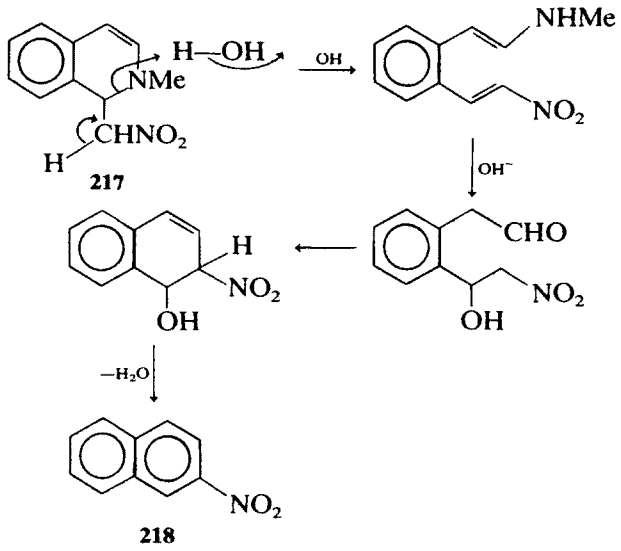
Scheme 19



215

216

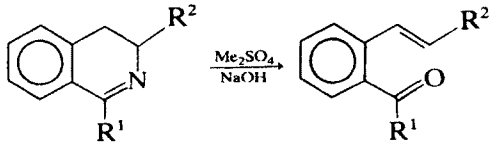
Scheme 20



Scheme 21

(c) *Cleavage of 3,4-Dihydroisoquinolines*

3,4-Dihydroisoquinolines are degraded to nitrogen-free *o*-substituted styrenes when they are treated with methyl sulfate and alkali (**219** → **220**),[339, 375–381] and the procedure constitutes a very useful method



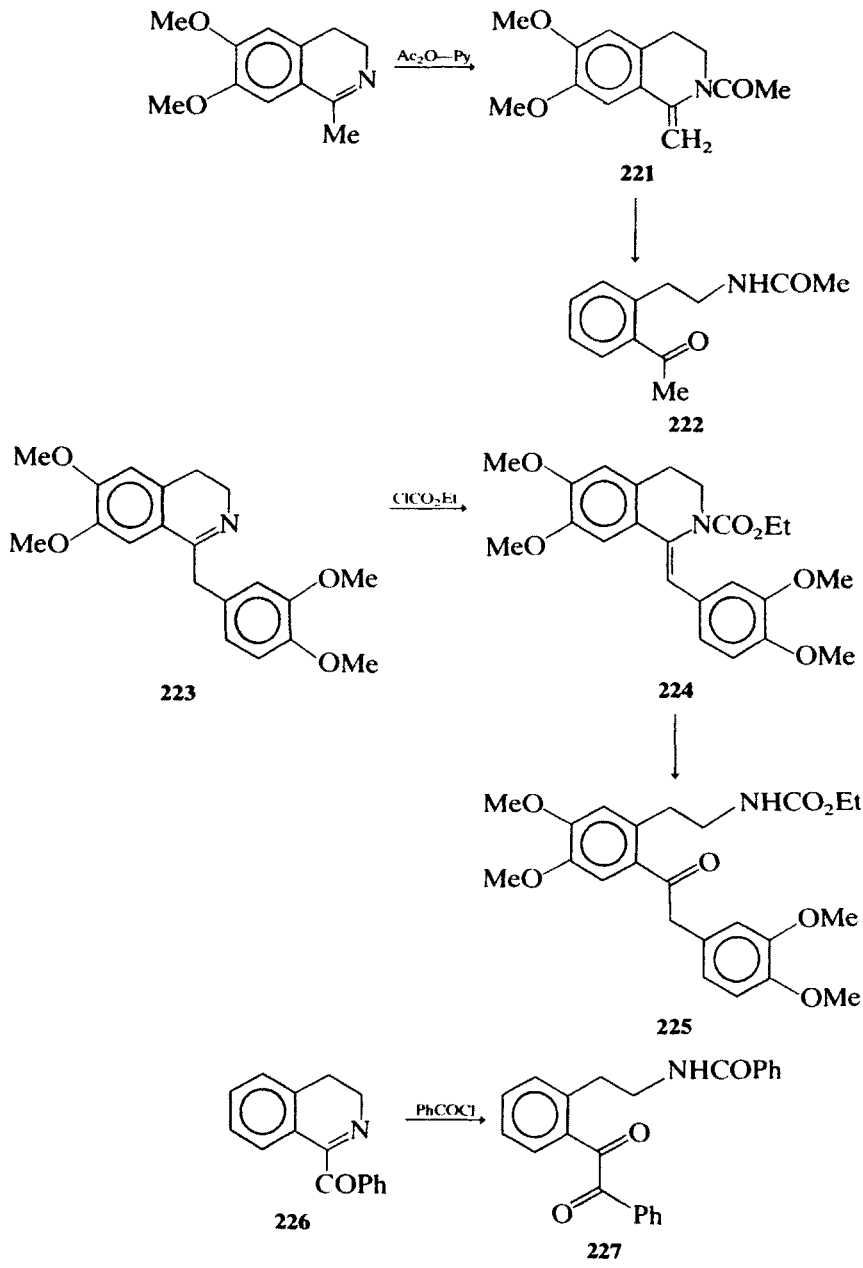
219 **220**

R^1 and R^2 = H or alkyl

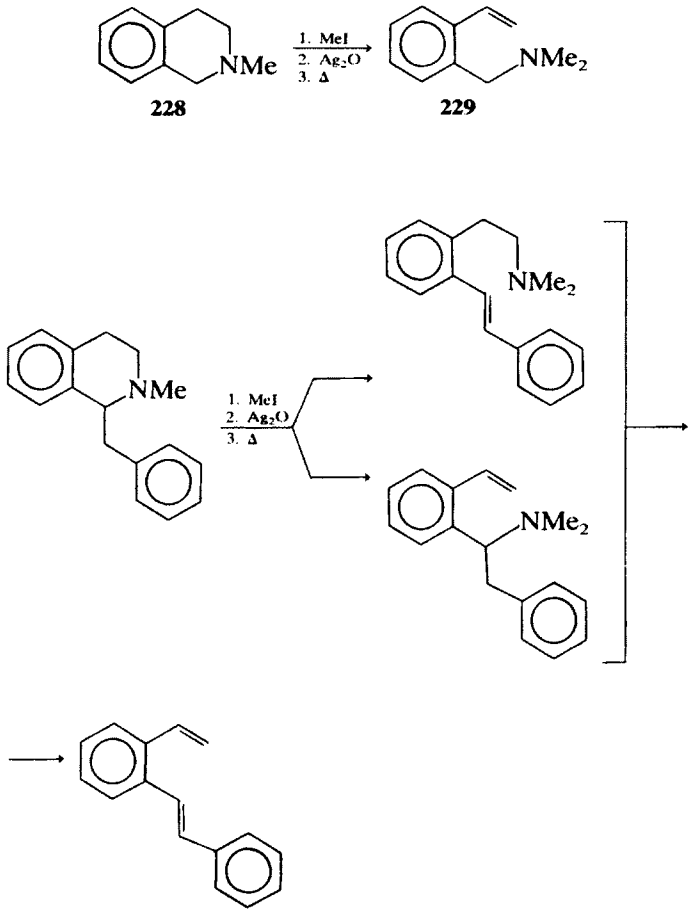
for degrading such structures. It is also useful as a synthetic procedure for certain *o*-disubstituted benzene derivatives.[380] After *N*-acylation, 1-methyl-3,4-dihydroisoquinolines give rise to the 1-methylene derivatives **221**, which can then be ring opened by base to **222**.[382–384] In a similar way, **223** is ring opened to the ketone **225** by way of **224**.[385] Chazerain and Gardent[386] found that when 1-benzoyl-3,4-dihydroisoquinoline (**226**) is benzoylated, ring opening occurs to yield the benzil **227**.

(d) *Degradation of Tetrahydroisoquinolines*

1,2,3,4-Tetrahydroisoquinolines with no substituent at C-1 undergo Hofmann degradation to styrene derivatives,[387] which are stable to further



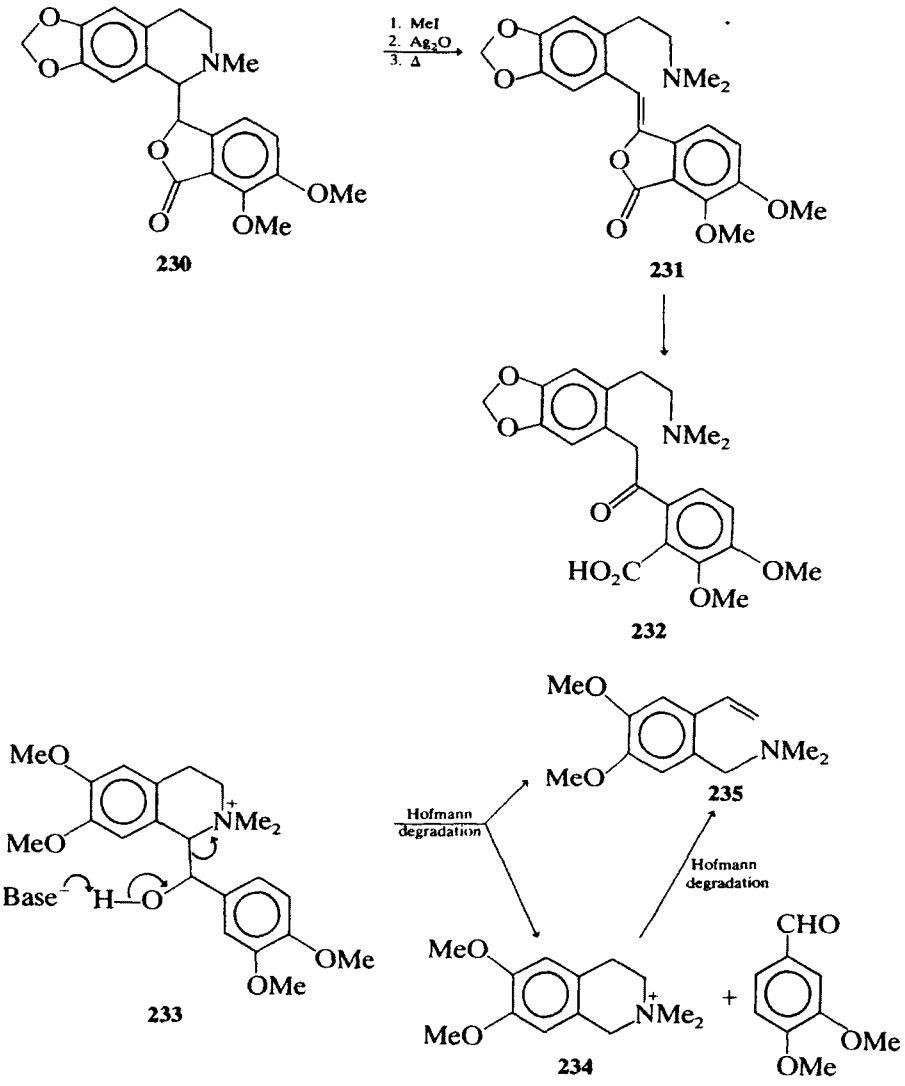
degradation by this method (**228** → **229**). 1-Benzyl-1,2,3,4-tetrahydroisoquinolines, however, can yield two different methine bases, either of which yields the same nitrogen-free product on further degradation (Scheme 22). Usually the stilbene is the preferred product of the first stage of the degradation, although exceptions to this are known.[38,39] Work by



Scheme 22

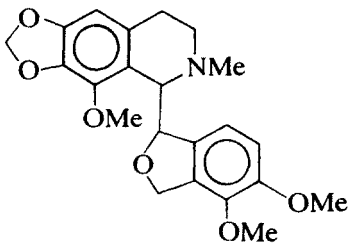
Battersby et al. has shown that a mixture of *cis*- and *trans*-stilbenes is produced.[388] Degradation of the methiodide of narcotine (**230**) yields narceine (**232**);[389] presumably the enol lactone **231** is the intermediate. Hofmann degradation of the hydroxylaudanosine (**233**) occurs with the formation of veratraldehyde and the styrenoid benzylamine **235**,[390–392] through the methosalt **234**. The ether **236** was degraded[393] to the enolether **237**, which gave, on acid hydrolysis, the ketoalcohol **238**. Hofmann degradation of the diols **239** (R = H or OMe)[392] gave the styrenes **240** (R = H or OMe), together with pseudomeconine, presumably arising from autoxidation of the initially formed aldehyde.

Few 1-methyl-1,2,3,4-tetrahydroisoquinolines seem to have been subjected to Hofmann degradation; thus generalizations are difficult to make. 1,2-Dimethyl-1,2,3,4-tetrahydroisoquinoline itself gives[394] the styrenes **241** (R = H); **241** ($R = C_6H_5CONH$) has been obtained[216,395] together with the

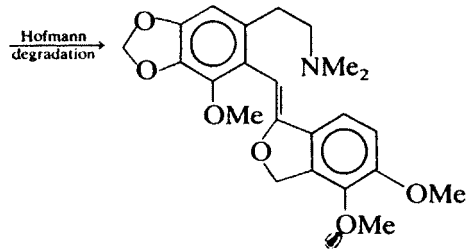


isomeric **242** from 1-methyl-6-benzoylamino-1,2,3,4-tetrahydroisoquinoline. An optically active sample of **243** is degraded[396] to an optically active methine, which must be **244**. The 1-phenethyl-1,2,3,4-tetrahydroisoquinoline **245** yields the methine **246** as the only product when subjected to Hofmann degradation.[397] Lophocerine (**247**) undergoes Hofmann degradation to **248**, and a second Hofmann degradation yields **249**.[398]

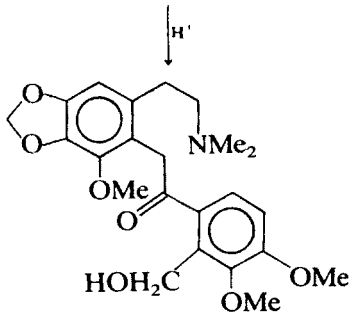
The Emde degradation (using sodium amalgam, or sodium in liquid ammonia) has also been applied to quaternary salts in the tetrahydroisoquinoline series, but, like the Hofmann degradation, most of the substrates have been alkaloids or their derivatives. When 2,2-dimethyl-1,2,3,4-



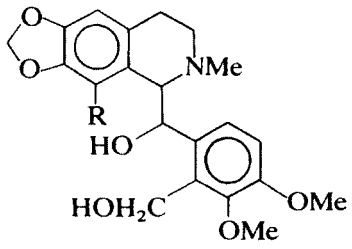
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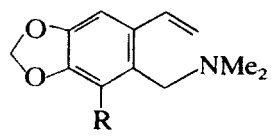
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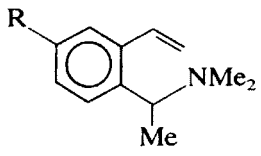
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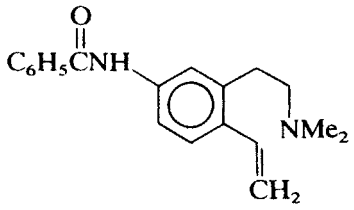
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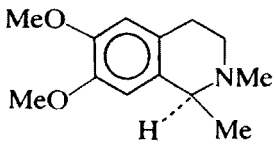
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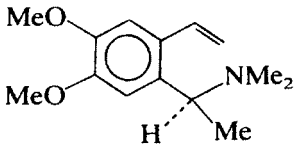
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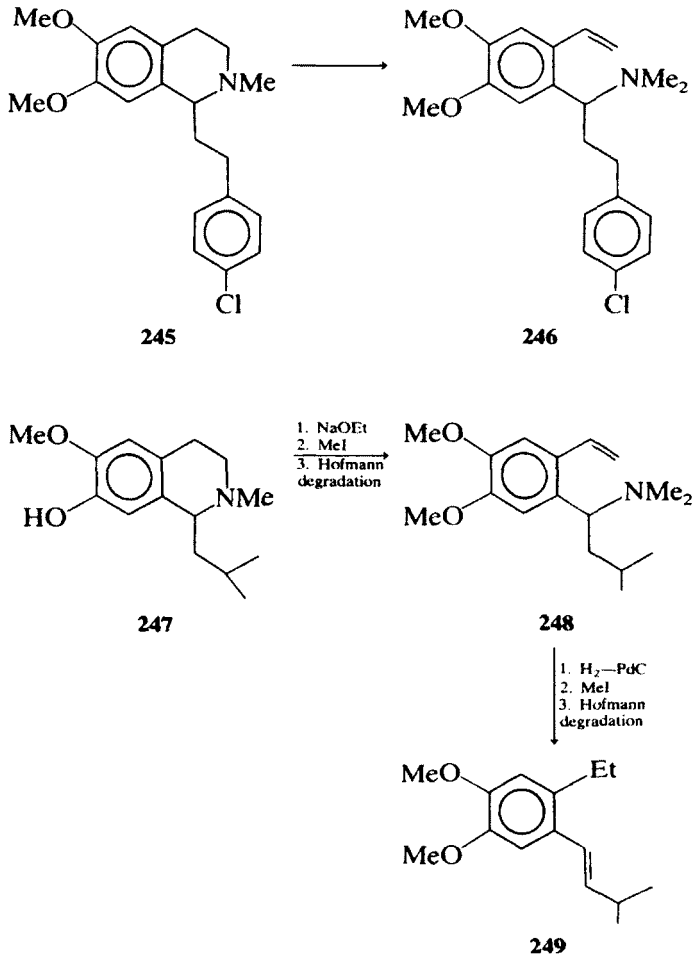
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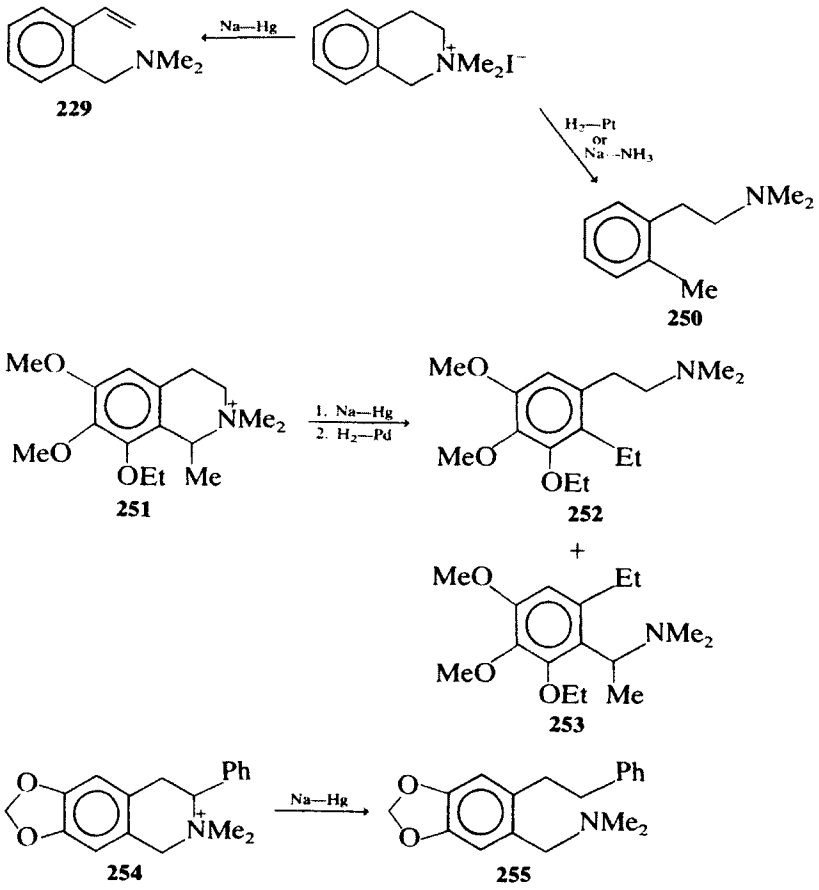
243



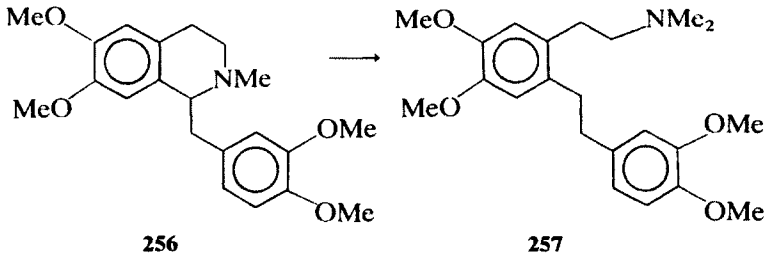
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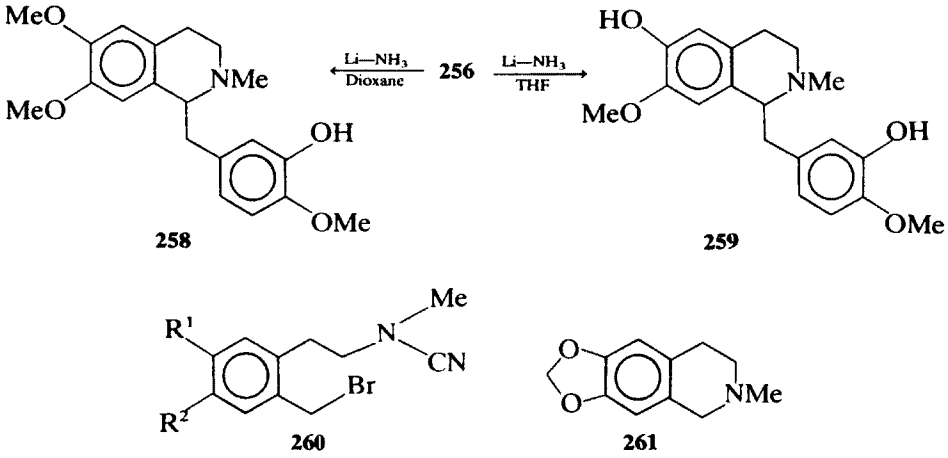
tetrahydroisoquinolinium iodide is reduced with sodium amalgam, the same styrene **229** is produced as is formed in the Hofmann degradation, but catalytic reduction yields[399–401] instead the toluene derivative **250**, which can be degraded to a nitrogen-free styrene by the Hofmann procedure. With the 1-methyl-1,2,3,4-tetrahydroisoquinoline **251**, reduction with sodium amalgam, followed by catalytic hydrogenation of the unsaturated products, gave a mixture of **252** and **253**, with the former predominating.[402] The 3-phenyltetrahydroisoquinoline **254** gave **255** when treated with sodium amalgam.[403] When sodium in liquid ammonia is used instead of sodium amalgam, the products of reductive cleavage are the same as those formed in catalytic reduction.[402] Thus the methiodide of laudanosine (**256**) is converted[404] into **257**. However, other reactions are possible in addition to, or instead of, Emde-type cleavage. The reductive fission of hydrocotarnine[265] has already been described [Section IV.B(b)(2)]. When **256** is treated[405] with lithium in



liquid ammonia, *O*-demethylation occurs to give **258** or **259**, depending on whether dioxane or tetrahydrofuran, respectively, is used as a cosolvent.

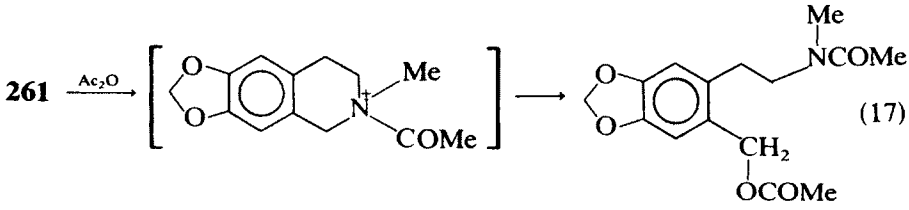


Although cyanogen bromide does cleave 1,2,3,4-tetrahydroisoquinolines, the reaction has not been used very widely. 2-Methyl-1,2,3,4-tetrahydroisoquinoline has been reported to undergo *N*-demethylation[406] and ring cleavage[407] to **260** (R^1, R^2 = H). Hydrohydrastinine **261** is also cleaved[408] by cyanogen bromide to yield **260** (R^1, R^2 = OCH_2O).



258 259 260 261

1,2,3,4-Tetrahydroisoquinolines have been found to undergo ring cleavage when treated with acid chlorides or anhydrides under acylating conditions (Eq. 17).[408–411]



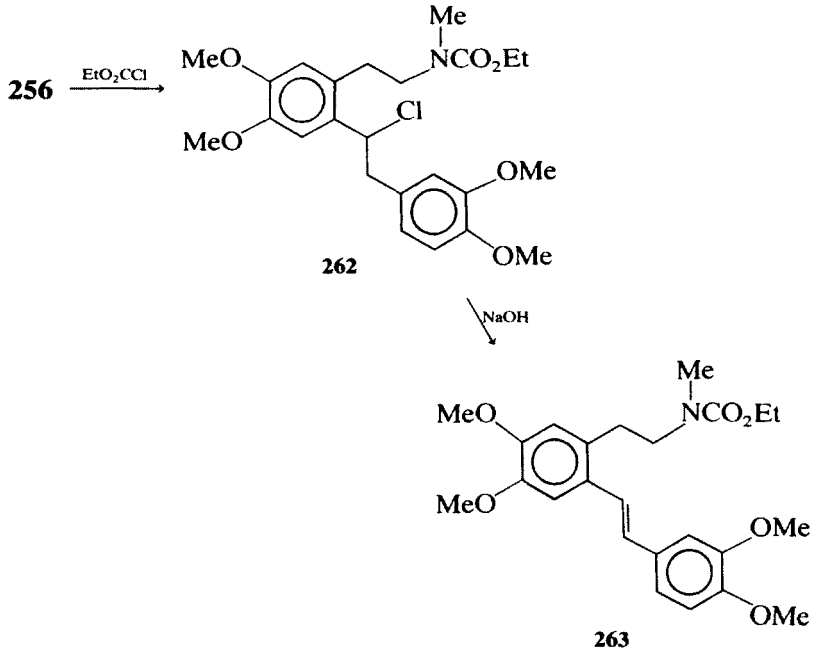
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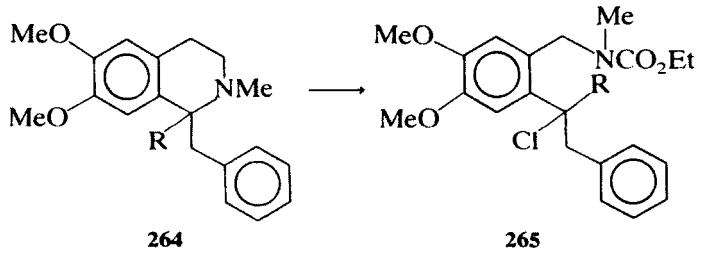
Ethyl chloroformate reacts with 1,2,3,4-tetrahydroisoquinolines in the presence of potassium hydroxide solution to give a ring-opened product, a reaction first reported in 1921.[412] Thus (−)-laudanosine (**256**) gives the optically active chloro compound **262** initially,[412,413] which then is converted by base into the urethane **263**. It has been established[413–417] that an electron-donating substituent at C-6 or C-8 is required before ring cleavage can occur. It has also been found[415,416] that the success of the reaction depends on the nature of substituents at C-1. Thus **264** (R = H) is degraded to **265** (R = H) in high yield, whereas with **264** (R = Me) the yield of product **265** (R = Me) is only about 30%, and **264** (R = Et) is not degraded at all under standard conditions.

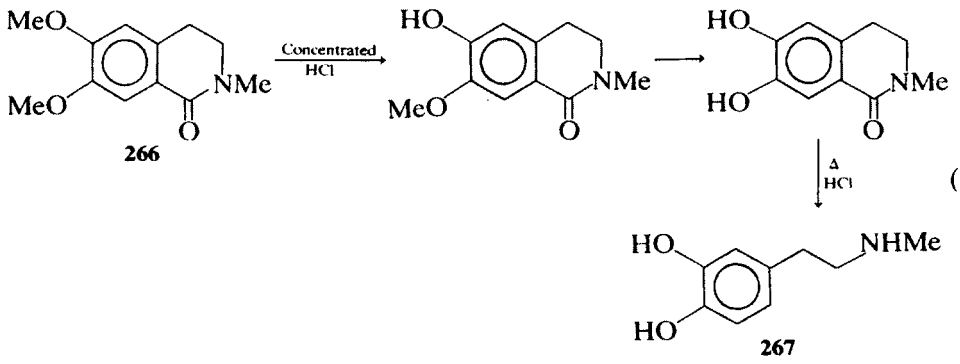
(e) *Miscellaneous Degradations*

Certain dihydroisocarbostyrils, such as **266**, on treatment with concentrated hydrochloric acid[418] are ring opened with decarboxylation to **267** (Eq. 18).

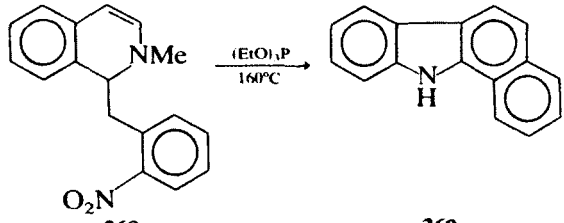
Kametani et al.[419] have found that when **268** is treated with triethylphosphite, it is transformed into the indole **269** in 37% yield.


256
EtO2CCl
Me
NCO2Et
MeO
MeO
Cl
OMe
OMe
262
NaOH
Me
NCO2Et
MeO
MeO
OMe
OMe
263


MeO
MeO
NMe
R
264
Me
NCO2Et
MeO
MeO
R
Cl
265


MeO
MeO
NMe
O
266
Concentrated
HCl
HO
MeO
NMe
O
HO
HO
NMe
O
Δ
HCl
HO
HO
NHMe
267

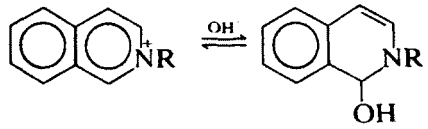
(18)



268 **269**

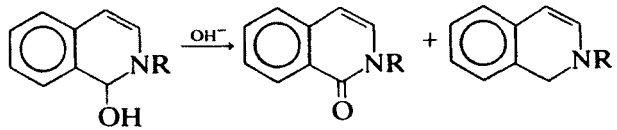
D. Pseudobases and Pseudosalts

Like many heterocyclic quaternary salts, isoquinolinium compounds form strongly basic quaternary hydroxides that are in equilibrium with the neutral, ether-soluble pseudobases (Eq. 19). The position of equilibrium

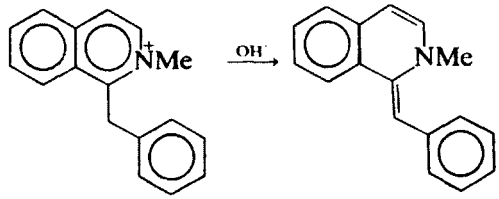


(19)

depends on the solvent, temperature, and substituents attached to either the homo- or heterocyclic ring; electron-withdrawing substituents will stabilize the pseudobase form, for example, 5-nitro-2-methyl-1-hydroxy-1,2-dihydroisoquinoline. Isoquinoline pseudobases, which easily revert to quaternary salts with mineral acid, are sensitive to air and are converted into isocarbostyrils. In the presence of an excess of aqueous alkali, pseudobases undergo a disproportionation reaction (Eq. 20).



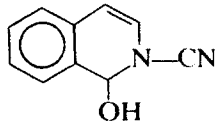
(20)



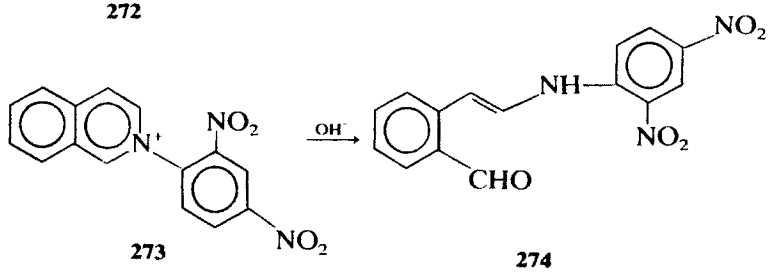
(21)

270 **271**

When a suitable substituent is present at C-1 in the isoquinolinium salt, an isobase may be formed (e.g., **270** → **271**) (Eq. 21). Pseudobases are also known in which the substituent on nitrogen is the cyanide ion,[420,421] such as **272**. If the *N*-substituent is strongly electron attracting, ring opening of the pseudobase may occur (Eq. 22).[1,422] Under certain conditions of base treatment,[423] **273** is converted into **275**. When the quaternary salt **273** is boiled

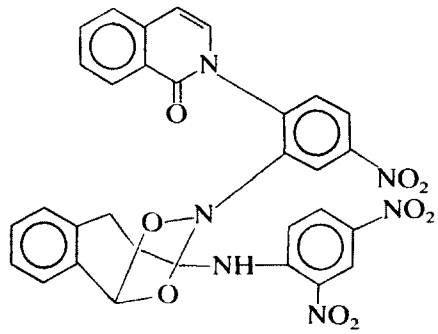


272



(22)

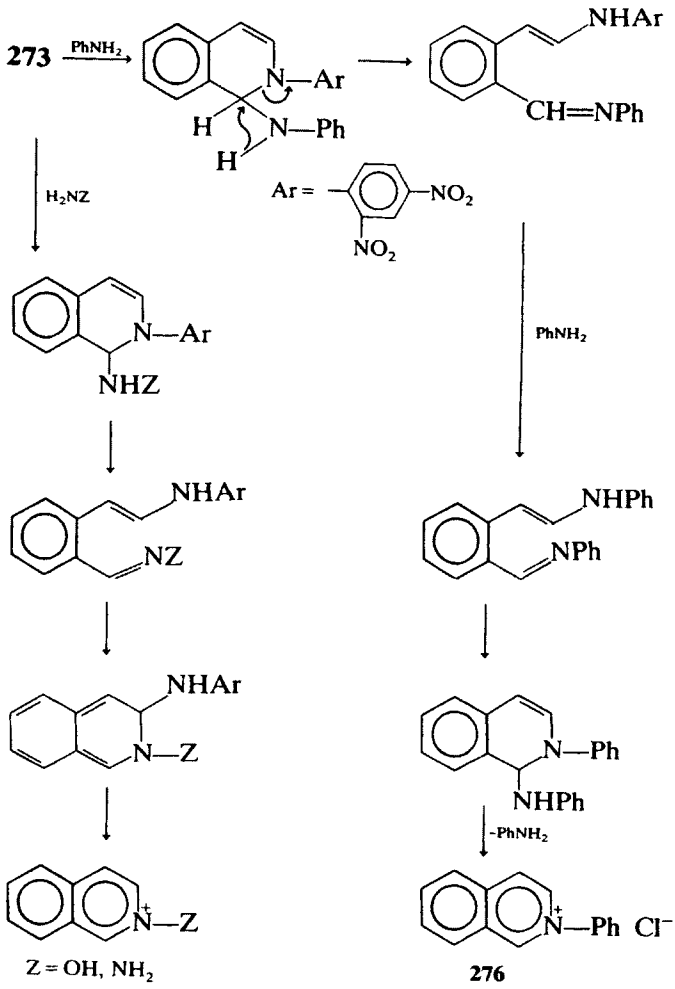
273 274



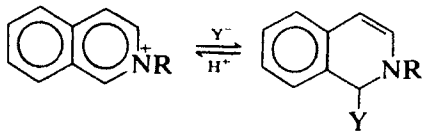
275

with aniline,[1,424] the *N*-phenylisoquinolinium salt **276** is formed (Scheme 23). If the salt **273** is reacted with hydroxylamine or hydrazine, isoquinoline *N*-oxide or *N*-amine, respectively, is produced (Scheme 23).[425] Various other nucleophiles may be added to the C-1 position of isoquinolinium salts to provide the pseudosalts (Eq. 23); the aromatic isoquinolinium cation is regenerated with acids. However, complications can arise; thus *N*-methylisoquinolinium iodide reacts with acetone in the presence of base to give a mixture of **277** and **278**. When sodium carbonate is used as the base and the mixture is left at room temperature for several days, a new compound can be isolated[61] that results from the interaction of 1 mole of the quaternary salt and 3 moles of acetone. The structure of this compound is as yet unknown. Nitromethane reacts with isoquinoline methiodide to give a substance originally thought to be **279**, but the compound is now known to be **280**.[426]

Some pseudo bases have been shown[427] to possess enamine properties; they react with aromatic aldehydes to yield C_4-substituted compounds of the type **281** (Eq. 24). It has also been found[428] that C_4-alkylation can be achieved in acetonyl adducts **282** to give the isoquinolinium compound **283** in moderate yields (Eq. 25).

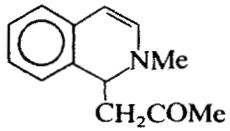


Scheme 23

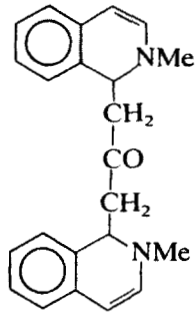


(23)

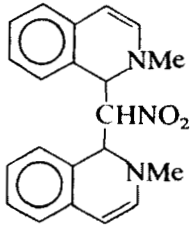
Y = CN, OH, CH_2NO_2, CH_2COCH_3, NHOH, etc.



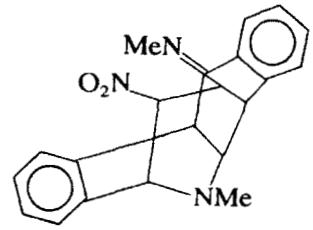
277



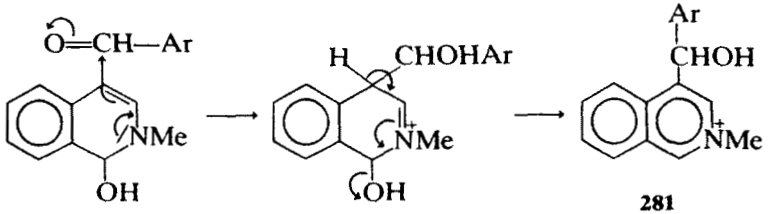
278



279

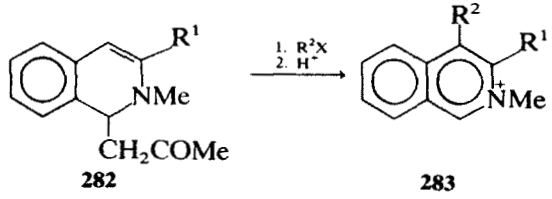


280



281

(24)



282 283

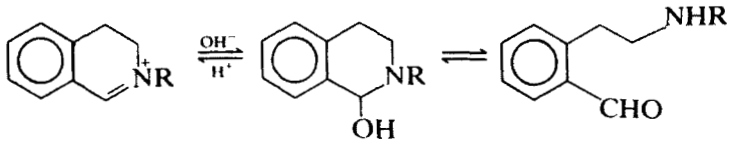
R^1 = H or Me

R^2 = alkyl, allyl, benzyl.

(25)

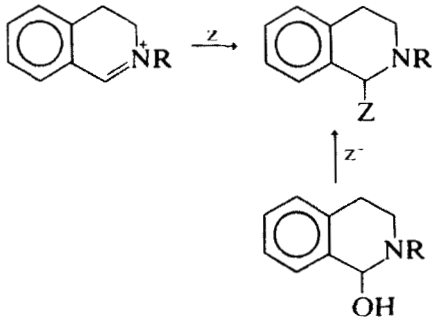
3,4-Dihydroisoquinolinium salts form pseudobases with alkali more readily than do the fully aromatic quaternary salts,[1,429] since there is less loss of conjugation energy. Like the pseudobases discussed previously, these pseudobases are readily decomposed by acids with the regeneration of the 3,4-dihydroisoquinolinium salt. Disproportionation occurs in the presence of excessive sodium hydroxide, and this reaction was originally interpreted[430]

as a Cannizzaro type of reaction. However, this was disproved.[411,431] A recent proposal[432] describes the reaction as being intermediate in type between an acid-catalyzed disproportionation of the benzhydrols and alkali-induced Cannizzaro reaction.



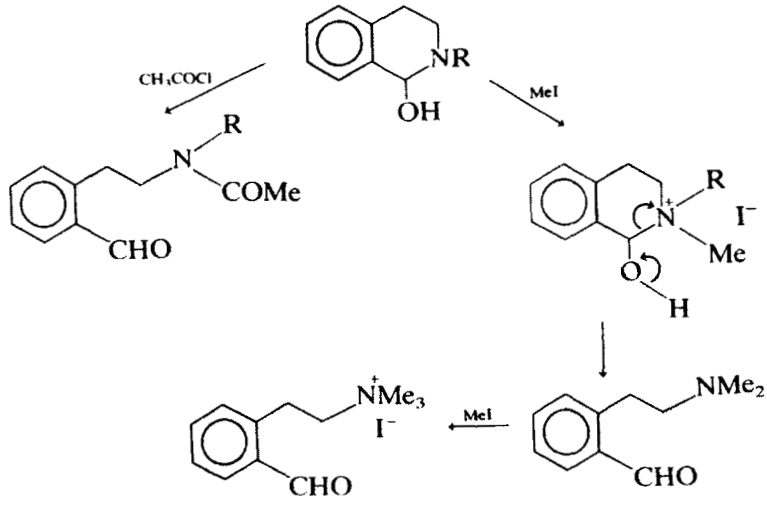
(26)

The widely held view of Gadamer that a threefold tautomerism is involved in pseudobases (and other pseudosalts) (Eq. 26). has not been thoroughly established for any of the examples studied.[433] The overall conclusion is that ring-chain tautomerism need not be postulated; thus nucleophilic reagents (e.g., CN^-) react by substitution at C-1 of the



(27)

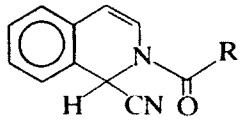
pseudobase or by addition to the quaternary salt to give a new derivative (Eq. 27). Electrophilic reagents, however, may be regarded to attack nitrogen in the pseudo base leading to the ring-opened product (Scheme 24).



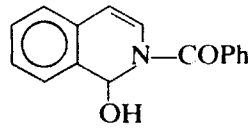
Scheme 24

E. 2-Acyl-1,2-Dihydroisoquinaldonitriles[434,435]

The so-called Reissert compounds **284** can be regarded as the pseudocyanides of *N*-acylisoquinolinium salts. They are prepared by treating the aromatic isoquinoline with the acyl halide and potassium cyanide in aqueous methylene chloride.[436] Under these conditions 1-substituted isoquinolines do not react;[437] isoquinolines with a C_3-methyl, C_4-bromo or C_7-methoxyl group all react normally. However 5-nitroisoquinoline and 3-methyl-5-nitroisoquinoline yield mainly the *N*-acyl pseudobases (**285**) with only a little of the Reissert compound.[438]

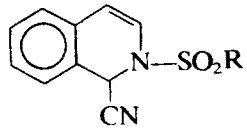


284a, R = C_6H_5
284b, R = Me



285

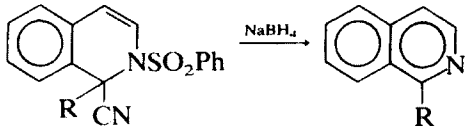
In the pmr spectrum of Reissert compounds[77] coupling occurs between the C_1-hydrogen atom and that at C-3, $J \simeq 0.8$ to 0.9 Hz. The value of the coupling constant suggests that the five atoms involved in the coupling are planar, which means that the C_1-hydrogen is quasiequatorial. If the carboxylic acid chloride is replaced by a sulfonyl halide in the preparation of the Reissert derivative, the analogous compounds **286** are produced.



286a, R = C_6H_5
286b, R = p-MeC_6H_4

Because acid-catalyzed hydrolysis yields the isoquinoline-1-carboxamide and the aldehyde derived from the *N*-acyl group,[434] this type of hydrolysis was one of the first reactions of Reissert compounds to be investigated.

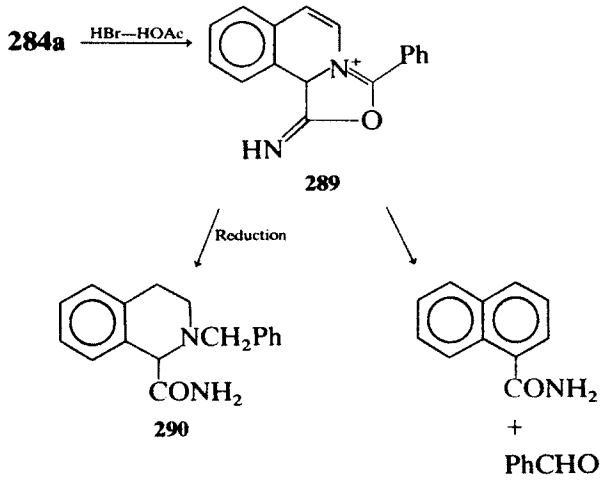
The sulfonyl Reissert compounds **286** are hydrolyzed by acid back to the unsubstituted aromatic isoquinoline.[439] However, when such compounds are treated with sodium borohydride[440] under mild conditions, 1-cyanoisoquinolines are produced. From the corresponding 1-alkyl sulfonyl Reissert derivatives **287** the 1-alkylisoquinolines **288** are formed by reaction with sodium borohydride under similar conditions.



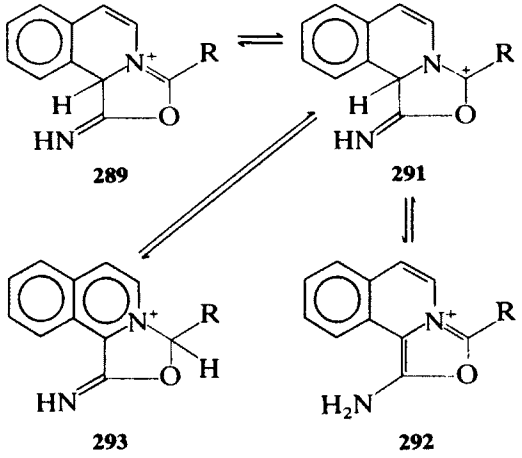
287 **288**

R = Me, Bu, $PhCH_2$

The mechanism of acid-catalyzed hydrolysis of Reissert compounds **284** has been investigated by a number of workers. A cyclic intermediate **289** is involved, and this has been isolated in some cases.[339,441,442] This intermediate can be reduced[443] catalytically, or better with sodium borohydride, to the 1,2,3,4-tetrahydroisoquinoline **290**.

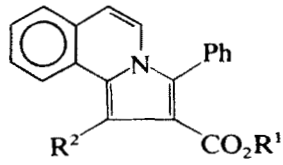


Examination[444] of the fluoroborate salt of the Reissert derivative **284** reveals that an equilibrium is established between **289**, **291**, **292**, and **293** (as determined by nmr studies with **284b**) (Scheme 25). The species **291** is a

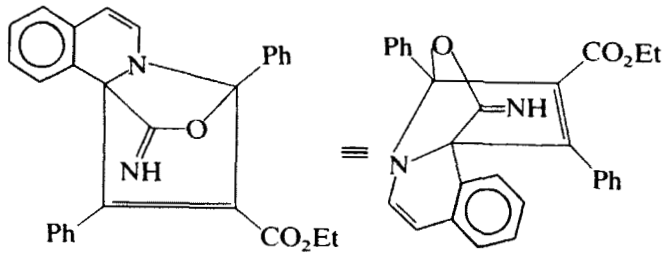


Scheme 25

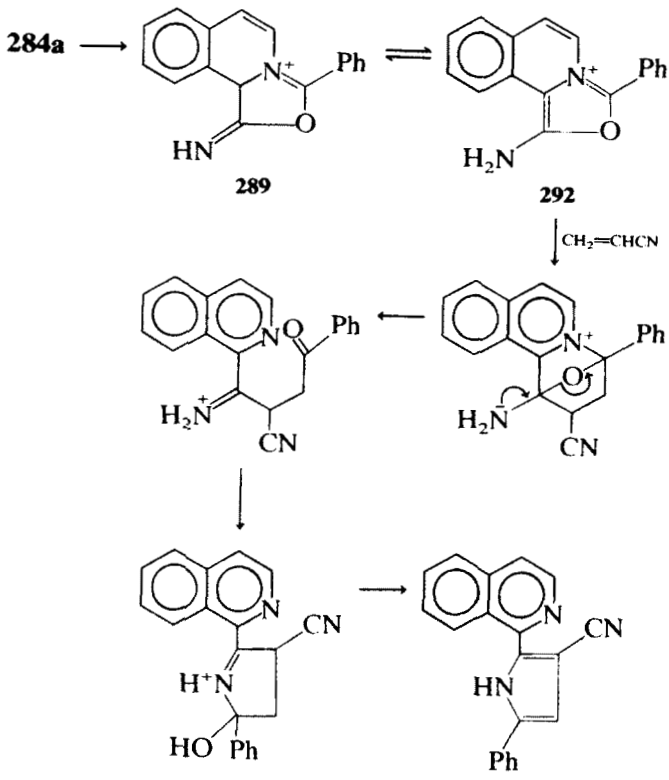
munchnone imine[445] and it was trapped as the 1,3-dipolar cycloadduct **294** with dimethylacetylene dicarboxylate in 90% yield. With phenylpropriolate the adduct **295** was accompanied by the primary 1,3-dipolar addition product **296**, which could be separately transformed into **295** by elimination



294, R^1 = Me; R^2 = CO_2Me
295, R^1 = Et; R^2 = Ph

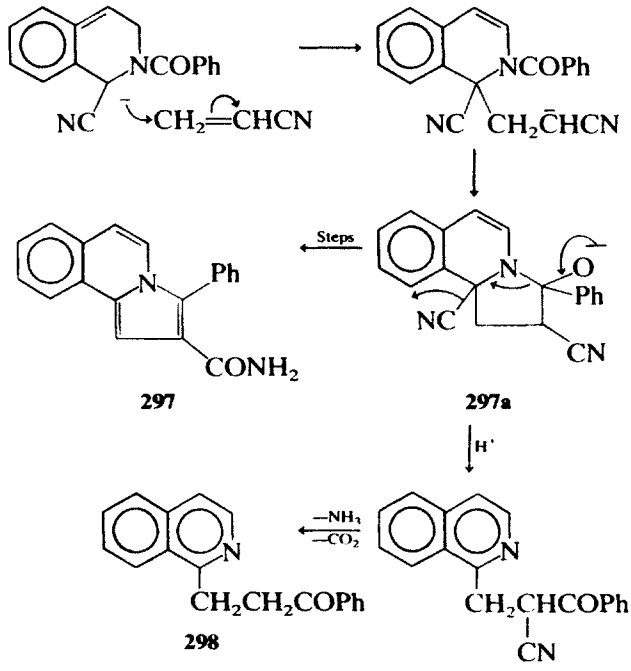


296



Scheme 26

of cyanide. Other, similar examples are known.[446,447] Diels–Alder additions to **289**, followed by complex condensations and rearrangements, occur[448] with acrylonitrile, ethyl cinnamate, dimethyl maleate, and ethyl acrylate (Scheme 26). However, if the anion of the Reissert compound is added to acrylonitrile,[449] the reaction takes a different course to yield **297** (Scheme 27). Hydrolysis of **297a** with concentrated hydrochloric acid gives a 95% yield of **298**.

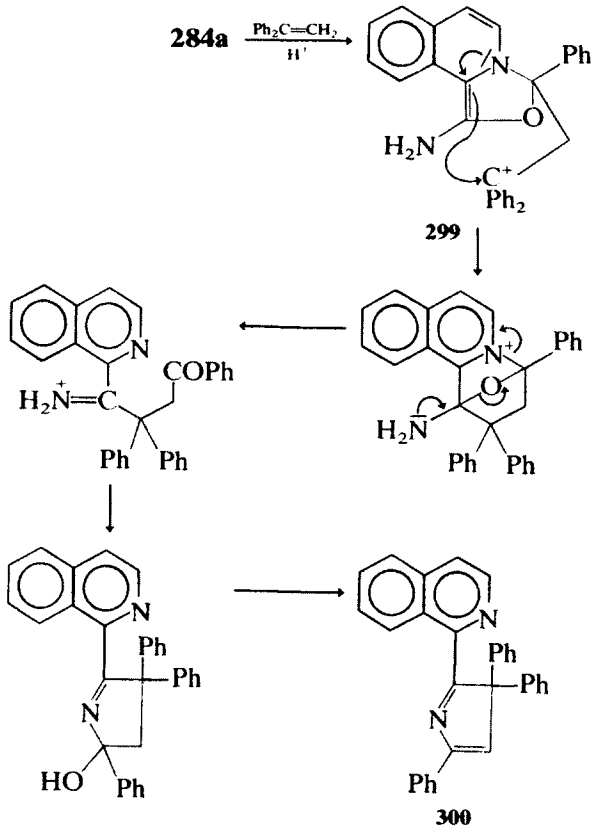


Scheme 27

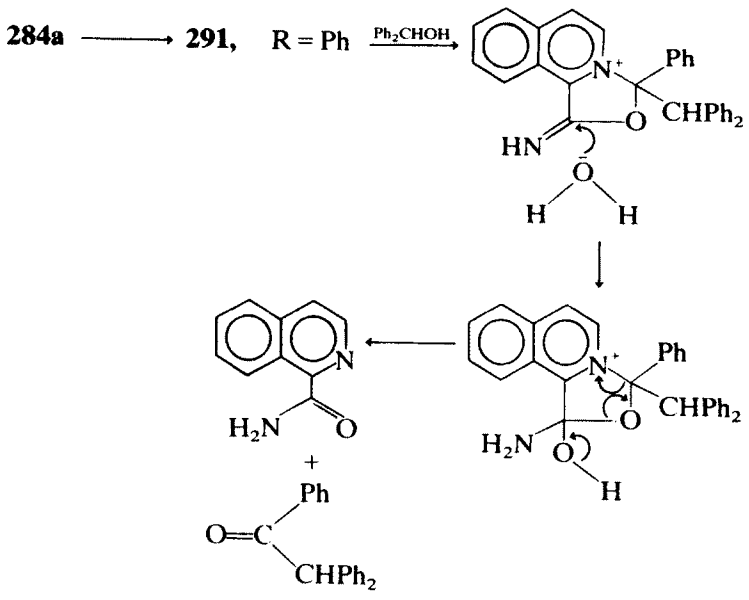
Compound **289** (R = Ph) has been investigated[450] to establish whether competition exists between 1,3-dipolar addition and Diels–Alder reactions. Only the (6 + 2)-cycloaddition occurred with stilbene, but products derived from both modes of addition were obtained in low yields when tolan was used.

1,1-Diphenylethylene reacts with **284a** in the presence of sulfuric acid to give **300**.[451–453] The reaction has been investigated by using ^{14}C-labeled compounds, and the mechanism proposed involves formation of **299** followed by the changes shown in Scheme 28. When **284a** was reacted[451] with benzhydrol and concentrated sulfuric acid, the products formed were isoquinalamide and α,α-diphenylacetophenone. These products can be rationalized as shown in Scheme 29.

When an isoquinoline Reissert compound (**284**) is treated with a strong base such as phenyl lithium[434,454] or, better, sodium hydride in dimethylformamide,[455,456] a proton is removed from C-1 to give an anion, which can be

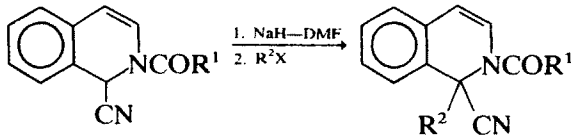


Scheme 28



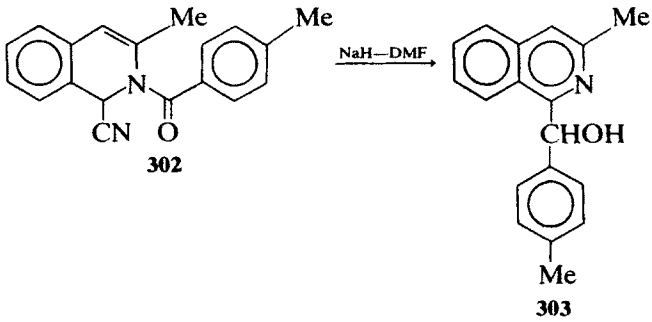
Scheme 29

alkylated by using a wide variety of alkyl and benzyl halides (Eq. 28).[456,457] The stereochemistry, in terms of ring conformations and inversion, acyl group configuration, and conformation about the ring-alkyl bond, has been examined[458] for a number of derivatives of **301**. Base-catalyzed hydrolysis of **301** with aqueous alkali, or preferably[459] with sodium methoxide, converts **301** into a 1-substituted isoquinoline. The sequence constitutes a useful preparation of such derivatives and has been used quite extensively for the synthesis of 1-benzylisoquinoline alkaloids.[460,461] The formation and benzylation of the Reissert anion has also been achieved[462] by using triethylbenzylammonium chloride in aqueous sodium hydroxide solution. Under such conditions (room temperature) *p*-chloronitrobenzene reacts to give **301** (R = Ph; R′ = *p*-$O_2NC_6H_4$).

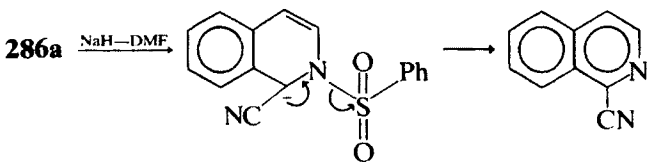


284 **301** (28)

The major by-product of alkylation of Reissert anions generated with bases such as NaH—DMF is the 1-acylisoquinoline, produced by the rearrangement of the acyl group from nitrogen to C-1 [Section IV.G(d)]. Under suitable conditions this may be made the major pathway of reaction and is a useful method for the preparation of 1-ketoisoquinolines.[463] When attempts were made[464] to alkylate the anion of **302**, the only product isolated was **303**, formed by rearrangement and reduction. The benzenesulfonyl Reissert compounds (**286a**) do not form stable anions with strong base; an elimination proceeds instead[439] to give the 1-cyanoisoquinoline (Eq. 29).

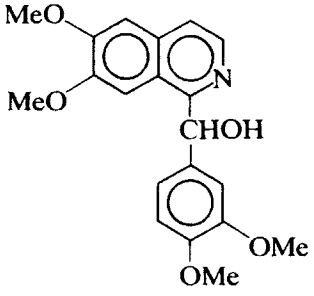


302 **303**

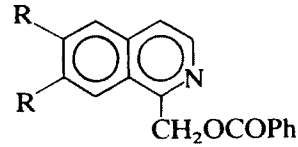


(29)

The anion derived from 2-benzoyl-1-cyano-1,2-dihydroisoquinolines can also add to aldehydes and ketones. Aromatic aldehydes in particular have been studied[465,466] in attempts to synthesize the 1-benzylisoquinoline alkaloids. High yields of alcohols such as **304** can be obtained. Formaldehyde reacts to give good yields of **305a** and **305b**.[467,468]

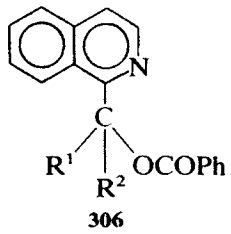


304



305a, R = H
305b, R = OMe

Isoquinoline Reissert derivatives (**284a**) have also been converted[469] into esters (**306**) in yields of 30 to 90% by treatment with aldehydes or ketones in the presence of 50% aqueous sodium hydroxide (Scheme 30).

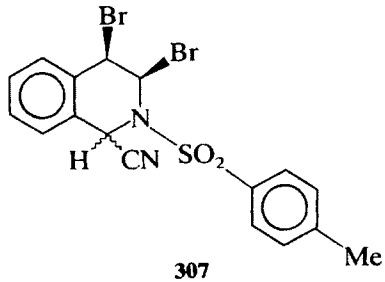


306

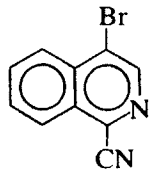
R^1	R^2
H	Ph
H	*o*-MeC_6H_4
H	*o*-ClC_6H_4
H	
H	$CHMe_2$
Me	Ph
Me	Me
—$(CH_2)_5$—	

Scheme 30

Bromine has been added to **286b**[148] to yield **307** in which the bromine atoms were assigned the cis configuration on the basis of nmr data. When **307** was treated with morpholine in dioxan, it was transformed into **308**. Rearrangement reactions that follow the addition of hypobromous acid to **284a** are discussed in Section IV.G(d).

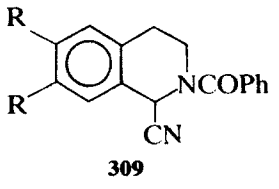


307

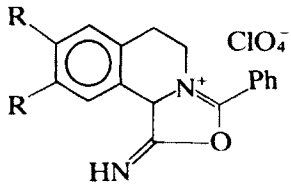


308

Dihydro-Reissert compounds have received very little attention. 3,4-Dihydroisoquinoline reacts[443] with benzoyl chloride and KCN to yield **309** (R = H), which forms a cyclic perchlorate (**310**) in a manner analogous to the Reissert compounds proper. The compound **309** (R = H) has also been



309



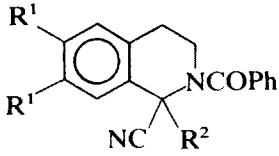
310

prepared[470] by adding hydrogen cyanide to 3,4-dihydroisoquinoline, followed by benzoylation of the 1-cyano-1,2,3,4-tetrahydroisoquinoline produced. It has been found[470,471] that **309** (R = H) can be alkylated in the presence of strong base to yield **311** (R^2 = Me, Et, Ph, $PhCH_2$, etc.) The dimethoxy derivative **309** (R = OMe) has also been prepared and benzylated by using NaH–DMF to give compound **312** ($R^2 = PhCH_2$). However, hydrolysis of **311** is not easily accomplished since the C_3–C_4 double bond of normal Reissert compounds and consequently the driving force of aromatization, is lacking. Hydrolysis of **312** ($R^2 = PhCH_2$) was achieved using phosphoric acid,[471] but when these conditions were applied[62] to dihydro Reissert compound **313** the reaction failed, probably as a result of interaction with the allyl group. Dihydro Reissert intermediates have also been utilized[472] to prepare compounds of the general type **314**.

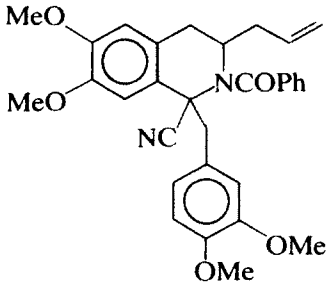
F. 1,2-Dihydroisoquinolines

Because 1,2-dihydroisoquinolines **316** are enamines, they are important as synthetic intermediates, especially for the preparation of certain groups of alkaloids.[248] Derivatives of **316** (R = alkyl) can be prepared by reducing isoquinolinium salts **315** with lithium aluminum hydride[309,473] in ether or tetrahydrofuran. Sodium borohydride in an aprotic solvent such as pyridine[78] or dimethylformamide[245,474] can also be used. However, if the latter reagent is used in the presence of a proton donor, further reduction[239] to the 2-alkyl-1,2,3,4-tetrahydroisoquinoline (**317**) usually occurs (Eq. 30). Recently the reduction of isoquinoline itself to **316** (R = H) has been reported[475] with the use of sodium hydride in HMPT.

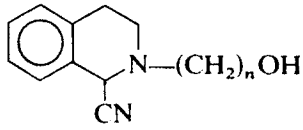
A very useful method for generating a 1,2-dihydroisoquinoline **316** (R = H or alkyl) involves[476,477] the treatment of *N*-benzylaminoacetaldehyde dialkyl acetals **318** with 6*N* hydrochloric acid. At room temperature 4-hydroxy-1,2,3,4-tetrahydroisoquinoline **319** is formed,[478] but at higher temperatures dehydration of **319** occurs[479] to yield the 1,2-dihydroisoquinoline **320** (Scheme 31). An alkoxy group meta to the side chain in **318**



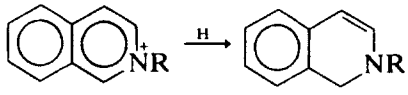
311, $R^1 = H$
312, $R^1 = OMe$



313

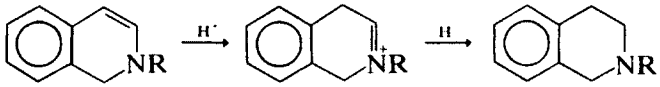


314

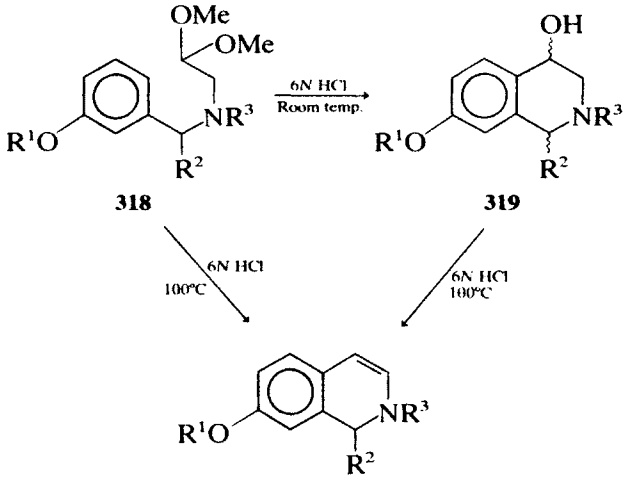


315 **316**

R = Me, $PhCH_2$, etc.



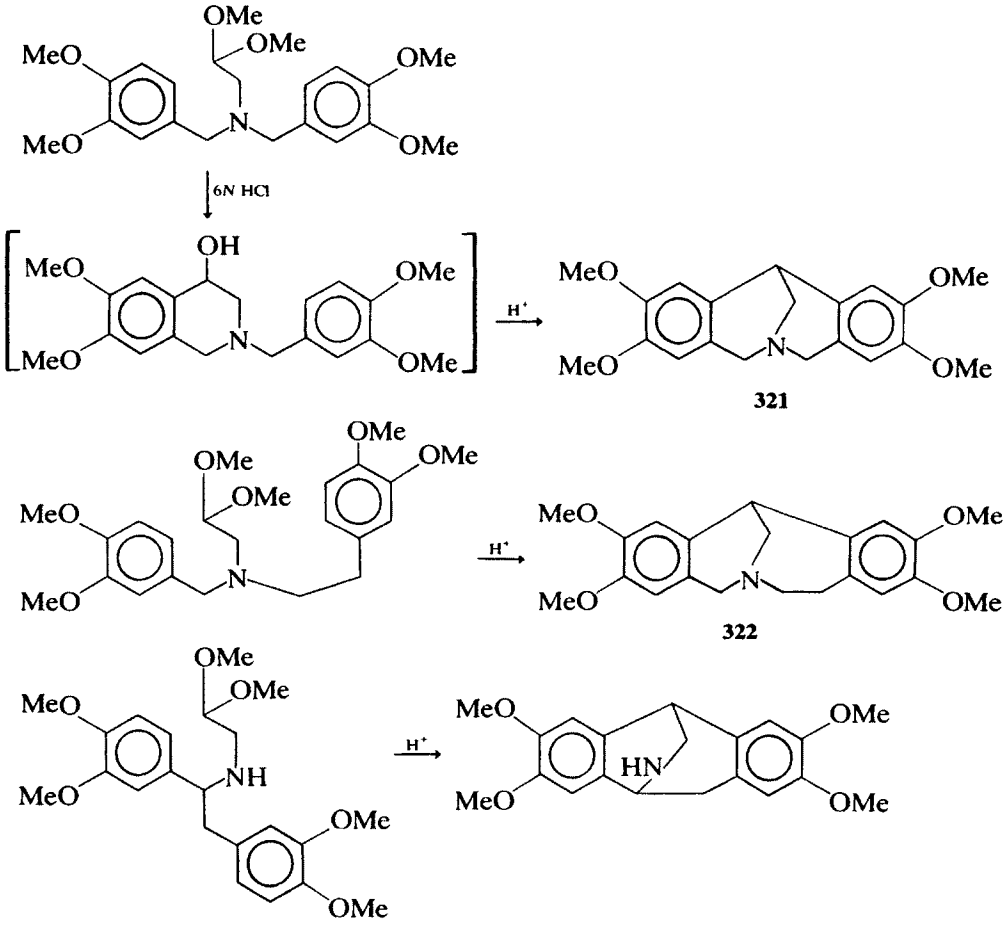
316 **317** (30)



318 **319** **320**

Scheme 31

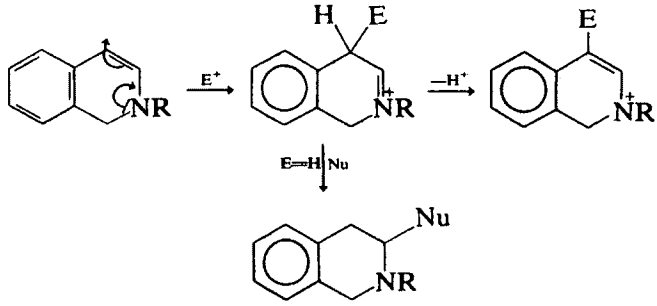
is required for successful cyclizations. The residue R^3 in **318** can be H, Me, or $C_6H_5CH_2$. However, if an electron-rich benzyl- or β-arylethyl group is used, the intermediate 4-hydroxy-1,2,3,4-tetrahydroisoquinoline undergoes a further cyclization[339,480] to yield compounds such as **321** and **322** (Scheme 32). If R^2 in **318** is a 3,4-dialkoxybenzyl group, a similar cyclization of the intermediate 4-hydroxy-1,2,3,4-tetrahydroisoquinoline occurs[481–483] to yield isopavines.



Scheme 32

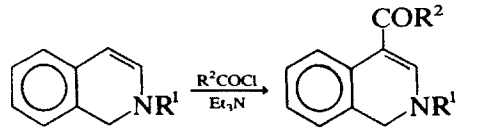
1,2-Dihydroisoquinolines are often[248] unstable compounds that are readily oxidized in air to isocarbostyrils or to isoquinolinium salts and are also easily polymerized by acids. Disproportionation reactions, whereby two molecules of the 1,2-dihydroisoquinoline yield one molecule each of the fully aromatic quaternary salt and the 1,2,3,4-tetrahydro-2-alkylisoquinoline are common, especially in acid solution.

As cyclic enamines, 1,2-dihydroisoquinolines are[484,485] susceptible to attack by electrophiles at C-4 and, in the derived iminium ion, nucleophilic attack at C-3 (Scheme 33).



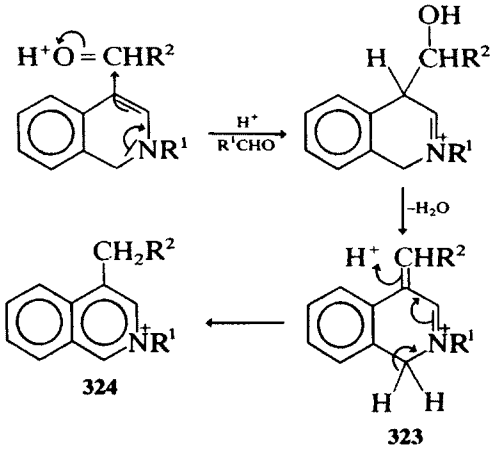
Scheme 33

The most extensively studied electrophilic reagents are acyl halides[309,486] and aldehydes.[487–490] (Eq. 31). The Vilsmeier reaction is also successful[491,492] The 4-benzylidene-1,4-dihydroisoquinolinium salt **323** is usually isolated when an aromatic aldehyde is used, and a prolonged acid (or preferably base) treatment is required to isomerize **323** to the 4-benzylisoquinolinium salt **324** (Scheme 34). In some cases with 3,4-dialkoxyaromatic



(31)

R^1 = Me, $PhCH_2$; R^2 = Ar, $ArCH_2$

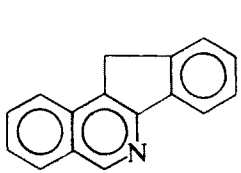


324 **323**

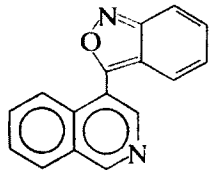
R^1 = H, Me, $PhCH_2$; R^2 = Ar, ArCO, CO_2H

Scheme 34

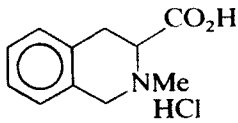
aldehydes, small amounts of derivatives of the indenoisoquinoline ring system **325** have been isolated.[201] If *o*-nitrobenzaldehydes are used in this reaction,[493] the products are anthranils of the type **326**. The reaction fails for aliphatic aldehydes. When 2-methyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid hydrochloride (**327**) is heated in acetophenone or benzaldehyde, good yields of the corresponding 4-substituted isoquinolines (**328**) are obtained.[494] Presumably, thermal decarboxylation provides[495] the iminium ion **329**, which then reacts with the carbonyl compound in the usual way for 1,2-dihydroisoquinolines.[248] Thermal *N*-demethylation of the isoquinolinium salt is unexceptional.



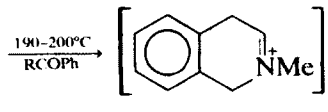
325



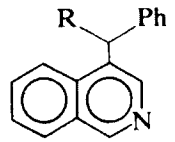
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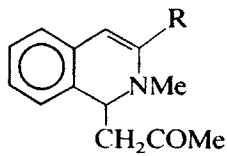
327



329



328, R = H or Me

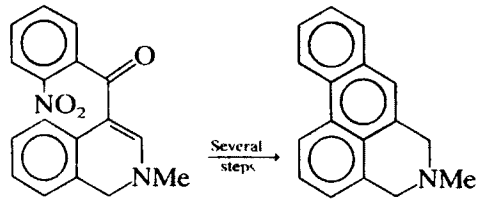


282, R = H or Me

Alkylation of 1,2-dihydroisoquinolines with benzyl halides results in poor yields, and no reaction at all occurs with aliphatic halides. Recently Chen and Bradsher[428] have found that C_4-alkylation of the acetonyl pseudosalts **282** can be achieved, in modest yields, with aliphatic, allylic, and benzylic

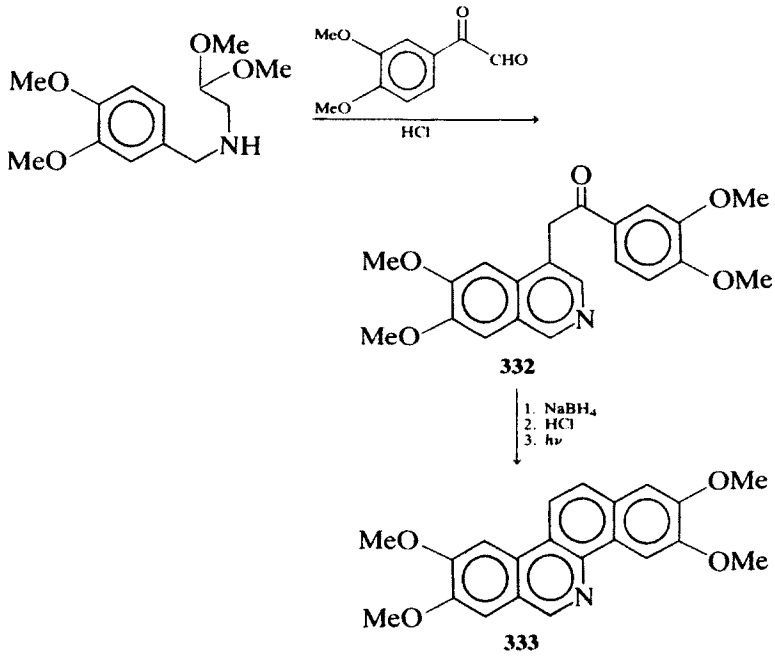
halides. Acid-catalyzed hydrolysis then regenerates the aromatic quaternary salts.

The synthetic potential of 4-acylisoquinoline derivatives, prepared from 1,2-dihydroisoquinolines, is illustrated[486] by the conversion of **330** to **331**.



330 **331**

The condensation products **332** with various glyoxals have been utilized in a new synthesis of benzo[*c*]phenanthridine alkaloids (**333**) (Eq. 32).

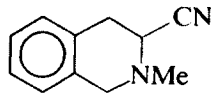


332

333

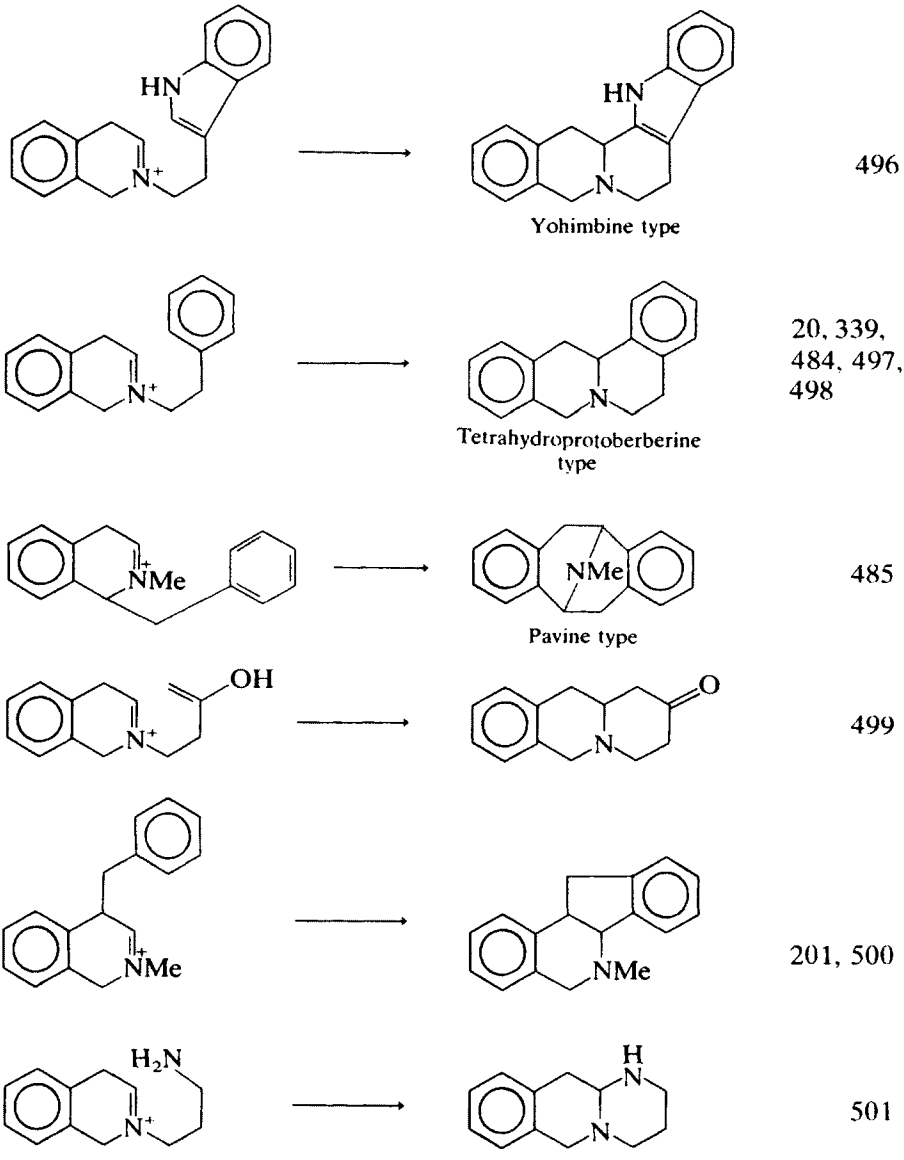
(32)

Although 2-methyl-3-cyano-1,2,3,4-tetrahydroisoquinoline (**334**) has



334

been obtained[61] by adding aqueous potassium cyanide to an ether solution of 2-methyl-1,2-dihydroisoquinoline, all the synthetically useful nucleophilic addition reactions at C-3 of a 1,4-dihydroisoquinolinium ion (formed by initial C_4 protonation of the enamine) have been intramolecular in type. Several of these cyclizations have been ulitized in the synthesis of some alkaloids; the essential features are outlined in Scheme 35.

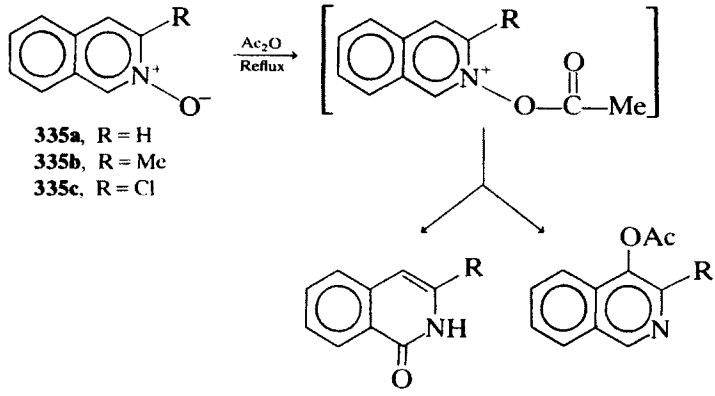


Scheme 35

G. Rearrangements

(a) *Aromatic Isoquinolines*

With isoquinoline *N*-oxide (**335a**) is heated under reflux with acetic anhydride, a rearrangement occurs to give isocarbostyril as the major product, together with a small amount of 4-acetoxyisoquinoline; a similar reaction occurs with 3-methylisoquinoline *N*-oxide (**335b**)[502] (Scheme 36).

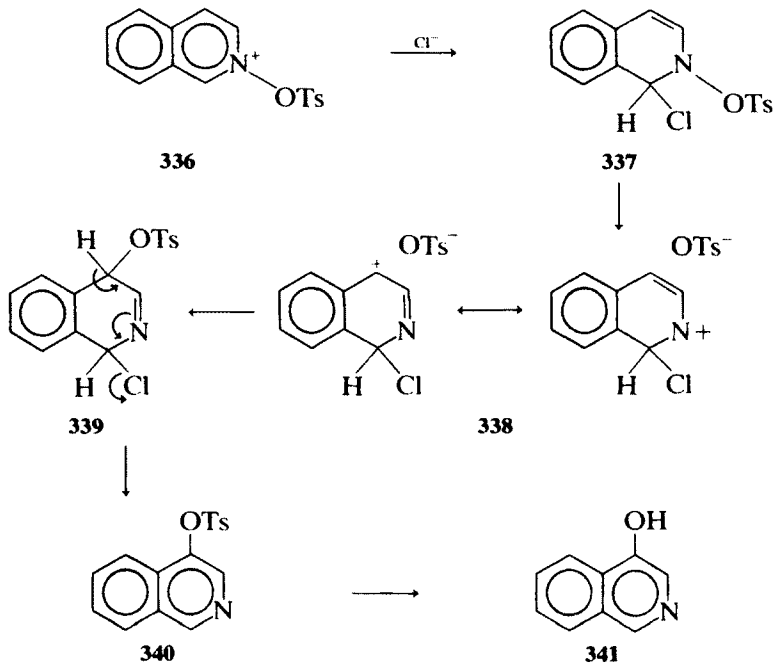


335a, R = H
335b, R = Me
335c, R = Cl

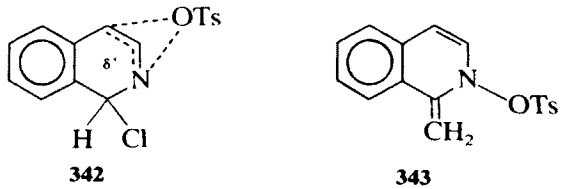
R = H	50–60%	9%
R = Me	40%	8–11%
R = Cl	1%	49%

Scheme 36

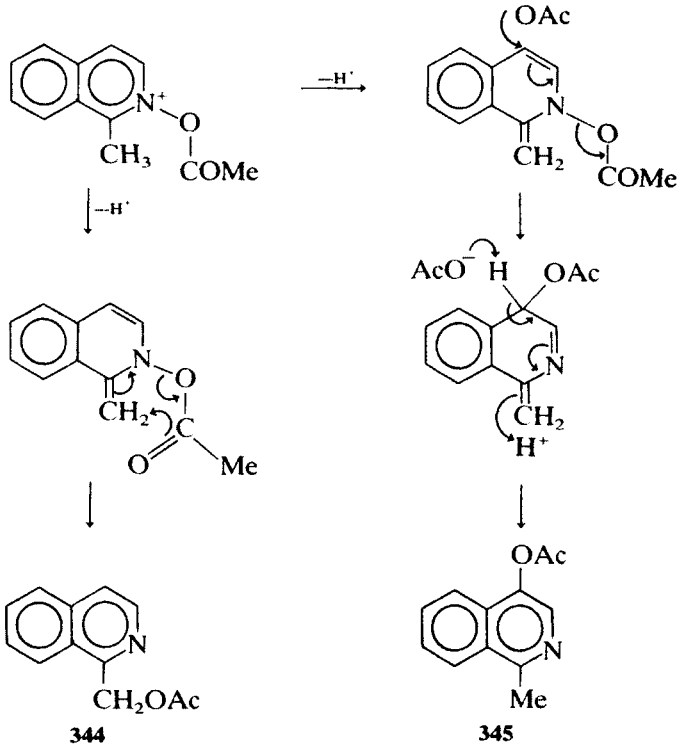
The 4-acetoxyisoquinoline derivative predominates when 3-chloroisoquinoline *N*-oxide (**335c**) is similarly treated.[503] This work has been reviewed, together with a discussion of mechanism of the reaction.[504] If isoquinoline *N*-oxide is heated under reflux in chloroform solution in the presence of two equivalents of *p*-toluenesulfonyl chloride, 4-tosyloxyisoquinoline (**340**) is the major product (70%), together with a little (10%) isocarbostyril.[505] A similar reaction occurs with 3-methylisoquinoline *N*-oxide.[506] The mechanism postulated for this reaction[505] (Scheme 37) involves addition of chloride ion to the *N*-tosyloxyisoquinolinium cation (**336**) to give **337**, which then fragments to the solvent separated ion pair **338**. Recombination of ions then yields **339**, which, by elimination of the chloride ion and a proton, provides the product **340**, which may then be hydrolyzed to 4-hydroxyisoquinoline (**341**). However, with the aid of ^{18}O-enriched *p*-toluenesulfonyl chloride, it was concluded that the ion-pair pathway including **338** accounts for only a minor amount of the rearrangement, with the major pathway involving a bridged ion pair such as **342**.[507] 1-Methylisoquinoline *N*-oxide reacts with *p*-toluenesulfonyl chloride[508,509] to yield 1-chloromethylisoquinoline, presumably through the anhydrobase **343**.



Scheme 37

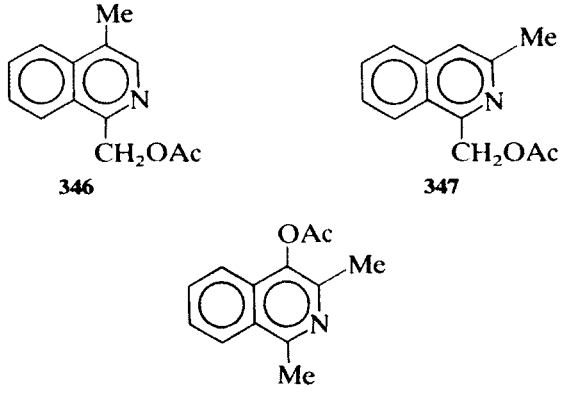


With acetic anhydride the same *N*-oxide gives a mixture of **344** and **345**. This has been rationalized[510] by the mechanism shown in Scheme 38. The mechanism of this reaction has also been studied using kinetic and ^{18}O-tracer methods.[511] When 1,4-dimethylisoquinoline *N*-oxide is refluxed with acetic anhydride,[512] the product is **346**, but with the 1,3-dimethyl compound, **347** and **348** are produced in modest yield. The mechanism of reaction is similar to that proposed for the reaction of 1-methylisoquinoline *N*-oxide. *N*-Hydroxyisocarbostyril (**349**) reacts with *p*-toluenesulfonyl chloride[513] to give the 4-tosyloxy compound **350**, and by using ^{18}O-labeled *p*-toluenesulfonyl chloride, it was concluded that the reaction proceeds through the solvent-separated ion pair as the major pathway, with a minor contribution from an oxygen-bridged ion pair. However, with 1-aminoisoquinoline *N*-oxide (**351**), rearrangement occurs to the 4-tosyloxyamine **352** in a reaction dominated by a bridged-ion-pair intermediate (Scheme 39).[513] The difference between the mechanisms in these two cases may be attributable to different stabilities of the anhydro bases.



344 345

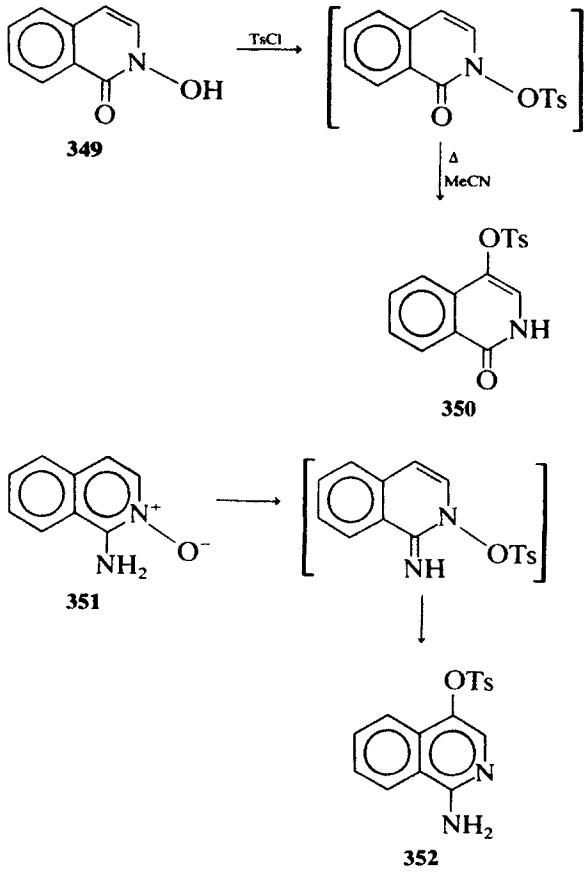
Scheme 38



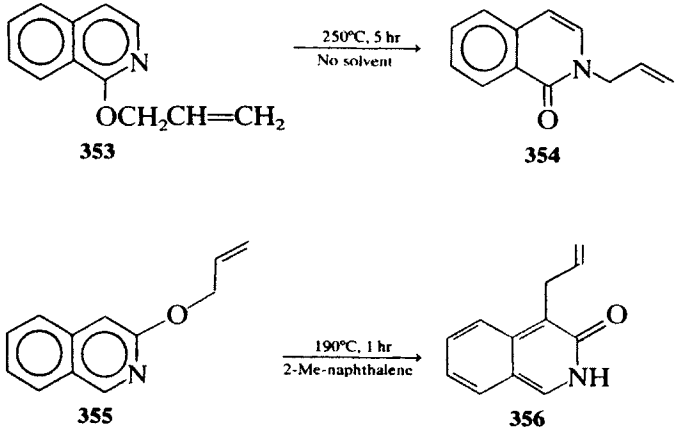
346 347 348

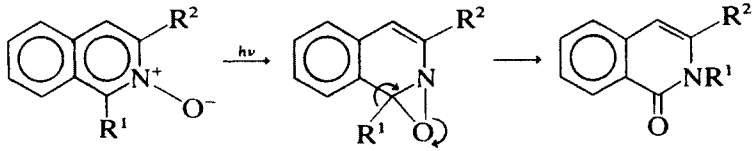
1-Allyloxyisoquinoline (**353**) undergoes a Claisen rearrangement[514] when heated to 250°C, and a 94% yield of **354** is obtained. When the isomeric 3-allyloxyisoquinoline (**355**) is heated to 190°C, **356** is produced in 56% yield and 34% of the starting material is recovered.

Irradiation of the isoquinoline *N*-oxides **357** gave the isocarbostyril in each case,[515] presumably through the oxide **358** (Eq. 33). When *N*-oxides


TsCl
OH
OTs
Δ
MeCN
OTs
NH
349
350
OTs
NH
NH2
351
352

Scheme 39


250°C, 5 hr
No solvent
OCH2CH=CH2
353
354
190°C, 1 hr
2-Me-naphthalene
355
356

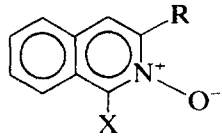


(33)

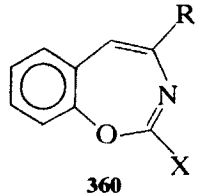
357a, $R^1 = R^2 = H$
357b, $R^1 = H$; $R^2 = Me$
357c, $R^1 = Me$; $R^2 = H$

358

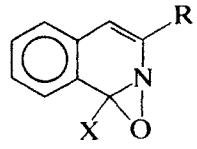
359 were irradiated,[516] the products, obtained in about 50% yields, were shown to be **360**. In some earlier work **359c** and **359d** were irradiated[517] to provide compounds formulated as **361**, but these structures were later[516] corrected to **360**. Irradiation of *N*-benzoyliminoisoquinolinium betaines **362**



359a, R = H; X = Ph
359b, R = Me; X = Ph
359c, R = H; X = CN
359d, R = Me; X = CN

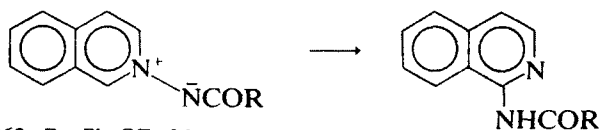


360



361

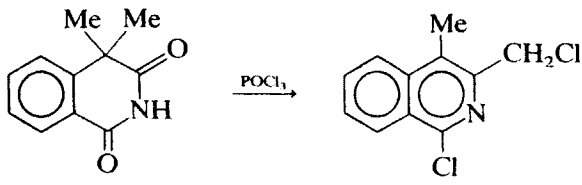
results in a $2 \rightarrow 1$ shift of the acyl amino group to give **363** in high



362, R = Ph, OEt, Me, *o*-$MeOC_6H_4$, *m*-$MeOC_6H_4$, *p*-$MeOC_6H_4$

363

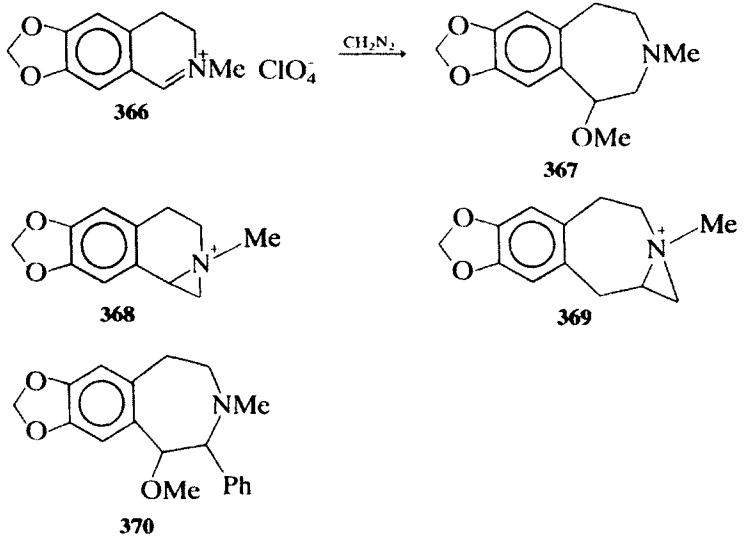
yields.[518–520] 4,4-Dialkylhomophthalimides **364** undergo a rearrangement reaction when they are treated with phosphorus oxychloride[521–525] to yield **365**.



364 **365**

(b) 3,4-*Dihydroisoquinolines*

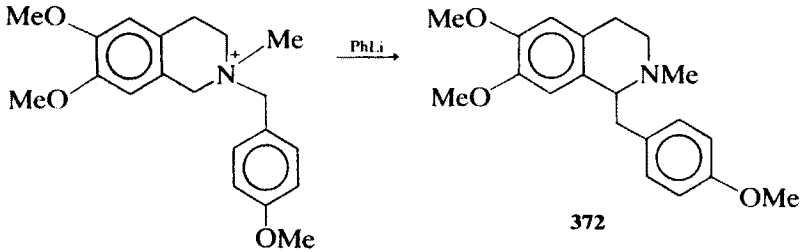
When hydrastinine **366** was treated with diazomethane,[526] the ring-expanded product **367** was formed. It was later shown[527] that the aziridinium salt **368** is the actual intermediate, which is converted into **367** under solvolytic conditions. Bernhard and Snieckus[527] also isolated some of the ring-expanded salt **369** from the reaction. When **366** is reacted with phenyldiazomethane,[528] the product, from a different mechanistic pathway, is **370**.



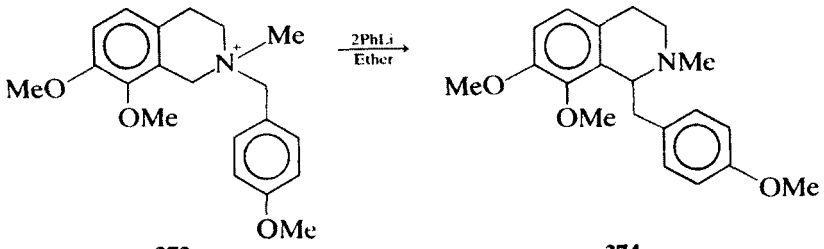
366 367 368 369 370

(c) 1,2,3,4-*Tetrahydroisoquinolines*

The Stevens rearrangement has been successfully applied to the preparation of some 1-benzylisoquinoline derivatives; thus when the quaternary salt **371** was treated[529] with strong base, the product was **372**. Yields vary over wide limits and a number of side reactions also occur. However, the method was successfully used[530] in a synthesis of petaline, when the rearrangement of **373** occurred to give **374** in 85% yield.

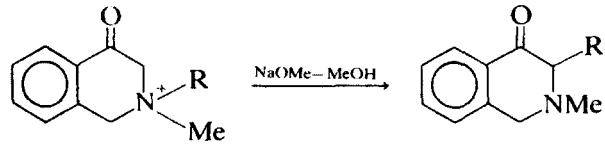


371 372



373 374

The rearrangement of **375** to **376**, a [2, 3] sigmatropic process, has also been reported.[531]



375, R = $CH_2CH{=}CHPh$, CH_2Ph **376**

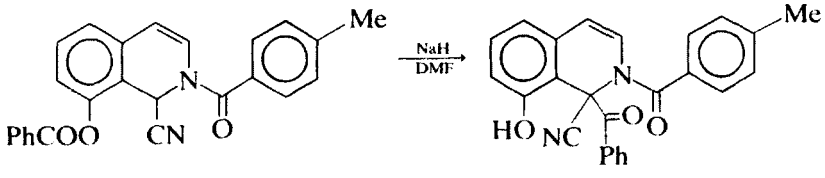
(d) 2-*Acyl*-1,2-*dihydroisoquinaldonitriles*

Some rearrangement reactions have been reported in Reissert compounds of the isoquinoline series;[434,435] when **284a** is heated in xylene, it is converted into **377**. The reaction has been used to prepare a number of 1-acylisoquinolines, where the rearrangement is best carried out with NaH–DMF.[463] The rearrangement has been investigated with the aid of ^{14}C-labeled compounds when it was shown to be intramolecular in nature.[152] An interesting variation was found when compound **378** rearranged[464] to **379** when treated with NaH–DMF.

A remarkable series of rearrangements has been discovered;[533] the Reissert compound **284a** reacts with hypochlorous acid to give the chlorohydrin

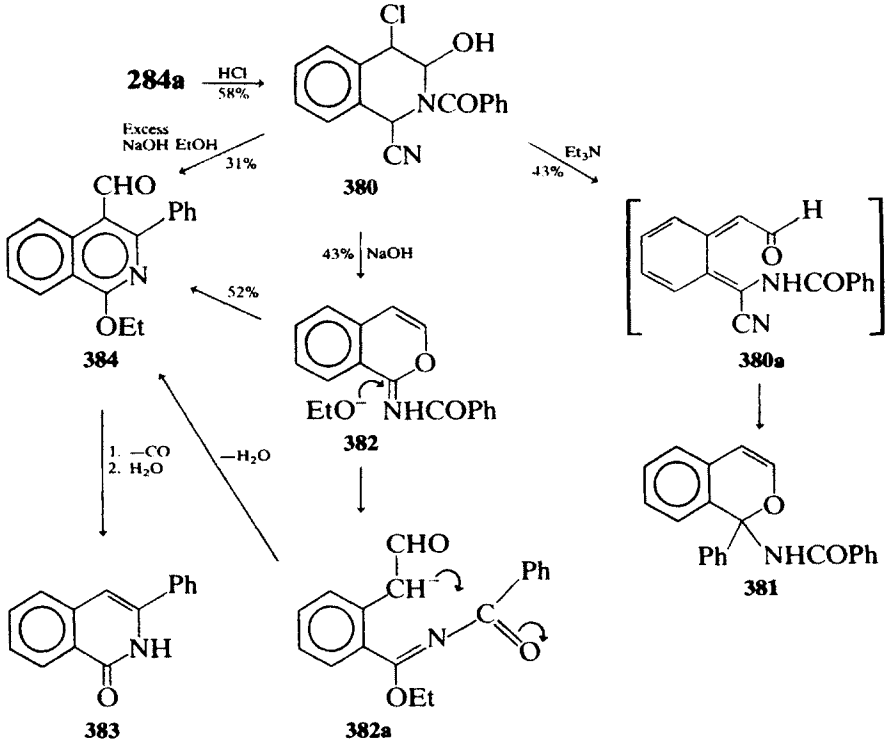


284a **377**



378 **379**

380, which, when treated with triethylamine, is converted into the isochromene **381**. Probably a 1,4-elimination of HCl and ring opening occur to give the intermediate **380a**, which can then cyclize to **381**. If **380** is reacted with aqueous NaOH instead of with Et_3N, the imine **382** can be isolated. Treatment of the latter with ethanolic sodium hydroxide provides **384** in 52% yield. Attack of ethoxide ion at C-1 in **382**, followed by ring opening, could provide the anion (**382a**), from which **384** could be formed by recyclization followed by dehydration. The same product (**384**) can be formed directly from **380** by reacting it with an excess of ethanolic sodium hydroxide solution. Decarbonylation of **384** with palladium gave the known 1-ethoxy-3-phenylisoquinoline, which could be hydrolyzed to 3-phenylisocarbostyril **383** (Scheme 40).

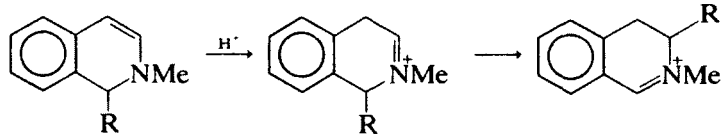


Scheme 40

(e) 1,2-*Dihydroisoquinolines*

Some interesting rearrangements occur in 1,2-dihydroisoquinolines, where, in the presence of dilute mineral acid, a 1-allyl (**385a**), a 1-propargyl (**385b**), or a 1-benzyl-1,2-dihydroisoquinoline (**385c**) is transformed by way

of the iminium ion **386** into the 3-substituted-3,4-dihydroisoquinoline **387a**, **387b** or **387c**, respectively (Eq. 34).[248]



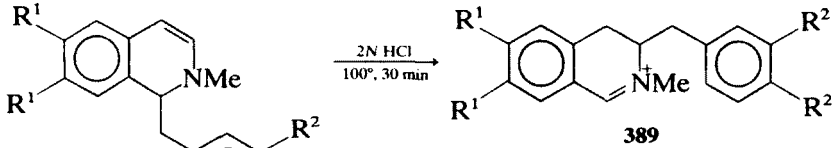
(34)

385a, R = $CH_2CH{=}CH_2$
385b, R = $CH_2C{\equiv}CH$
385c, R = Ph

386

387a, R = $CH_2CH{=}CH_2$
387b, R = $CH{=}C{=}CH_2$
387c, R = CH_2Ph

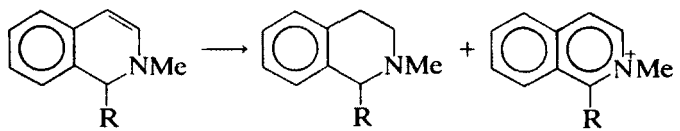
In 1963 it was reported[336] that treatment of 2-methyl-1,2-dihydropapaverine (**388**; $R^1 = R^2 = OMe$) with 2*N* HCl at 100°C for a few minutes produced a high yield of the 3-benzyl-3,4-dihydroisoquinolinium salt **389** ($R^1 = R^2 = OMe$). This was confirmed[254] by rearranging **388** ($R^1 = OMe$; $R^2, R^2 = -OCH_2O$) to the corresponding salt **389** ($R^1 = OMe$; $R^2, R^2 = -OCH_2O-$). An intramolecular mechanism was proposed,[254] but the reaction was shown[534] to be intermolecular by carrying out a crossed migration experiment with **388** ($R^1 = R^2 = OMe$) and **388** ($R^1 = R^2 = OEt$). It has been



388

389

found[535] that whereas rearrangement occurs with a benzyl- or alkoxy-substituted benzyl at C-1 in the 1,2-dihydroisoquinoline, the reaction fails if the group is alkyl, phenyl, or β-phenethyl. Only disproportionation of the starting material is observed to give a mixture of **390** and **391** (Eq. 35).



(35)

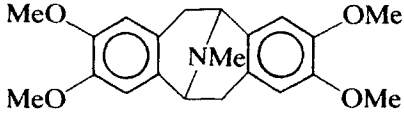
385d, R = Me
385e, R = Bu
385f, R = Ph
385g, R = CH_2CH_2Ph

390

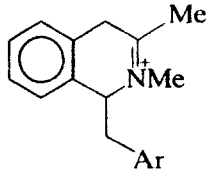
391

It has been known for some time[485] that when **388** ($R^1 = R^2 = OMe$) is treated with strong acids at elevated temperatures, cyclization to the pavine derivative **392** occurs rather than rearrangement, and a study was made[536] of the factors that cause rearrangement or pavine formation. The driving force for rearrangement is probably the movement of the $>C{=}N^+<$ group

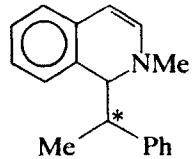
of **386** ($R = CH_2Ar$) into conjugation with the aromatic ring. The reported[537] failure of 2,3-dimethyl-1-benzyl-1,2-dihydroisoquinoline to rearrange can be explained in terms of the stabilizing factors acting on the iminium system **393**. It has been established[538] that rearrangement is favored by a C_6-oxygen function and by electron-withdrawing substituents in the benzyl ring and that[539] the yield of rearrangement product decreased progressively with increase in the size of the alkyl group attached to nitrogen. It has been reported[540] that when an optically active sample of **394** was rearranged, racemization occurred, but a reinvestigation of this reaction



392

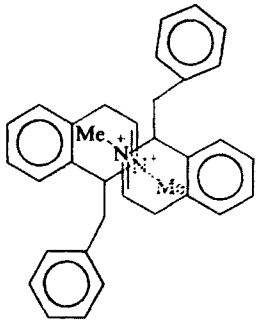


393

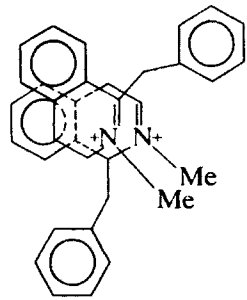


394

established[541] that some optical activity is retained. After a survey of the reported experimental work on the benzyl rearrangement reaction, it was proposed[542] that the mechanism of reaction involved a novel bimolecular exchange and two transition states, **395** and **396**, were considered. The C-1 atom of one 1,4-dihydroisoquinolinium ion lies opposite the C-3 atom of the second molecule and vice versa, and the benzyl group at C-1 of each is oriented toward its receptor molecule. It is proposed that the exchange of benzyl groups and the rearrangement of double bonds may proceed in a concerted manner. In **395**, where a four-center overlap is envisaged, the participating molecules have opposite configurations at C-1, whereas in the six-center transition state **396** both partners have the same configuration at

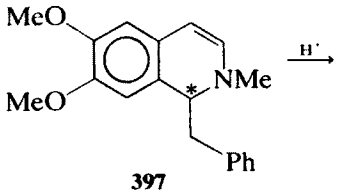


395

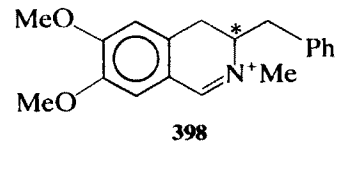


396

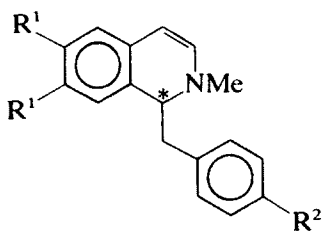
this center. Transition state **396** must be involved in the rearrangement of optically active **397**, which yields[543] an optically active product **398**. An attempt has been made[541] to differentiate between transition states **395** and **396** by rearranging a mixture of (+)-**399** and (−)-**400**. If the rearrangement proceeds through transition state **395**, only the "crossed" products **403** and **404** should be produced, whereas if the six-center overlap transition state **396** is preferred, the products should be **401** and **402** only. In practice, all four products were obtained in similar amounts, suggesting that the energy difference between **395** and **396** is very small. It would be anticipated that the reaction should involve a high negative entropy of activation for either transition state, and this has been[544] found to be true. A value of −180 J/(°K)/(mole) [−43 cal/(deg)/(mole)] in a second-order reaction was established by using 2-methyl-1,2-dihydropapaverine.



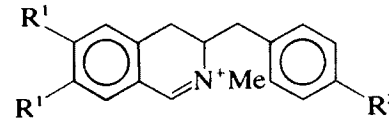
397



398



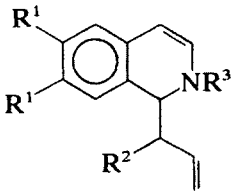
399, $R^1 = R^2 = OMe$
400, $R^1R^1 = OCH_2O$; $R^2 = OEt$



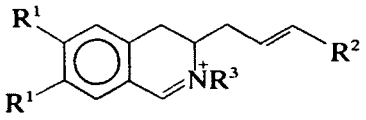
401, $R^1 = R^2 = OMe$
402, R^1, $R^1 = OCH_2O$; $R^2 = OEt$
403, $R^1 = OMe$; $R^2 = OEt$
404, $R^1R^1 = OCH_2O$; $R^2 = OMe$

When 1-allyl-2-methyl-1,2-dihydroisoquinoline (**405a**) is treated with dilute acid, under the conditions of the benzyl rearrangement, the 3-allyl-3,4-dihydroisoquinoline salt **406a** is produced in high yield.[122] Similar treatment of **405b** gave the "inverted" product **406b** in high yield,[122] thus supporting the view of a suprafacial [3,3] sigmatropic process. The reaction was proved to be concerted in nature when it was shown[122] that optically active **405a** (chiral center at C-1) was rearranged to **406a** with essentially 100% retention of activity. Strong evidence of the intramolecular nature of the reaction was forthcoming from the observation[122] that when an equimolecular mixture of **405c** and **405d** was subjected to the conditions of the rearrangement, no crossover products could be detected. Only **406c** and **406d** could be found in the reaction mixture.

As in the benzyl migration, the allyl group would not migrate in the 3-methylisoquinoline derivative **407a** under the normal conditions.[545] Thermodynamic control of the reaction was demonstrated by showing that **407b**

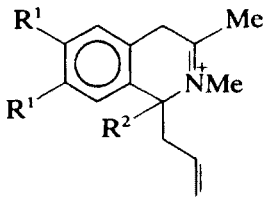


405a, $R^1 = R^2 = H$; $R^3 = Me$
405b, $R^1 = OMe$; $R^2 = R^3 = Me$
405c, $R^1 = OMe$; $R^2 = H$; $R^3 = Me$
405d, $R^1 = OMe$; $R^2 = Me$; $R^3 = H$

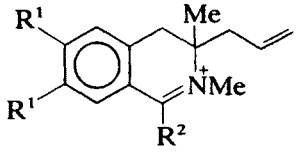


406a, $R^1 = R^2 = H$; $R^3 = Me$
406b, $R^1 = OMe$; $R^2 = R^3 = Me$
406c, $R^1 = OMe$; $R^2 = H$; $R^3 = Me$
406d, $R^1 = OMe$; $R^2 = Me$; $R^3 = H$

rearranged readily. Presumably, the hyperconjugative stabilization of the $\rangle C{=}N^{+}\langle$ double bond in **407a** is more important than the stabilization in **408a** by conjugation with the aromatic ring. In **407b** this stabilization is canceled by the extra stabilization in **408b**. It was also shown[545] that the additional stabilization of the 3,4-dihydrosystem could be provided by a C_6-methoxyl group, and an equilibrium was set up in which the **407c**:**408c** ratio was 2:1.

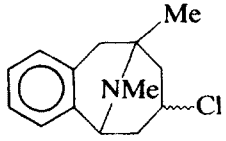


407a, $R^1 = R^2 = H$
407b, $R^1 = H$; $R^2 = Me$
407c, $R^1 = OMe$; $R^2 = H$



408a, $R^1 = R^2 = H$
408b, $R^1 = H$; $R^2 = Me$
408c, $R^1 = OMe$; $R^2 = H$

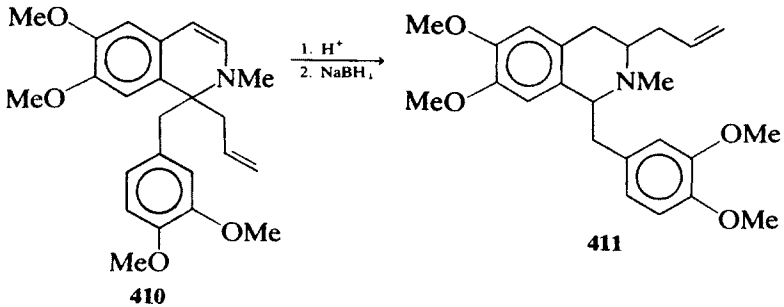
Although **407a** would not rearrange under the usual conditions (2*M* HCl, water bath, for several hours), it was found[546] that prolonged reflux (14 days) gave **409** in high yield.

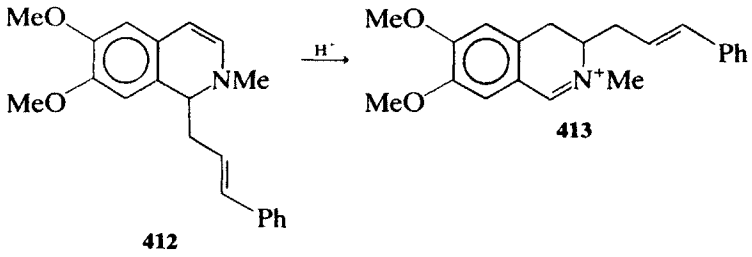


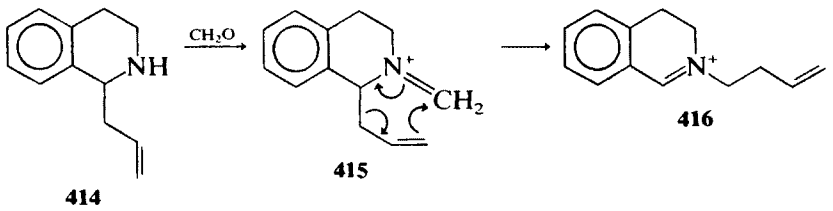
409

When 1-allyl-2-methyl-1,2-dihydropapaverine (**410**) was subjected to rearrangement conditions,[62] it was the allyl group that migrated to give **411** in high yield. An interesting situation arises with **412**, which may migrate either as a vinylogous benzyl group or as a phenyl-substituted allyl group; the former mode of reaction was established[62,547] to yield **413**.

An allyl group migrates from C-1 in the 1,2,3,4-tetrahydroisoquinoline **414** when attempts are made[544] to *N*-methylate the compound using formaldehyde. Presumably, the reaction proceeds as shown in Eq. 36.







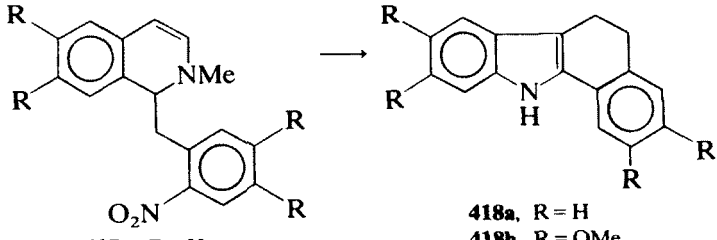
(36)

(f) *Miscellaneous Rearrangements*

When 1,2-dihydroisoquinolines **417a** and **417b** are treated with triethyl phosphite, the indole derivatives **418a** and **418b** are found in 37% and 38.5% yields, respectively, possibly through a nitrene intermediate.[419,548] However, when 6′-nitro-papaverine (**419**) is similarly treated,[549] the products are **420** and **421**.

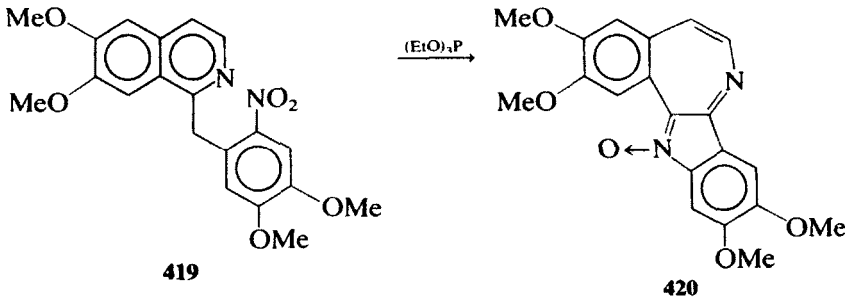
H. Cycloaddition Reactions

The double bonds in the heterocyclic ring of isoquinoline and its dihydro derivatives undergo olefin-type reactions to form cyclic products. When isoquinoline itself reacts with two molecules of maleic anhydride, the expected dianhydride **422** is obtained.[550] A similar reaction with diethyl



417a, R = H
417b, R = OMe

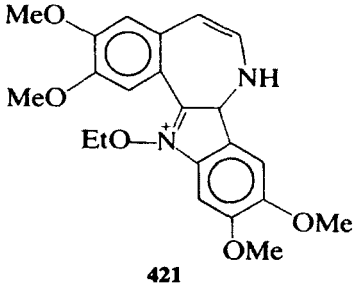
418a, R = H
418b, R = OMe



419

420

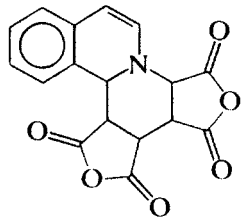
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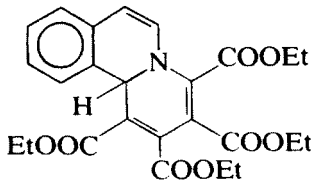
421

acetylenedicarboxylate in ether produces[551] the labile compound **423**, which isomerizes to the stable structure **424**. When this reaction is carried out in methanol, however, solvent incorporation leads to the pyrroloisoquinoline **425**. When both double bonds are present in the heterocyclic ring, the more polar C=N bond reacts. In the 1,2-dihydroisoquinoline **426** a stepwise addition of two molecules of diethyl acetylenedicarboxylate to the C_3=C_4 bond, followed by oxidation, yields **427** as the stable product.[552]

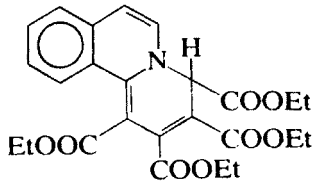
The expected 1:2 adduct **429** is formed[553] when the 3,4-dihydroisoquinoline **428** (R = OMe) is treated with dimethyl acetylenedicarboxylate in ether, but when the same compounds react in methanol the presence of a proton source allows the isoquinoline **428** (R = OMe or H or $-OCH_2O-$) to revert to its enamine form, and the only product is the benzoquinolizone



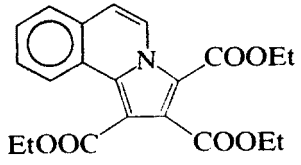
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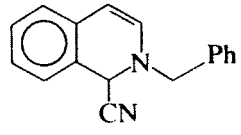
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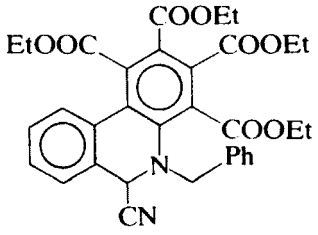
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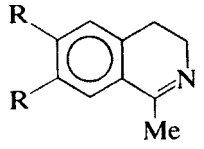
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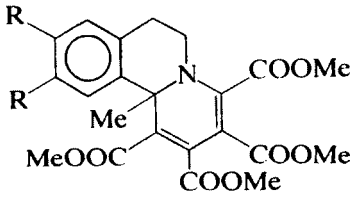
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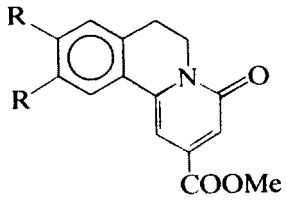
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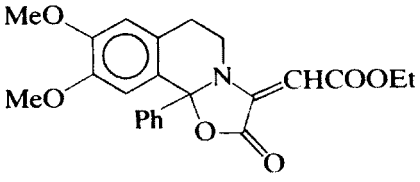
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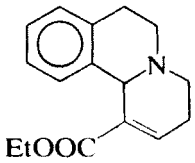
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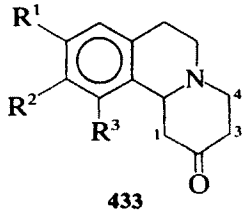
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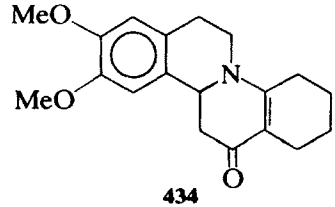
432

430. A similar reaction of the enamine form has been noted with phenyl isocyanate and isothiocyanate.[554] A 1:1 adduct is also formed between 6,7-dimethoxy-1-phenyl-3,4-dihydroisoquinoline and diethyl acetylenedicarboxylate, but in this case a lactone (**431**) is produced.[555] 3,4-Dihydroisoquinoline acts as a dienophile toward 1-carbethoxybuta-1,3-diene[556] to form **432** after isomerization of the double bond in the initial adduct.

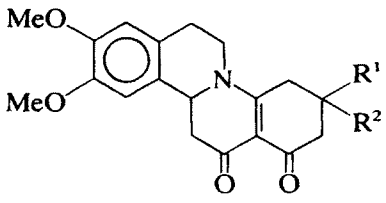
α,β-Unsaturated ketones react[557] with 3,4-dihydroisoquinolines by a Michael-type condensation mechanism to yield benzo[*a*]quinolizones **433**, which can be substituted at the 1-, 3-, and 4-positions by using the appropriate ketone. In a similar two-step process, using substituted β-diketones, high yields of a wide range of substituted benzoquinolizones have been obtained, such as **434**[558] and **435**,[559] starting from 2-acetylcyclohexanone and 5,5-disubstituted-2-acetylcyclohexa-1,3-diones, respectively.



433

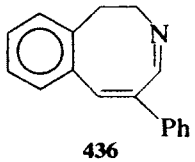


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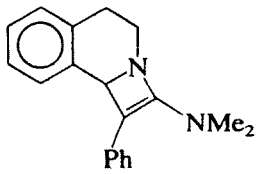


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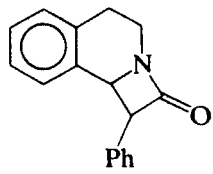
An interesting reaction occurs[560] between the C=N bond of 3,4-dihydroisoquinoline and ynamines from which the isolated products are benzazocines; for example, **436** is obtained in 75% yield from phenyldimethylaminoacetylene. The reaction proceeds through the intermediacy of the adduct **437**, as can be demonstrated by the isolation of its hydrolysis product **438**. A photochemical cyclization occurs[561] when isocarbostyril is irradiated in ethanol, and the dimer **439** is obtained in high yield. In the presence of tetramethylethylene the reaction leads to the isolation of the adduct **440** in 90% yield, and nmr studies indicate a cis configuration at the ring fusion. Photocycloaddition with 1,1-disubstituted ethylenes could give rise to "head-to-head" (**441**) and "head-to-tail" (**442**) isomers. When isobutylene was used, only **441** (R = Me) was found, but with 1,1-dichloroethylene both isomers, **441** (R = Cl) and **442** (R = Cl), were found in a ratio of 4:1. This contrasts with the reactions of carbostyril, when only the "head-to-tail" isomer was formed in each case.



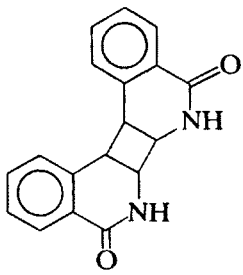
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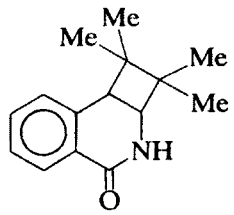
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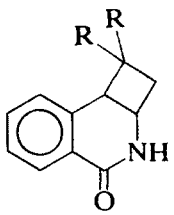
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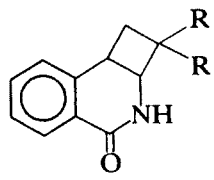
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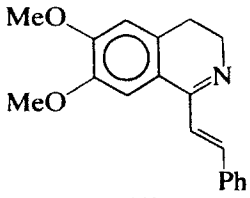
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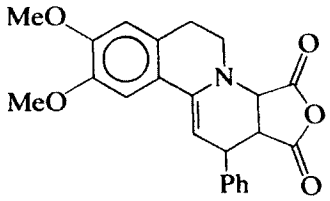
442

The 1-aza-1,3-diene system of substituted 1-vinyl-3,4-dihydroisoquinolines undergoes normal Diels–Alder addition with maleic anhydride. Thus the 1-styryl- (**443**)[562] and 1-cyclohexenyl- (**445**)[563] derivatives lead to the formation of 1,4-adducts **444** and **446**, respectively. More recently[491,492] 4-vinylisocarbostyrils **447** have been added to maleic anhydride, acrylic acid, *p*-benzophenone, propiolic acid, and benzyne to give moderate to good yields of the expected adducts, sometimes with aromatization; for example, **447b** with *p*-benzoquinone gave **448** in 72% yield.

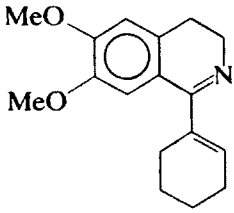
1,4-Polar cycloadditions have been reported[564–566] in which 2,3-dimethylisoquinolinium ions add to methyl vinyl ether to give high yields of the adduct **449**. The orientation of the methoxyl group over the benzene ring was established by X-ray crystallography. Structure **450** has been similarly confirmed[567] for the adduct formed with cyclopentadiene. With a nitrogroup at C-5 the diene reactivity is sufficiently enhanced that the presence of the C_3-methyl group is no longer necessary to promote reaction.[568] 3-Hydroxyisoquinoline, reacting in its tautomeric amide form, adds[569] to *N*-phenylmaleimide to give the endo Diels–Alder adduct **451**. Analogous adducts have been obtained[570] from the corresponding *N*-methyl derivative



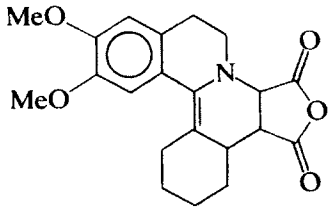
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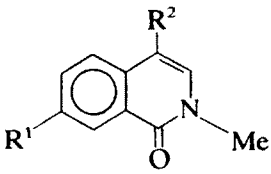
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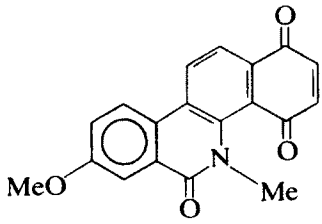
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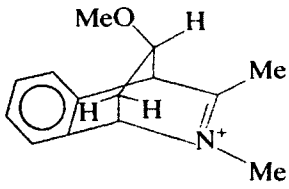
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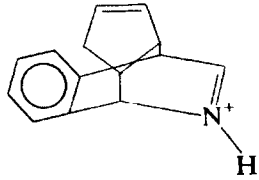
447a $R^1 = H$; $R^2 = CH = CHCOOMe$
447b $R^1 = OMe$; $R^2 = C(OAc) = CH_2$
447c $R^1 = OMe$; $R^2 = CH = CH_2$



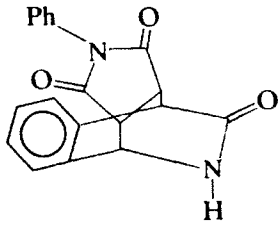
448



449



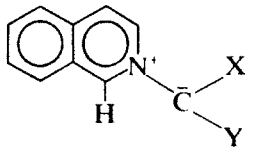
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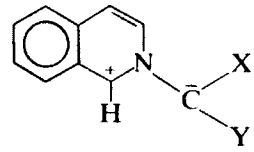
451

with both tetracyanoethylene and maleic anhydride; however, exo geometry has been assigned to the product in the latter case.

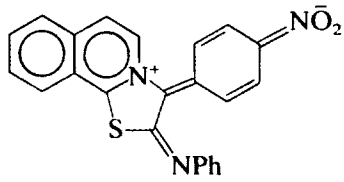
Isoquinolinium ylides are obtained when a suitably substituted isoquinolinium salt is treated with a base (usually triethylamine). The ylides **452** undergo 1,3-dipolar addition reactions via the mesomeric form **453**. The primary adducts are frequently not isolated but isomerize and aromatize to more stable species. An early reported[571] adduct was between the azomethine ylide **452** (X = H; Y = *p*-$NO_2C_6H_4$) and phenylisothiocyanate to which the aromatic structure **454** was assigned; a similar reaction occurs[572]



452



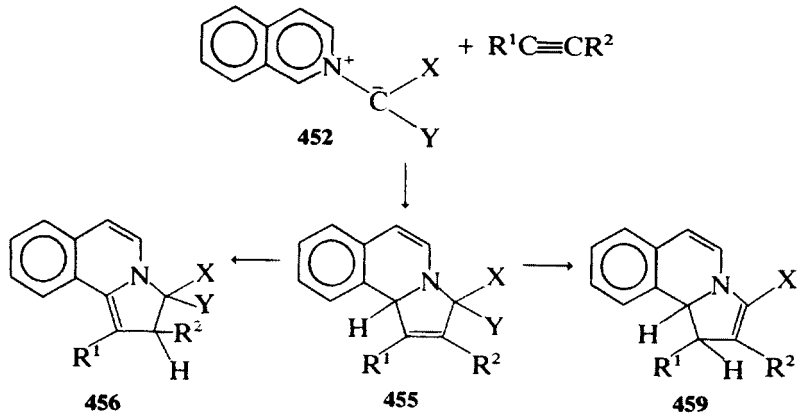
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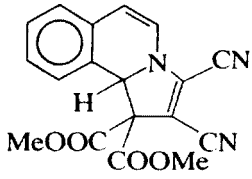
454

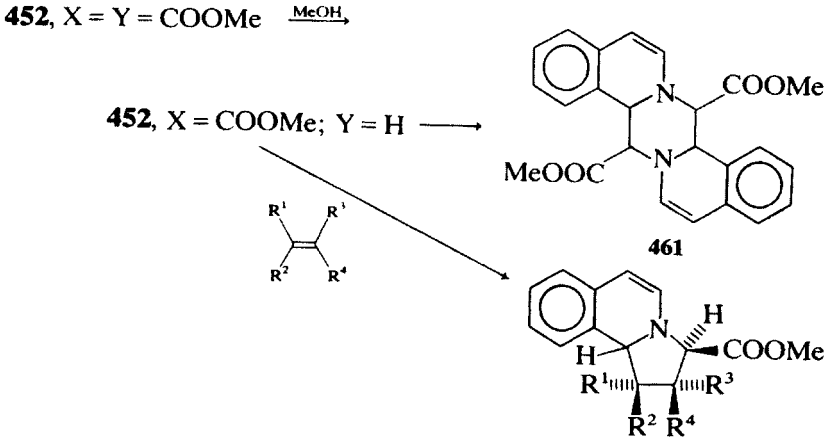
with carbon bisulfide. The primary adduct **455** formed initially on reaction with acetylenic dipolarophiles readily undergoes isomerization and aromatization (Scheme 41). The primary adduct is rarely isolated but has been obtained in the reactions between **452** (X = Y = COOMe or X = COOMe; Y = CN) and methyl propiolate[573,574] or dialkyl acetylenedicarboxylate;[574-576] the adducts from reaction with methyl propiolate are exclusively R^1 = COOMe, R^2 = H. With **452** (X = Y = CN), only the 2,3-dihydro- **456** (X = Y = CN) and aromatic **458** (X = CN) pyrroloisoquinolines were isolated.[577] From the reaction between the ylide **452** (X = Y = COOMe) and dicyanoacetylene a rearranged addition product (**460**) was obtained[578] in addition to the expected isomer **456** (X = Y = COOMe; R^1 = R^2 = CN).

The treatment of **452** (X = Y = COOMe) with methanol alone gives the more reactive monoalkoxycarbonyl ylide **452** (X = COOMe, Y = H), which dimerizes to **461** or reacts with added olefins to give 1,2,3,10*b*-tetrahydropyrrolo[2.1-*a*]isoquinolines (Eq. 37).[577] The monosubstituted ylides **452** (Y = H; X = $COCH_3$, CN, and COPh) react[579] with dialkyl acetylenedicarboxylate to give the corresponding 1,10*b*-dihydro- **459** and aromatized compounds **458**. Treatment of compounds **459**[579] or primary adducts **455**[575,576] with hydrochloric acid followed by potassium carbonate leads to isolation of the 2,3-dihydro-isomer **456**, whereas omission of the base treatment gives the isoquinolinium salt **457**. An interesting reaction has been reported[580] between **452** (X = Y = COOEt) and aldehydes or ketones


+ R¹C≡CR²
452
456
455
459
457
458

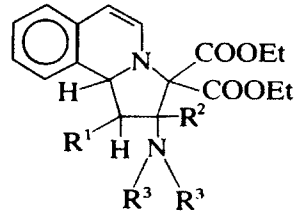
Scheme 41


460


452, X = Y = COOMe
MeOH
452, X = COOMe; Y = H
461

(37)

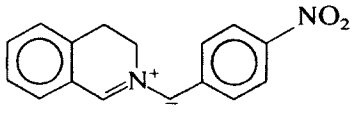
in the presence of amines. The reactive species is considered to be the enamine, and an intermediate amine (**462**) is proposed. The isolated pro-



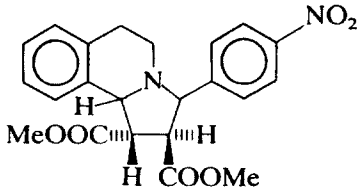
462

ducts are the aromatic pyrroloisoquinolines **458**, and with aldehydes, the addition is regiospecific with R^2 always hydrogen. Acetone gives rise to the alternative isomer **458** ($R^1 = H$; $R^2 = Me$) in 36% yield, whereas 2-butanone gives a mixture of **459** ($R^1 = H$, $R^2 = Et$, and $R^1 = R^2 = Me$).

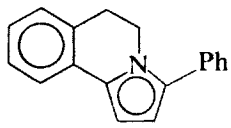
The first azomethine ylide **463** was prepared[571] from *N*(*p*-nitrobenzyl)-3,4-dihydroisoquinolinium bromide with triethylamine in hot pyridine. It is not sufficiently stable to be isolated but adds readily to dimethylfumarate *in situ*.[581] The adduct **464**, isolated in 69% yield, is converted in several steps to 3-phenylbenzo[g]pyrrocoline (**465**). Analogous additions of the 1,3-dipole onto phenylisothiocyanate or carbon bisulfide are followed by elimination of hydrogen, for example, the CS_2 adduct **466** leads to the aromatic sydnone **467**. Another short-lived methine ylide (**468**), from *N*-phenacyl-3,4-dihydroisoquinolinium bromide, also undergoes cycloadditions with dipolarophiles; with *N*-phenylmaleimide a 73% yield of adduct is formed.



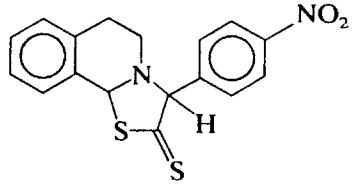
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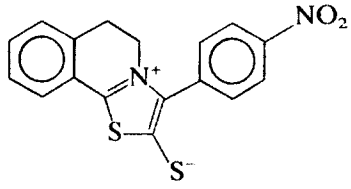
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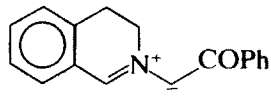
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466

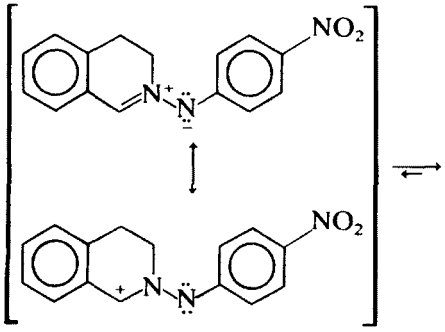


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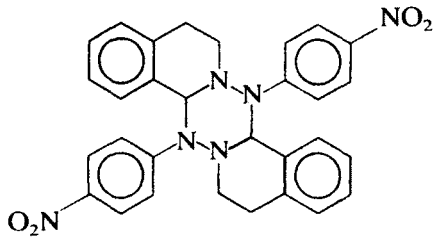


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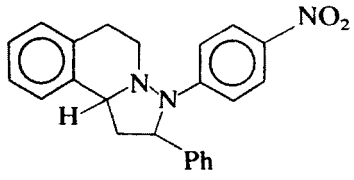
A reactive class of azomethine imines is available through proton abstraction from the hydrazonium salts of 3,4 dihydroisoquinolines.[582] These imines (e.g., **469**) dimerize in the absence of dipolarophiles. The resultant stable hexahydrotetrazine **470** serves as a convenient source for the monomeric zwitterion when in solution. This reactive compound gives very high yields of stereospecific 1 : 1 adducts with dipolarophiles, cumulative systems, and alkenes; thus reactions with styrene, phenylisocyanate, and cyclopentene afford the products **471**, **472**, and **473**, respectively. The 1-alkoxy derivative **474** also serves as a stable generator for the reactive



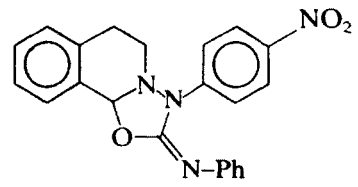
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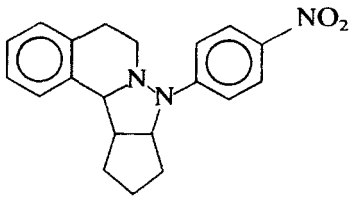
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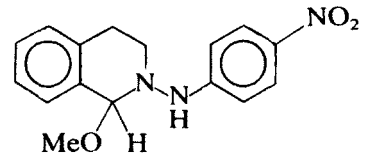
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472



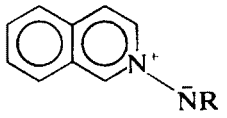
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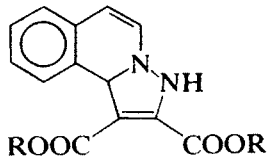
474

imine, and when heated with methyl propiolate, gives a theoretical yield of the expected adduct. Isoquinoline-*N*-imine **475** (R = H) also exists as a dimer and reacts[572] with dialkyl acetylenedicarboxylate to form the primary adduct **476**. Isoquinoline *N*-arylimines **475** (R = Ar) are readily formed and yield 1 : 1 adducts with phenylisocyanate (e.g., **477**), phenyl isothiocyanate, acenaphthalene, and 1,4-naphthaquinone. However, other 1,3-dipolar additions are followed by aromatization with ring opening.[571] Addition of ethyl phenylpropiolate to **475** (R = Ph) at 20°C is accompanied[572] by a rather

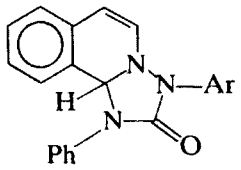
unorthodox rearrangement to give **478** in 57% yield. Diketene reacts with **475** (R = H) to give 3-acetyl-2-hydroxypyrrazolo[1,5-*a*]isoquinoline (**479**).[583]



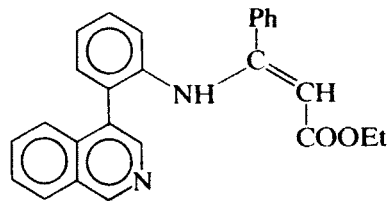
475



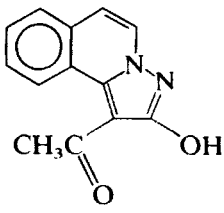
476



477

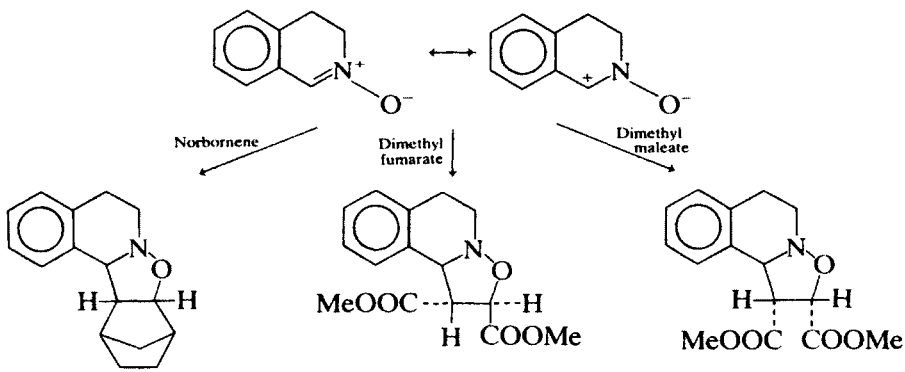


478



479

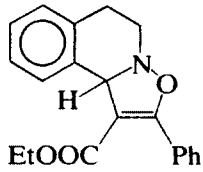
Azomethine oxides (nitrones) react with all kinds of double bond to give high yields of the 1:1 adduct[584] (Scheme 42). Acetylenes react faster than



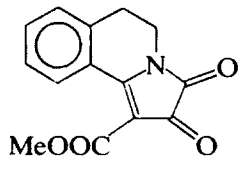
Scheme 42

do the analogously substituted ethylenes, but some of the adducts obtained undergo further reactions.[585] Ethyl phenylpropiolate gives the primary adduct **480** in 69% yield, but that formed with dimethyl acetylenedicarboxylate undergoes ring opening and lactimization to yield the pyrrolinedione **481**. A comparison[586] of the rates of reaction of 3,4-dihydroisoquinoline-*N*-oxide and isoquinoline-*N*-oxide with ethyl crotonate shows

that the former reacts at a rate 40,000 times greater than that of the latter, reflecting the loss of aromaticity during cycloaddition of this nitrone.

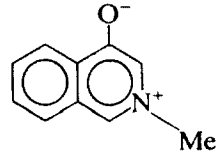


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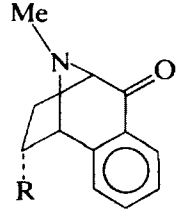


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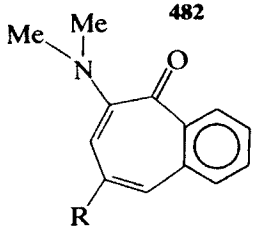
The 2-methyl-4-oxidoisoquinolinium ion (**482**) reacts with acrylonitrile to form a 1:1 cycloadduct, which has been shown[587] to be the endo product **483** (R = CN). With methyl acrylate, a mixture of endo and exo adducts is obtained, the methiodides of which undergo Hofmann degradation and spontaneous aromatization to give benzotropones **484** in good yield.



482

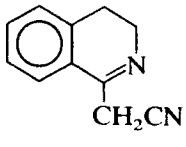


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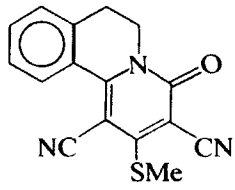


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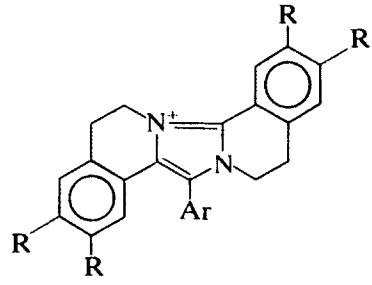
Condensation of isoquinolines such as **485** with methyl 1-cyano-2,2-bis-(methylthio)acrylate leads to the benzoquinolizine (**486**).[588] 1-Aryl-3,4-dihydroisoquinolines dimerize to **487**.[589] This is a special example of a more general reaction demonstrated by the addition to α,β-unsaturated ketones



485

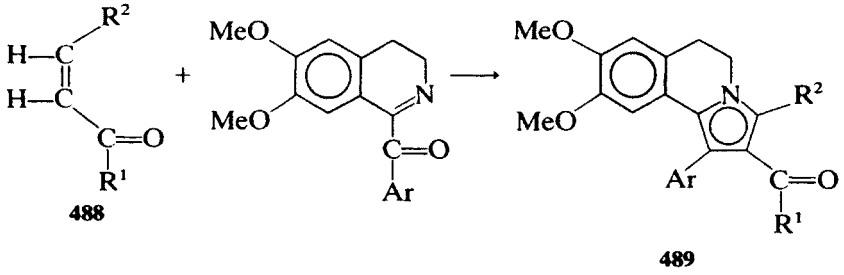


486



487

488 to give 5,6-dihydropyrrolo[2,1-*a*]isoquinolines **489a** through **489f** (Eq. 38) in yields better than 90%.



(38)

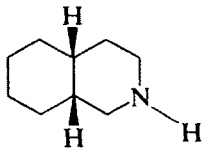
488 **489**

	Ar	R^1	R^2
a,	$(MeO)_2C_6H_3$—	Me	H
b,	*m*-$MeOC_6H_4$—	Me	H
c,	*m*-MeC_6H_4—	Me	H
d,	*p*-ClC_6H_4—	Me	H
e,	$(MeO)_2C_6H_3$—	Et	H
f,	$(MeO)_2C_6H_3$	Me	Me

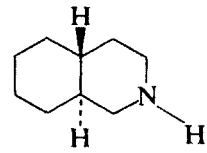
V. BENZORING REDUCED ISOQUINOLINES

Catalytic reduction of isoquinoline over platinum under acidic conditions[213] leads to a mixture of *cis*- (**490**) and *trans*- (**491**) decahydroisoquinolines in a ratio of 4:1; the cis isomer can be isolated as its picrate. Dehydrogenation of this mixture over palladium black at 210°C converts the cis isomer to a mixture of 5,6,7,8-tetrahydro- and aromatic isoquinoline but leaves the trans isomer unaffected. This procedure is similar to that developed for the quinoline system.[590] Under these reduction conditions the benzenoid ring is reduced first, as shown by the isolation of a 95% yield of 5,6,7,8-tetrahydroisoquinoline when the reaction is interrupted at the appropriate theoretical take-up of hydrogen.[591] The hydrogenation of ethyl 1-isoquinolylpyruvate (**492**) over copper chromite catalyst causes a reductive ring closure to occur, thus forming 1,2-trimethylenedecahydroisoquinoline (**493**) in 66% yield.[592] By varying the reduction conditions, all the isomers of the 5-, 6-, and 7- hydroxydecahydroisoquinolines have been prepared;[593] they are found to share considerable spectroscopic similarities with the corresponding decalols.

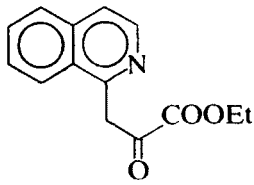
Hydrogenation of **494** (R = H) over PtO_2 did not occur in ethanol until hydrochloric acid was added[162] when reduction of the ring was accompanied by hydrogenolysis of the hydroxyl group to give largely the cis isomer **495**. This side reaction is suppressed by using Raney nickel catalyst under slightly basic conditions or through initial formation of the *N*-acetyl derivative **494** ($R = COCH_3$). Hydrogenolysis has also been found when 5-acetoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (**496**; $R = COCH_3$) is reduced over



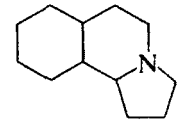
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491

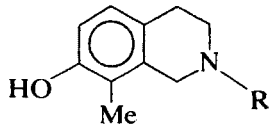


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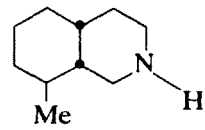


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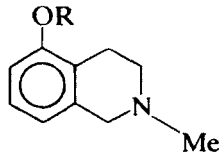
PtO_2 in acetic acid to *cis*-2-methyldecahydroisoquinoline.[594] Reduction of **496** (R = H) over Raney nickel gave two *trans*- and one *cis*-decahydro-alcohol, but chromic oxide–pyridine oxidation of the *cis*-alcohol is reported to yield the *trans*-ketone **497**.



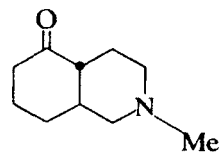
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495



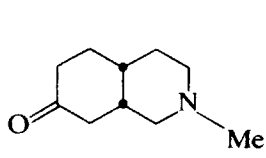
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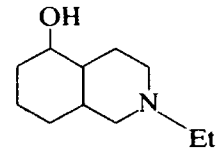
497

Conversely, the 7-hydroxydecahydroisoquinolines, produced by several different reduction methods, are all oxidized to the *cis*-ketone **498**, thus suggesting a greater stability of the cis than the trans isomer in this case.[595] Catalytic reduction of 5-hydroxyisoquinoline in ethanol, over W7 Raney nickel in the presence of base, led to the 2-ethyl derivative **499**.[191] Reductive alkylation was avoided by *N*-acetylation at the 1,2,3,4-tetrahydroisoquinoline stage, and the expected decahydroisoquinoline was then obtained in good yield. Stereospecific reductions of 2-methyl-hexahydro-5(1*H*)-isoquinolone (**500**) over palladium-on-charcoal lead exclusively[596] to the *trans*-ketone **501** in ethanol and the *cis*-ketone **502** in 5% aqueous hydrochloric acid.

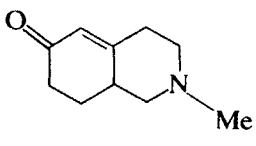
The pmr spectra of the decahydroisoquinolines show the trans isomer to have a signal envelope broader than that of the cis isomer.[597] This is similar to the decalin case, where the rigidity of the trans isomer leads to distinct axial and equatorial protons, whereas in the cis isomer, rapid inversion of the ring system leads to near-equivalence of the axial and equatorial



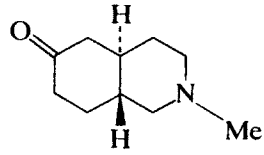
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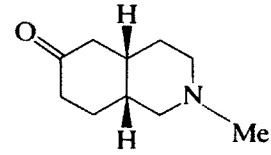
499



500

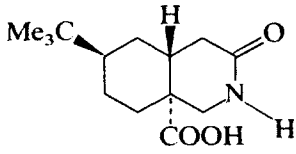


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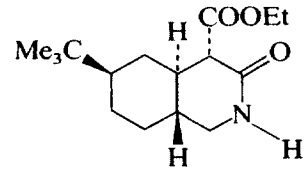


502

protons. The pK_a values of the two isomers (trans = 11.32; cis = 11.35) are too similar to be of use in structural assignments. Proton magnetic resonance studies[598] of **503** and **504** indicate a "twist-boat" conformation for the cyclohexane ring of the former and confirm the expected chair and half-chair conformations for the alicyclic and heterocyclic rings, respectively, of the latter isomer. Hydrolysis, decarboxylation, and reduction of **504** gave *trans*-6-*t*-butyldecahydroisoquinoline, but attempted decarboxylation of the 8a-acid **503** resulted only in tarry decomposition.

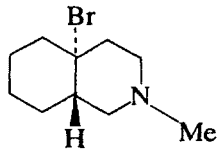


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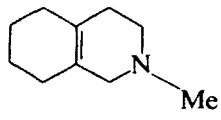


504

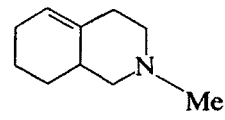
10α-Bromo-*N*-methyldecahydroisoquinoline (**505**) is formed[599] from the 10β-hydroxy derivative and from $\Delta^{4a,8a}$- (**506**) or $\Delta^{4a,5}$-octahydroisoquinolines (**507**) by treatment with hydrogen bromide in acetic acid at 50°C. At 85°C structure **505** is converted by way of the axial 5β-bromide (**508**) into the equatorial 5α-epimer **509**. At 140°C an equilibrium mixture of 6β-(**510**), 6α-(**511**), and 7α-*trans*-bromides (**512**) are obtained. Analogous isomerizations are found in the *N*-H series. The observed stability order of the bromides correlates well with their relative free energies. Treatment of epimeric pairs of bromides with lithium bromide in butan-2-one leads to an equilibrium mixture of 74% equatorial and 26% axial isomers, corresponding to a free-energy difference of 0.73 kcal/mole at 80°C. These multiple isomerizations are explained by a series of HBr eliminations and additions or, alternatively, by successive 1,2-hydride shifts. A similar isomerization is found when 10-hydroxy-*N*-methyl-*cis*-decahydroisoquinoline is treated with boiling 60% perchloric acid.[86] In addition to the expected $\Delta^{4a,8a}$- octahydroisoquinoline, an equilibrium mixture of 10-, 5α-, 6α-, 6β-, 7α-, and 7β-hydroxy isomers is formed.



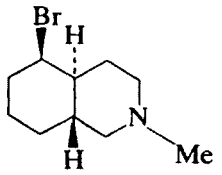
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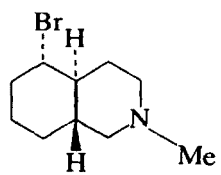
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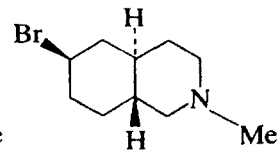
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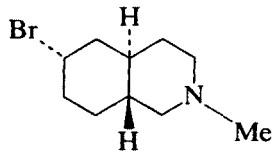
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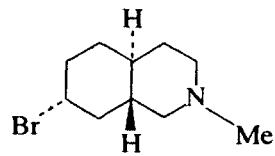
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510



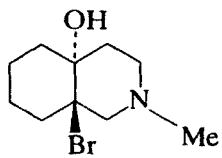
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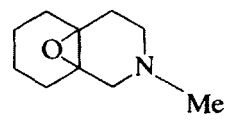
512

Reaction of the octahydroisoquinoline **506** with HOBr and hydrogenation of the resultant bromohydrin **513** leads[600] to a mixture of *cis*- and *trans*-4a-hydroxydecahydroisoquinolines. The epoxide **514**, obtained from **513** by base treatment, yields *trans*-8-hydroxydecahydroisoquinoline (**515**) on reduction with lithium aluminum hydride, but with catalytic reduction over Raney nickel the product is mainly the cis isomer **516**. The configurations assigned to **515** and **516** were based on the temperature dependence of the pmr spectra of these compounds. The spectrum of the trans isomer remains essentially unchanged on cooling to −60°C, but signals in the spectrum of the cis isomer are distinctly broadened, or split, below −30°C, which is considered to be indicative of the two conformational isomers that rapidly interconvert at normal temperatures.

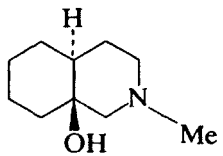
Catalytic reduction of 3,4,5,8-tetrahydroisoquinolines **517**[601] and of



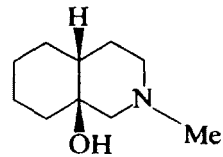
513



514

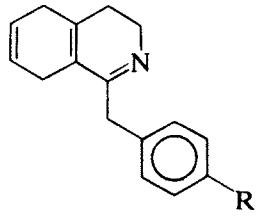


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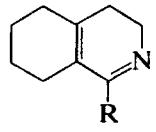


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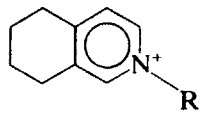
3,4,5,6,7,8-hexahydroisoquinolines **518**[602] in methanol over Raney nickel leads to the formation of $\Delta^{4a,8a}$-octahydroisoquinolines; the same system is also obtained[603] from 5,6,7,8-tetrahydroisoquinolines **519** by reduction with



517



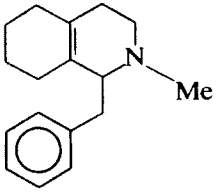
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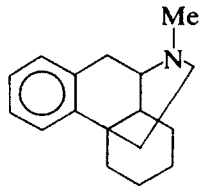
R = CH_2CN, CH_2COOMe, $CH_2CH_2NMe_2$

519

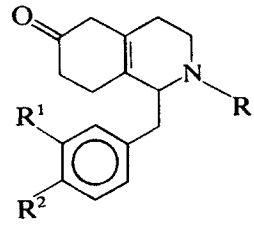
borohydride in aqueous methanol. Addition of Grignard reagents to 5,6,7,8-tetrahydroisoquinolinium salts yields 1-substituted-1,2,5,6,7,8-hexahydroisoquinolines from which the corresponding $\Delta^{4a,8a}$-octahydro derivatives, such as **520**, can be obtained by catalytic reduction.[604] Strong-acid treatment of **520** causes a cyclization to form the morphinan **521**. 6-Keto-$\Delta^{4a,8a}$-octahydroisoquinolines **522** undergo similar cyclization in acid;[605] for example, the two isomers **523** and **524** are obtained from **522** (R^1 = OH;



520

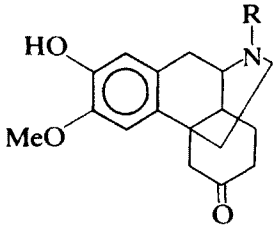


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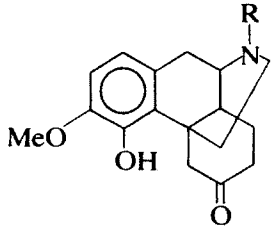


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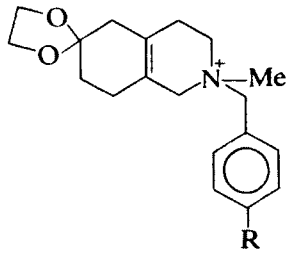
R^2 = OMe). The structures required for these Grewe cyclization reactions have been obtained by Stevens rearrangement of compounds such as **525**. In a preliminary experiment,[606] however, base treatment of the simple *N*-benzyl derivative **526** was found to produce structures **527**, **528**, and **529** in addition to the expected compound (**520**). Grewe-type cyclizations have also been reported for 1-indolylmethyl compounds **530**[607] and **531**,[608] leading to formation of **532** and its 15-one derivative **533**, respectively. Cyclization to the 4a-position also occurs[609] in the case of 1-(*o*-hydroxyphenyl)-$\Delta^{4a,8a}$-octahydroisoquinolines **534** when heated with concentrated aqueous hydrogen bromide, thus resulting in the formation of hexahydro-9,4α-iminoethano-4a*H*-xanthenes **535**.



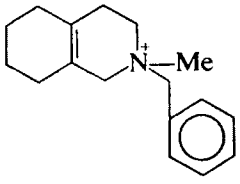
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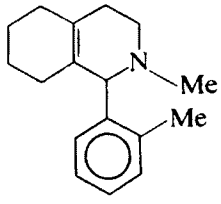
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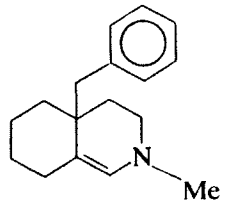
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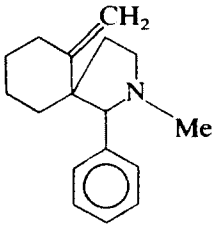
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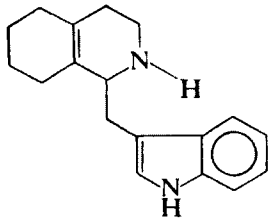
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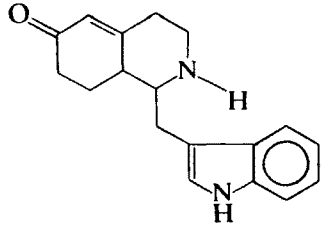
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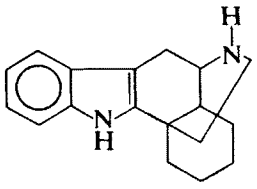
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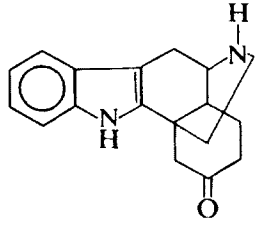
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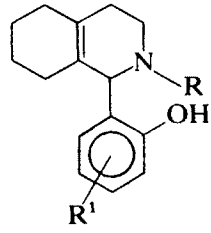
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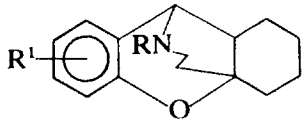
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533

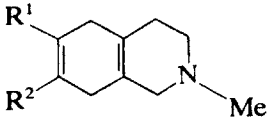


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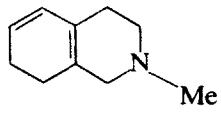


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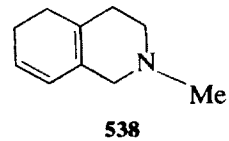
Birch reduction of 1,2,3,4-tetrahydroisoquinolines leads[269] to the 1,2,3,4,5,8-hexahydro derivatives (**536**). Treatment of **536** with potassium *t*-pentyl oxide in *t*-pentyl alcohol causes double-bond isomerizations to occur; when $R^1 = R^2 = H$, dienes **537** and **538** are formed initially, followed by conversion into **539**, **540**, and **541**, depending on the temperature and duration of the reaction. When $R^1 = OMe$; $R^2 = H$ and $R^1 = H$; $R^2 = OMe$, conjugated dienes **542** and **543** are formed in 70% yields, respectively. Diene **537** is better prepared[610] by reduction and dehydration of 6-keto-$\Delta^{4a,8a}$-octahydroisoquinoline. These conjugated dienes readily form Diels–Alder adducts with appropriate dienophiles.[611] Both endo and exo adducts have been isolated from **542** with ethyl acrylate, methylvinylketone, and acrylonitrile, and the product from the reaction with acrylate is **544**. A similar series has been prepared from the 7-methoxy diene **543**.



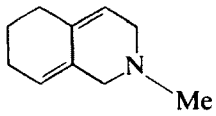
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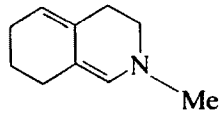
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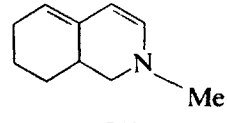
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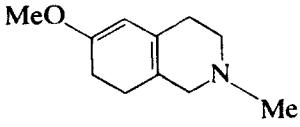
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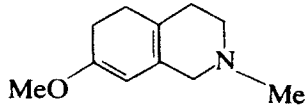
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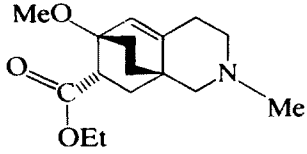
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542

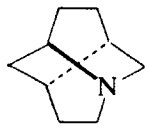


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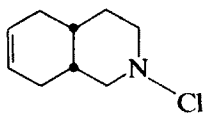


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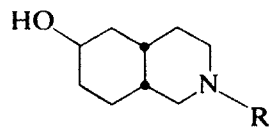
The 1-azatwistane structure **545** is obtained by linking the C-6 atom of a *cis*-decahydroisoquinoline to the nitrogen atom. This has been achieved by uv irradiation of the *N*-chloro-$\Delta^{6,7}$-octahydroisoquinoline (**546**)[612] and by heat treatment of the *O*-mesyl[613] and *O*-tosyl derivatives[614] of the 6-hydroxydecahydroisoquinoline **547**. Azatwistane formation has been emp-



545

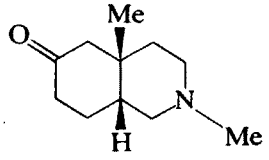


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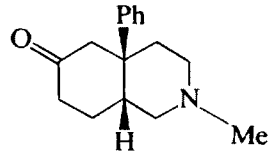


547

loyed[615] to confirm cis geometry at the ring junction following the addition of dimethyl cuprolithium to 6-keto-$\Delta^{4a,5}$-octahydroisoquinoline to give **548**. This stereospecificity of cuprolithium reagents is also demonstrated[616] by the exclusive formation of the cis isomer **549** by reaction with the diphenyl reagent.



548

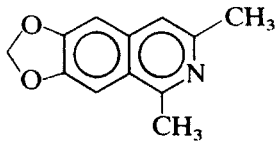


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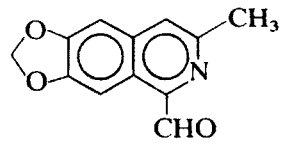
VI. NUCLEUS SUBSTITUENT INTERACTION

Recorded data concerning effects of substituent groups on the nature of the isoquinoline nucleus are sparse. Several examples are known, however, of modifications of substituent-group reactivities by interaction with the nucleus and in particular with its nitrogen atom.

Methyl groups ortho to the ring nitrogen in aromatic *N*-heterocyclic compounds possess enhanced reactivity,[617] and this might be expected in both 1-methyl and 3-methylisoquinoline, but in practice the methyl group in the 1-position is found to resemble that in α-picoline and is more reactive than the methyl group in the 3-position. Oxidation of activated methyl groups with selenium dioxide occurs with relative ease[618] and both 1-methylisoquinoline[296] and 3-methylisoquinoline[619] can be converted into the corresponding aldehydes. The oxidation of 1,3-dimethyl-6,7-methylenedioxyisoquinoline (**550**), however, gives a product considered to be 3-methyl-6,7-methylenedioxyisoquinoline-1-carboxaldehyde (**551**).[296] Both



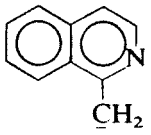
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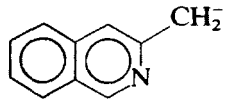
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the 1-methyl and 3-methylisoquinolines (as well as 1-methyl-3,4-dihydroisoquinoline) condense with aldehydes in the presence of zinc chloride[620,621] but higher temperatures and longer reaction times are required with the 3-isomer. Quaternization of the nitrogen atom increases the activity of both methyl groups, and condensations then occur without the catalyst.[622] In these reactions the methyl group participates in the form of a carbanion and a comparison of the resonance stabilizations of the anions **552** and **553** derived from the respective methylisoquinolines explains the observed reactivities. The major contributor to stabilization of **552** is **554**, in which the

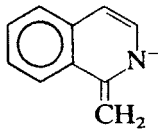
charge resides on the electronegative nitrogen atom. The corresponding species **555** from the 3-substituted anion **553** can be achieved only by



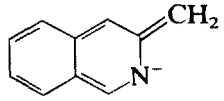
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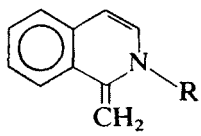


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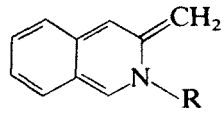


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disruption of the benzenoid aromatic system. Enhanced reactivity in the quaternary salts can be explained by the involvement of uncharged canonical forms **556** and **557**. The situation in which a methyl group acts through a radical intermediate may be treated in a similar manner; again, reactions with the 1-methyl group will be favored over those with the 3-isomer.

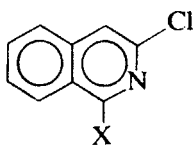


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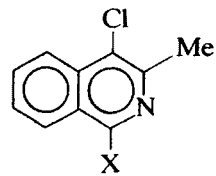


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Chloro substituents in the heteroring of isoquinoline are reactive and undergo nucleophilic substitution. This activity is associated with the reduced electron densities at these positions, coupled with the favorable loss of a stable chloride ion from the transition state. Thus the relative reactivities would presumably be 1 > 3 > 4, and this is found in practice. 1,3-Dichloroisoquinoline (**558**; X = Cl) and 1,4-dichloro-3-methylisoquinoline (**559**; X = Cl), reacted with sodium ethoxide, yield 3-chloro-1-ethoxyisoquinoline (**558**; X = OEt)[623] and 4-chloro-1-ethoxy-3-methylisoquinoline (**559**; X = OEt),[624] respectively. Removal of chlorine by treatment with red phosphorus and hydriodic acid occurs from the 1-position of 1-chloro and 1,3-dichloroisoquinoline at 170°C, but the latter compound loses its second chlorine only at temperatures in excess of 200°C.[258,623,624]



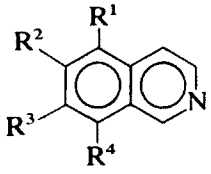
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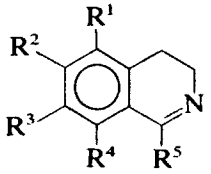
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Tautomerism in the hydroxy and amino derivatives of isoquinoline, and its effect on ionization constants (Section II.D) and on ir (Section III.A) and uv spectra (Section III.B) has been discussed in the relevant sections. The aminoisoquinolines undergo diazotization in the normal manner, but the 1-isomer gives a reactive diazonium salt that is rapidly converted to isocarbostyril in sulfuric acid[142,625] and to a mixture of isocarbostyril and 1-chloroisoquinoline in concentrated hydrochloric acid.[175] Isoquinoline 1-, 3-, 4-, and 5-diazonium fluoborates have been isolated[626] and, surprisingly, the 1- and 5-isomers were found to be the most stable.

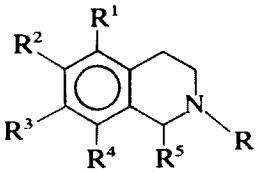
Selective demethylations of polymethoxylated isoquinolines, 3,4-dihydroisoquinolines, 1,2,3,4-tetrahydroisoquinolines, and oxocompounds have been reported. The cleavage is effected by treatment with halogen acids, and some of the results obtained are presented in Table I.15.



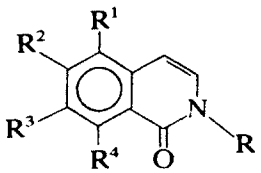
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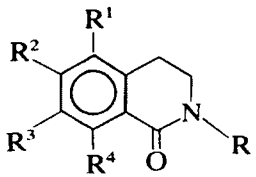
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TABLE I.15. SELECTIVE DEMETHYLATION

Structure type	R	R^1	R^2	R^3	R^4	R^5	Ref.
560	—	H	OMe	OMe[a]	H	—	627
561	—	OMe[a]	OMe	H	H	H	628
	—	OMe	H	OMe[a]	H	H	
	—	OMe[a]	H	H	OMe	H	
	—	H	OMe[a]	H	OMe	H	
	—	H	H	OMe	OMe[a]	H	
	—	H	OMe	OMe[a]	H	H	629
	—	H	OMe	OMe[a]	H	Me	627
	—	H	OMe	OMe[a]	OMe	Me	630
562	Me	H	OMe	OMe[a]	OMe	Me	631
563	H	H	OMe	OMe	OMe[a]	—	632
564	Me	H	OMe[a]	OMe	H	—	418

[a] Denotes group selectively dealkylated.

Exploitation of this process offers a useful preparative route to hydroxymethoxy-substituted structures, but the rationale for the observed selectivities is not clear, although it probably depends on a combination of electronic and steric influences. For further discussion, see Chapter V.

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CHAPTER II

Synthetic and Natural Sources of the Isoquinoline Nucleus

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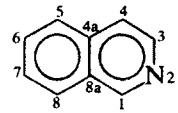
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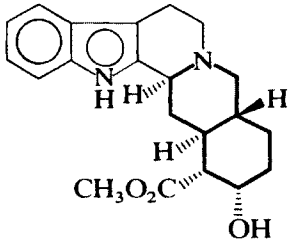
I. INTRODUCTION

Isoquinoline (**1**) was first reported in 1885 by Hoogewerff and van Dorp,[1] who isolated a small amount of this base from the crude quinoline fraction

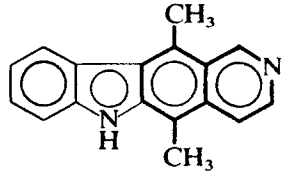


1

of coal tar. Many types of isoquinoline have been provided from three major natural sources: coal tar, petroleum, and plants. Kruber[2] reported the isolation of 1-methylisoquinoline, 3-methylisoquinoline, and 1,3-dimethylisoquinoline as well as isoquinoline from coal-tar bases. Ochiai[3] succeeded in separating a mixture of isoquinoline and quinoline obtained from coal tar by distilling the respective *N*-oxides of these compounds. Petroleum also provides isoquinoline.[4] By far the largest number of isoquinoline derivatives have been isolated from plants. These isoquinoline alkaloids[5,6] are biosynthesized from tyrosine (Chapter IV). Some alkaloids such as yohimbine (**2**) and ellipticine (**3**), which are usually classified as indole alkaloids, have an isoquinoline part in their structure, as indicated by bold lines in the formulas.



2

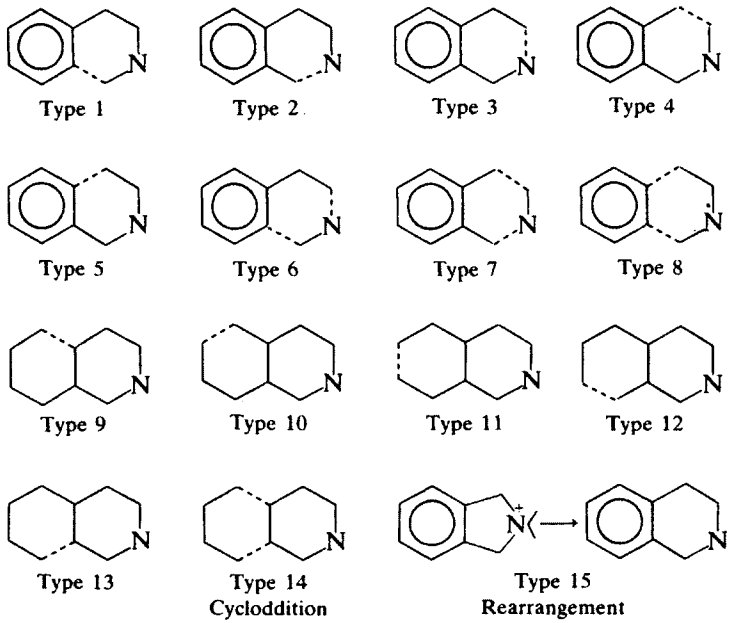


3

The frequent occurrence of the isoquinoline nucleus in alkaloids and in some physiologically active compounds has led to a considerable interest in the synthesis of isoquinolines. Moreover, the preparation of degradation products required for the structure determination of naturally occurring isoquinolines and their total synthesis, and the development of medicinal drugs containing an isoquinoline ring, have contributed to the progress in isoquinoline chemistry. The classical methods of isoquinoline synthesis are the Bischler–Napieralski reaction,[7] the Pictet–Spengler reaction,[8] and the

Pomeranz–Fritsch reaction.[9] However, recent advances in isolation techniques by chromatography and identification methods by spectroscopy as well as the development of new reagents have produced many new synthetic reactions and modification of the three classical methods.[7–9]

The syntheses of isoquinoline and derivatives can be divided systematically into 15 different types, depending on the mode of formation of the pyridine (types 1 through 8, and 15) and the nonpyridine ring (types 9 through 14) illustrated in Scheme 1, where the dotted lines indicate bonds being formed. Types 6, 8, and 14 are cycloaddition reactions developed recently.



Scheme 1

II. TYPE 1 SYNTHESES

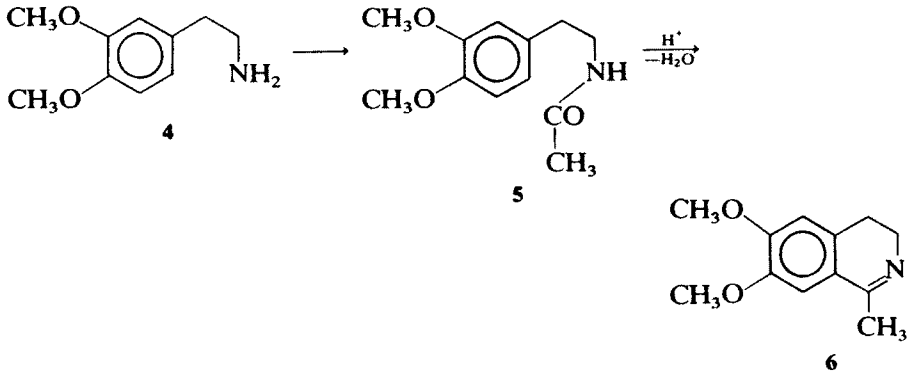
The type 1 synthesis involves ring closure between the benzene ring and the carbon atom that forms C-1 of the resulting isoquinoline ring. Into this category belong the very useful and general methods of Bischler–Napieralski and Pictet–Spengler.

A. Bischler–Napieralski Reaction and Modifications

(a) *Bischler–Napieralski Reaction*

The most valuable and frequently used method for the synthesis of isoquinoline compounds is the Bischler–Napieralski reaction,[7] which consists

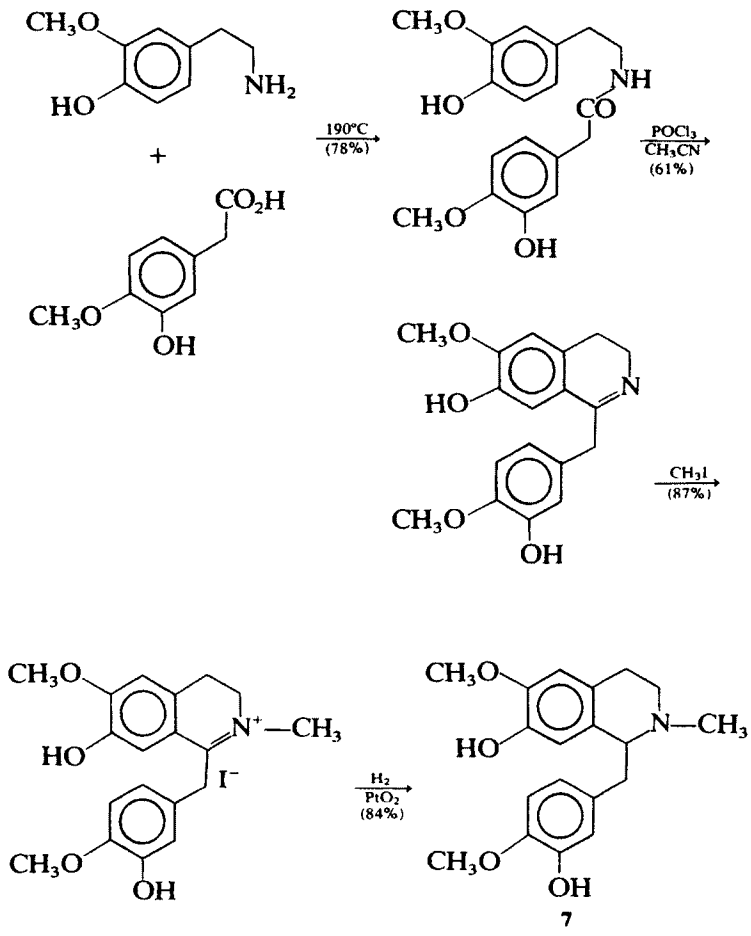
of the cyclodehydration of *N*-acyl derivatives (**5**) of β-phenethylamines (**4**) to 3,4-dihydroisoquinolines (**6**) with Lewis acids such as phosphoryl chloride or polyphosphoric acid in a dry inert solvent.



(i) GENERAL. This reaction was discovered by Bischler and Napieralski[10] in 1893, who treated β-phenethylamide with phosphorous pentoxide or zinc chloride at high temperature. Modifications of dehydrating agent and solvents permit the reaction to proceed at lower temperature, and this reaction has now become the most popular method for the synthesis of isoquinoline derivatives. It has been used very frequently in the total synthesis of isoquinoline alkaloids,[5,6] as shown in Scheme 2 for the preparation of reticuline (**7**).[11]

Since the Bischler–Napieralski reaction affords 3,4-dihydroisoquinolines, it is often necessary to reduce or dehydrogenate the product to obtain the more desired 1,2,3,4-tetrahydroisoquinoline or isoquinoline derivative, respectively. Some of the more common transformations employed for this purpose are shown in Scheme 3 for the synthesis of the alkaloids laudanosine (**11**) and papaverine (**12**). The hydrochloride of the 3,4-dihydroisoquinoline **8** can be directly reduced with sodium borohydride or by catalytic hydrogenation to give the tetrahydroisoquinoline derivative **9**.[12] If the *N*-methyl derivative **11** is desired, the Eschweiler–Clarke reaction of **9** with formalin and formic acid or formalin and sodium borohydride gives the expected *N*-methyl compound **11**.[13] Reduction of the methiodide **10** of a 3,4-dihydroisoquinoline with sodium borohydride to **11** is also advisable. Mild dehydrogenation of the 3,4-dihydroisoquinoline **8** yields the aromatized isoquinoline **12**.[14]

Recently, optically active 1,2,3,4-tetrahydroisoquinolines have been synthesized by an asymmetric reduction of 3,4-dihydroisoquinolines (Scheme 4). Amides **13** derived from optically active phenethylamines were cyclized with phosphoryl chloride in dry toluene to give the 3,4-dihydroisoquinolines **14**. Reduction of **14a,b** with sodium borohydride and subsequent hydrogenolysis of the resulting tetrahydroisoquinolines (**15a,b**) over 10% palladium hydroxide on charcoal afforded optically active salsolidine

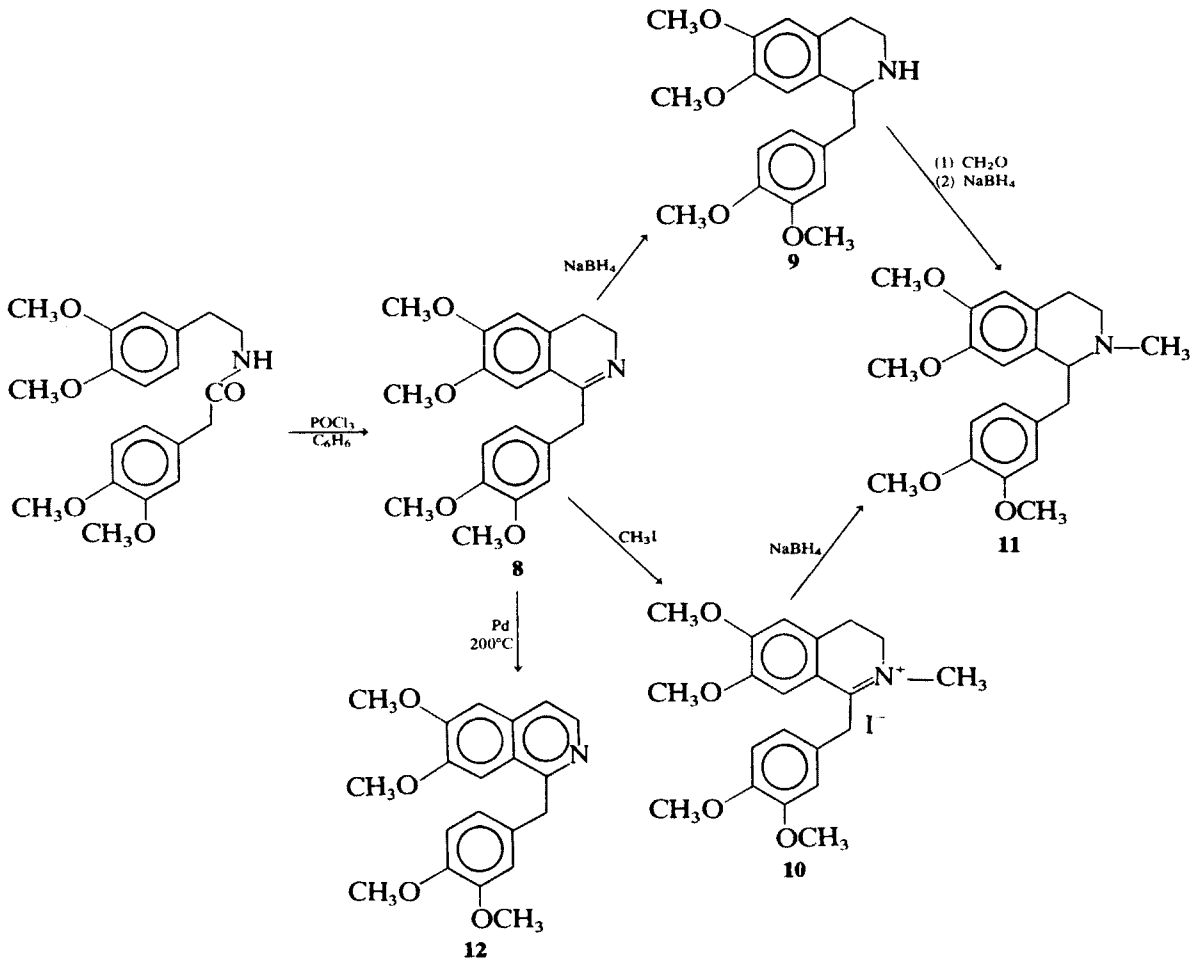


Scheme 2

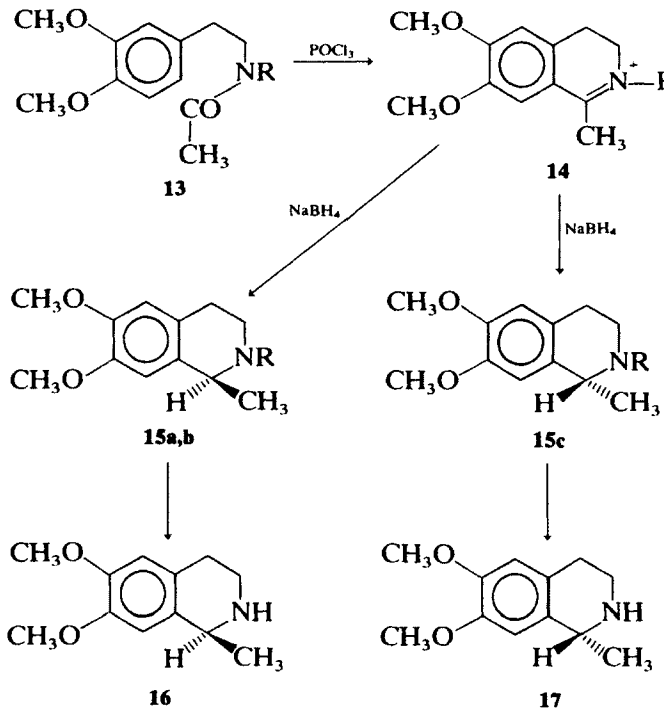
(**16**). Analogously, amide **13c**, prepared from (+)-(*R*)-phenethylamine yielded the *R*-enantiomer **17** of salsolidine. The optical purities ranged from 15 to 44%.[15] A chiral rhodium complex with (+)-diop [(+)-2,3-O-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane] as ligand has been used as a catalyst in the asymmetric synthesis of salsolidine (**16**).[16]

Recently, Stang proposed a mechanism for the Bischler–Napieralski reaction, which proceeds through the intermediacy of a nitrogen-stabilized vinyl cation as shown in Scheme 5. The vinyl cation has been trapped as a stable crystalline SbF_6 salt and shown to subsequently ring close to the 3,4-dihydroisoquinoline in solution.[17]

Similarly, the phosphate intermediate in a Bischler–Napieralski-type cyclization of carbamate has been isolated and converted into isocarbostyril by treatment with boron trifluoride etherate in boiling benzene. (Eq. 1).[18]


CH3O
CH3O
NH
CO
CH3O
CH3O
POCl3
C6H6
NaBH4
(1) CH2O
(2) NaBH4
CH3I
Pd
200°C
N
N+—CH3
I−
OCH3
8
9
10
11
12

Scheme 3



a, R = (S)-(−)—CH(CH3)—C6H5

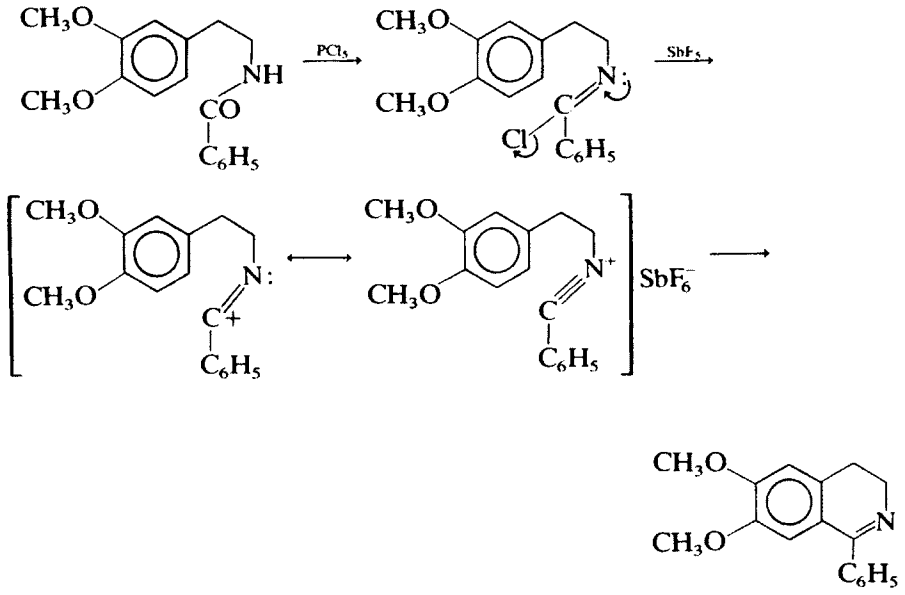
b, R = (S)-(−)—CH(C2H5)—C6H5

c, R = (R)-(+)—CH(CH3)—C6H5

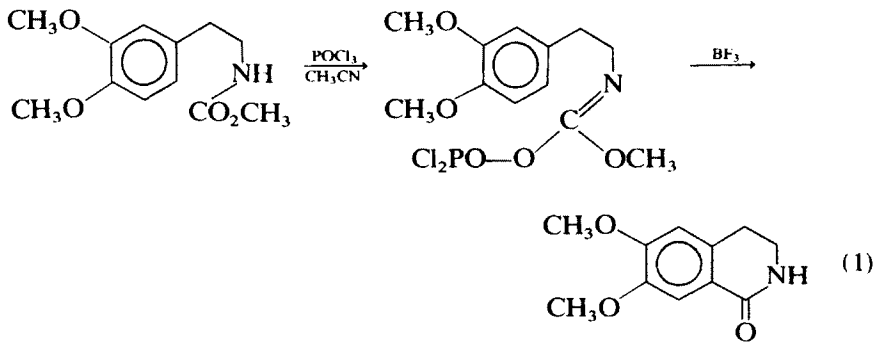
Scheme 4

(ii) Reaction Conditions. The Bischler–Napieralski reaction is usually carried out by heating the appropriate amide with a dehydrating agent in the presence of an inert and dry solvent. The selection of the solvent is determined on the basis of the desired reflux temperature; solvents frequently used are chloroform, benzene, toluene, xylene, nitrobenzene, or tetralin. Sometimes the cyclization is conducted in the presence of an excess of phosphoryl chloride without solvent. Recently, acetonitrile[11] has been used in this cyclization. The reaction proceeds under mild conditions to give higher yields than with other solvents (Eq. 2).[19]

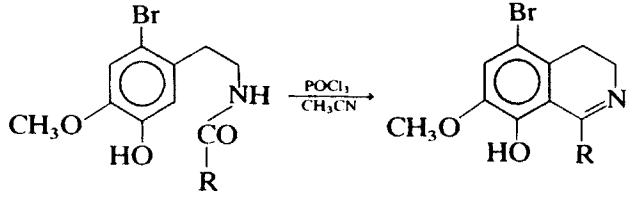
Phosphoryl chloride is the most popular dehydrating agent (Eq. 3),[20] but phosphorus pentoxide and phosphorus pentachloride are also important in specific cases, such as in the synthesis of 1-(2-nitrobenzyl)-3,4-dihydroisoquinolines (Eq. 4).[21] Furthermore, various reagents such as polyphosphoric acid (Eq. 5)[22] and its ester (Eq. 4)[23,24] have been found



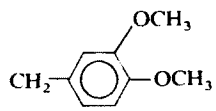
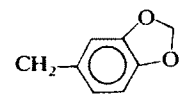
Scheme 5

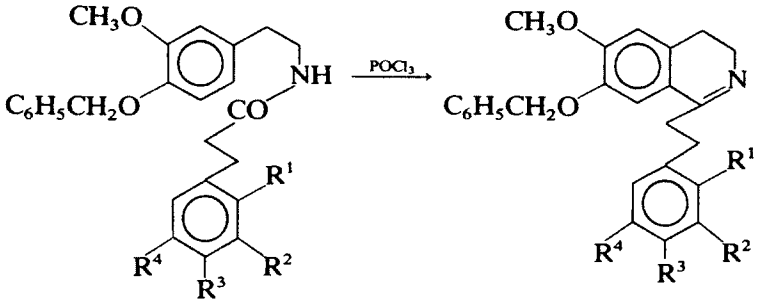


(1)



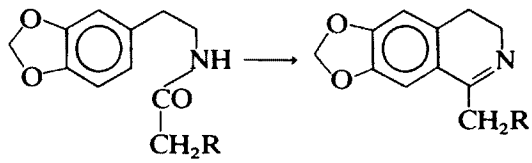
(2)

R		
Yield (%)	89	86

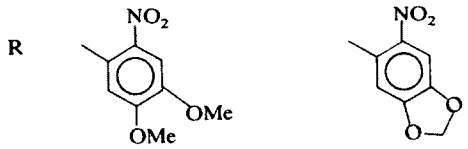


(3)

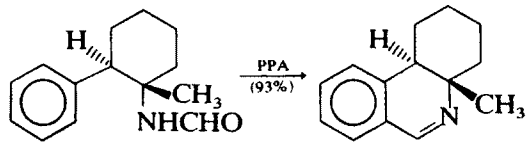
R^1	R^2	R^3	R^4	Yield (%)
H	H	$OCOC_2H_5$	H	96
H	OCH_3	OCH_3	$OCOC_2H_5$	96
H	OCH_3	$OCOC_2H_5$	H	94
H	OCH_3	$OCOC_2H_5$	OCH_3	86
OCH_3	H	$OCOC_2H_5$	H	93



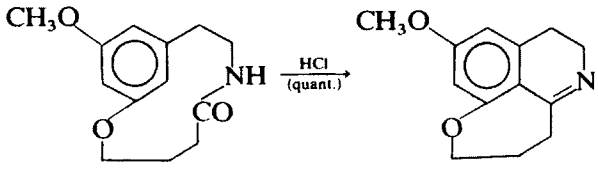
(4)



Reagent	PCl_5	PPE
Yield (%)	53	57



(5)

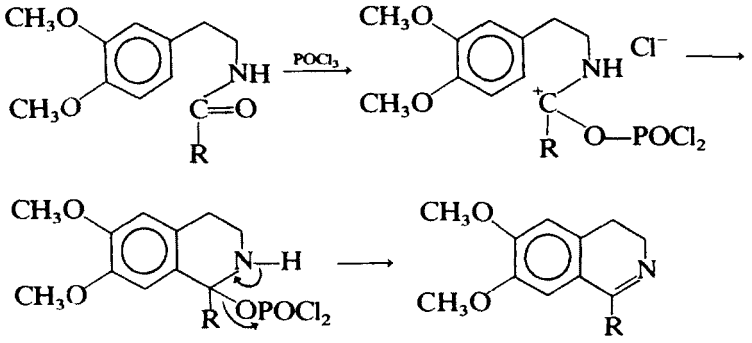


18 **19**

(6)

useful. In a special case aluminum chloride was used,[25] and Yonemitsu et al.[26] employed hydrochloric acid as the dehydrating agent for the preparation of **19** from the cyclic amide **18** (Eq. 6).

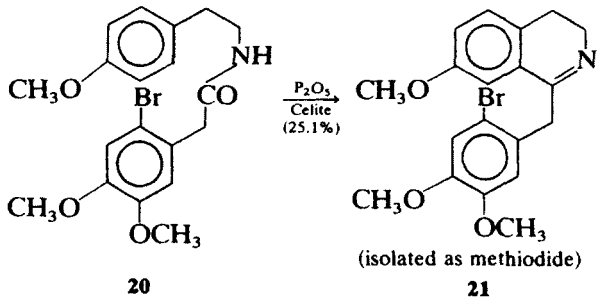
(iii) SUBSTITUENT INFLUENCE. The mechanism of the Bischler–Napieralski reaction probably involves an electrophilic attack by the amide carbonyl carbon atom ortho to the aminoethyl residue (Eq. 7). Therefore, the success of the action depends on the electron density at the benzenoid carbon



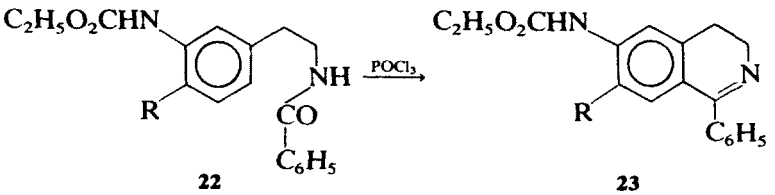
(7)

undergoing cyclization. Hence the nature and position of substituents in the aromatic ring have a profound effect on the cyclization. Whereas β-phenethylamines with an alkoxyl group in meta position cyclize very easily, the para-substituted derivative **20** gives **21** only with great difficulty. For example, 3,4-dihydroisoquinoline was obtained from **20** in poor yield only following the use of phosphorus pentoxide absorbed on Celite.[27] Electron-releasing groups other than alkoxyl groups in meta position also have a beneficiary effect on the cyclization[28] (**22** → **23**), whereas the yields decrease considerably in the absence of any activating group. This was demonstrated by the high yields obtained in the preparation of 3,4-dihydro-6,7-methylenedioxyisoquinoline as compared to 3,4-dihydro-1-methyl-isoquinoline under identical conditions.[29] Obviously, electron-attracting groups such as a nitro group will inhibit the cyclization.

The nature of the acyl residue has only a minor influence on the ease of cyclization, and aryl- and aralkylamides have been successfully employed in cyclization reactions, but the yields of 1-alkylisoquinolines or isoquinolines unsubstituted at C-1 tend to be somewhat lower under similar conditions. The influence of substituents in the ethylamine side chain is usually significant. Isoquinolines having alkyl, aralkyl, or aryl groups at C-3 have generally been obtained in lower yields than have the 3-unsubstituted isoquinolines (Eq. 8).[29] All attempts to cyclize the *N*-acetylacylamine **24** to the corresponding isoquinoline **27** have failed; only the oxazole **26** was obtained.[30] However, the ethylene ketal of ω-benzamidoacetoveratrone **25** was cyclized with phosphorus pentoxide in pyridine to the corresponding 3,4-dihydroisoquinoline (Eq. 9)[31]



20 **21**



22 **23**

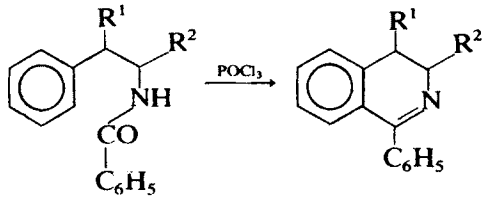
R	H	OCH_3
Yield (%)	85	85

Cyclization of *m*-methoxy-β-phenethylamide would be expected to give either 6-methoxy- (**30**) or 8-methoxy-3,4-dihydroisoquinoline (**29**), depending on the direction of ring closure. When the position para to the methoxy group is unsubstituted, cyclization preferentially occurs at this position to give the 6-methoxyisoquinoline derivatives **30**.[32] When the para position is blocked, cyclization will take place ortho to the methoxyl group. For example, *N*-acetyl-2,5-dimethoxyphenethylamine (**31**) was readily converted to 3,4-dihydro-5,8-dimethoxy-1-methylisoquinoline (**32**).[33]

In an attempt to synthesize a berberine, the formamide **33** was treated with phosphoryl chloride to yield the bromine-free compound **35** rather than the expected bromodihydroberberine **36**. This result is a remarkable example for the preferred direction of the ring closure, with a bromine atom removed to allow cyclization to proceed at the position para to the electron releasing group.[34] However, Tani et al.[35] achieved cyclization of the formamide **34** to the expected bromodihydroprotoberberine **37**. This route provides a useful method for the total synthesis of 9,10-disubstituted protoberberine alkaloids.

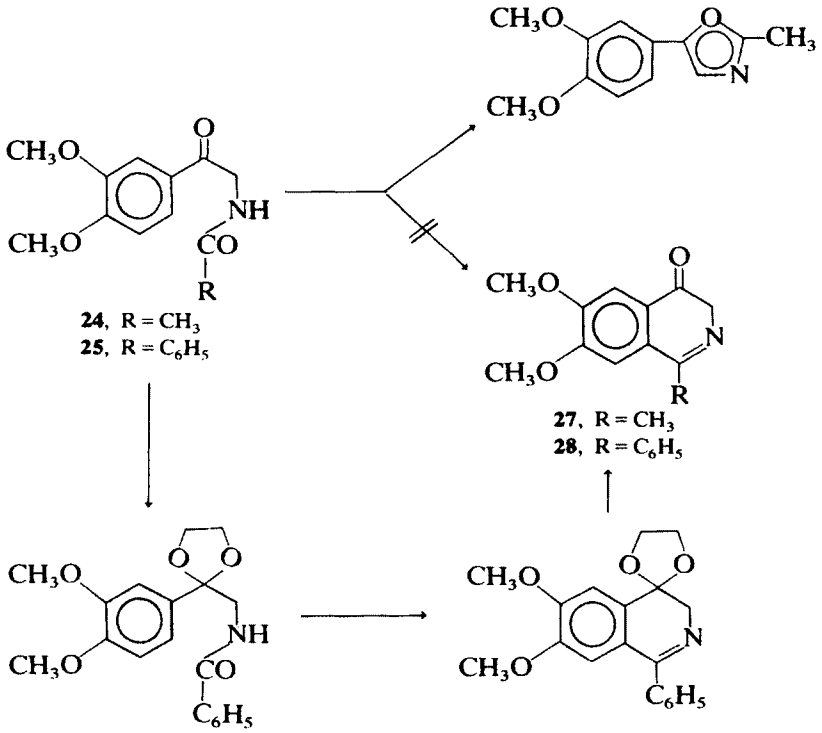
In general, the synthesis of 7,8-disubstituted 3,4-dihydroisoquinolines by the Bischler–Napieralski reaction has been very difficult. Recently, the 8-oxygenated isoquinoline derivative **39** was obtained by cyclization of *trans*-*N*-[2-(3-methyoxyphenyl)-cyclohexyl]benzamide (**38**), but the main product was the 6-methoxyisoquinoline derivative **40**.[36]

A regiospecific synthesis of 7,8-disubstituted 3,4-dihydroisoquinolines by the Bischler–Napieralski reaction has been developed by Kametani[20,37] on



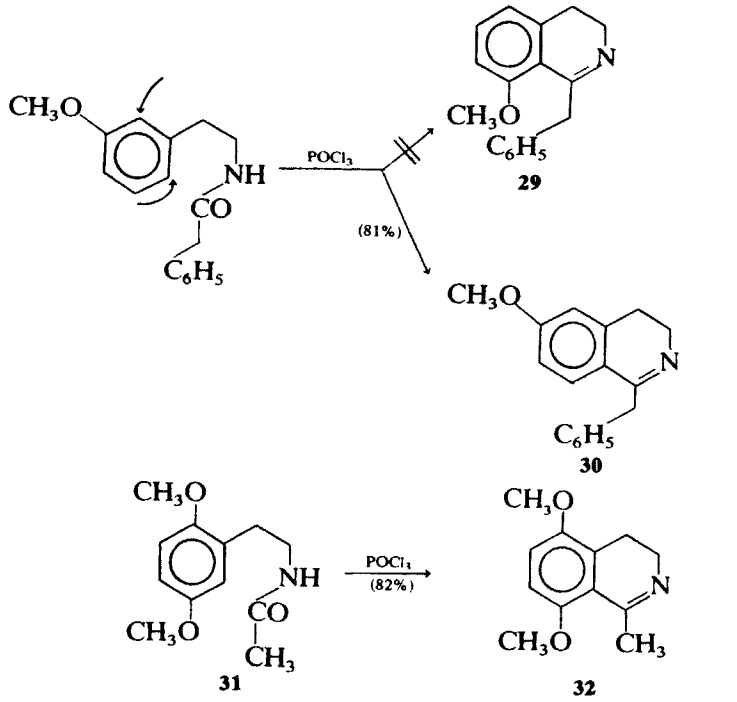
(8)

R^1	H	H	H	H	CH_3	C_6H_5
R^2	H	CH_3	$CH_2C_6H_5$	C_6H_5	H	H
Yield (%)	26	35	11	0	45	53



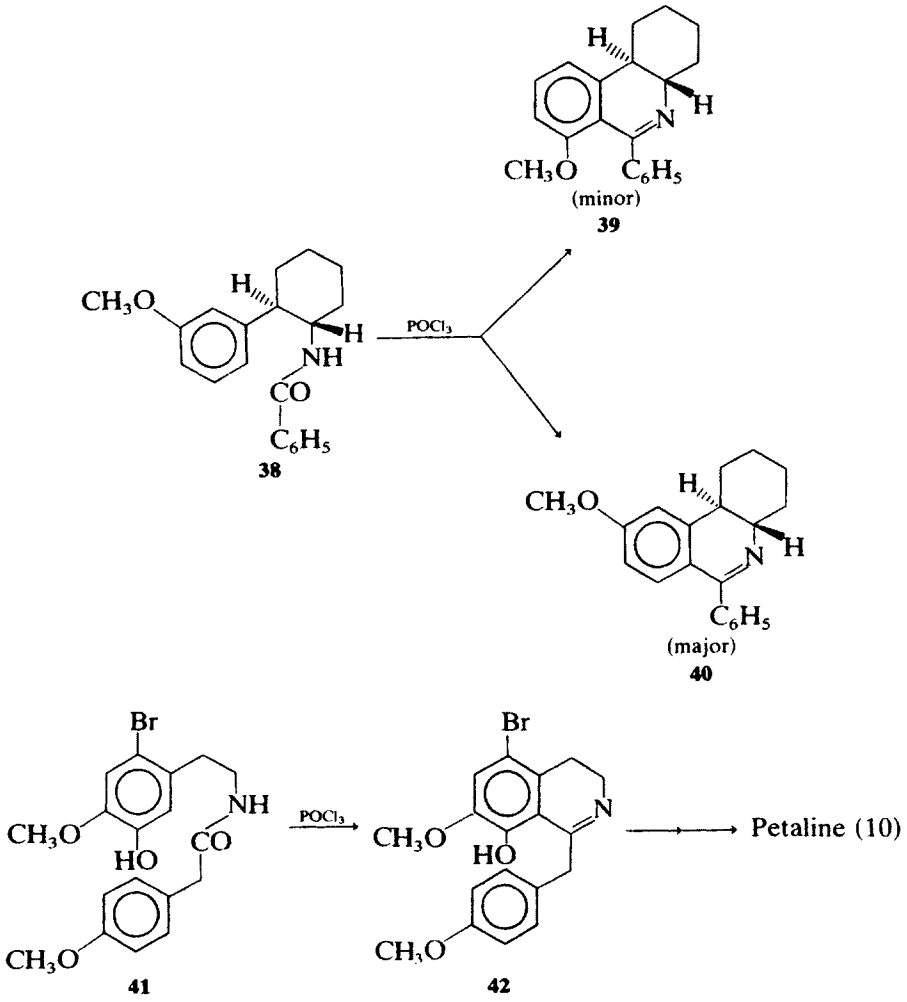
(9)

the assumption that the replacement of methoxyl by hydroxyl would offset the inactivation of the nucleus caused by the *I* effect of the bromine atom, thus leading to cyclization ortho to the hydroxyl group. Thus *N*-(2-bromo-5-hydroxy-4-methoxyphenethyl)-4-methoxyphenylacetamide (**41**) by the action of phosphoryl chloride in chloroform gave the 5-bromo-3,4-dihydro-8-hydroxy-7-methoxyisoquinoline derivative **42**, which was converted into petaline by standard methods (Eq. 10).[37] Iida and his co-workers[38] synthesized many 7,8-dioxygenated isoquinolines by this method.



33, R^1, $R^2 = CH_2$; $R^3 = R^4 = CH_3$
34, $R^1 = CH_2C_6H_5$; $R^2 = CH_3$; R^3, $R^4 = CH_2$

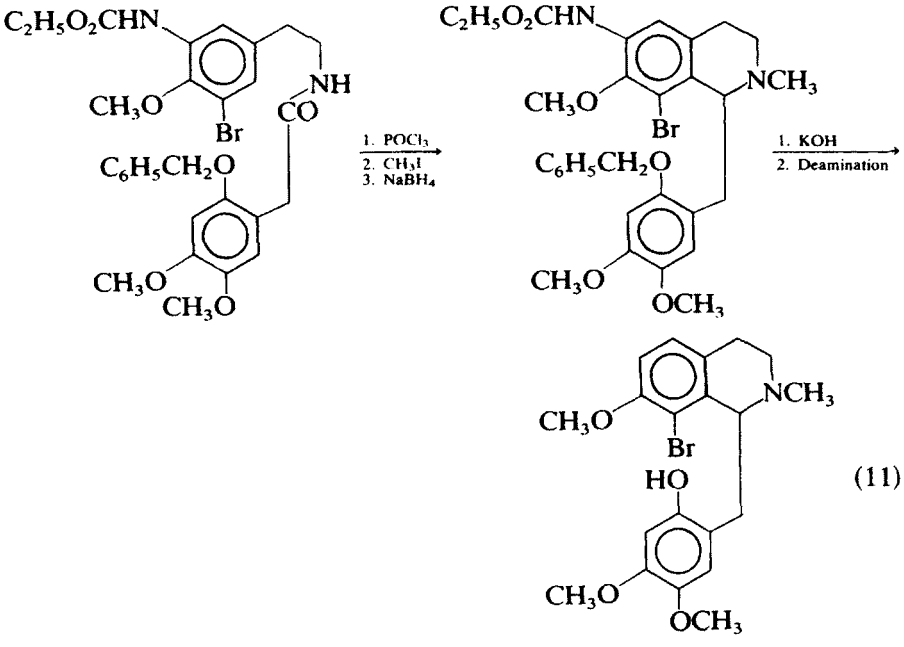
36, R^1, $R^2 = CH_2$; $R^3 = R^4 = CH_3$
37, $R^1 = CH_2C_6H_5$; $R^2 = CH_2$; R^3, $R^4 = CH_2$



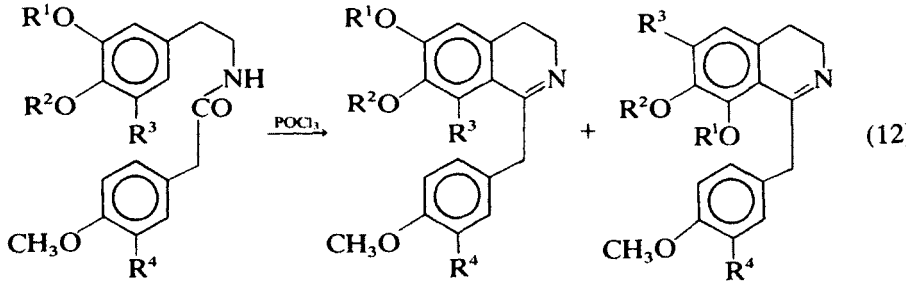
Taking advantage of the fact that the ethoxycarbonylamino group promotes the Bischler–Napieralski reaction and can easily be hydrolyzed to an amino group, which, in turn, can be diazotized and removed, Ishiwata et al.[39] developed a new synthesis of 7,8-disubstituted isoquinolines (Eq. 11). Although this method lacks regioselectivity, it served to accomplish a total synthesis of cularine, for example.[40]

An interesting example in respect to the direction of the ring closure was observed in the cyclization of amides derived from 3,4-dialkoxy-5-bromophenethylamines.[41–44] Treatment of the amide with phosphoryl chloride gave the sterically less favored 8-bromoisoquinoline.

If both available positions are activated to a similar extent in a trisubstituted phenethylamine, a mixture of the two possible cyclization products is obtained, as in the cyclization of **43**[45] and **44**[39] (Eq. 12).



(11)



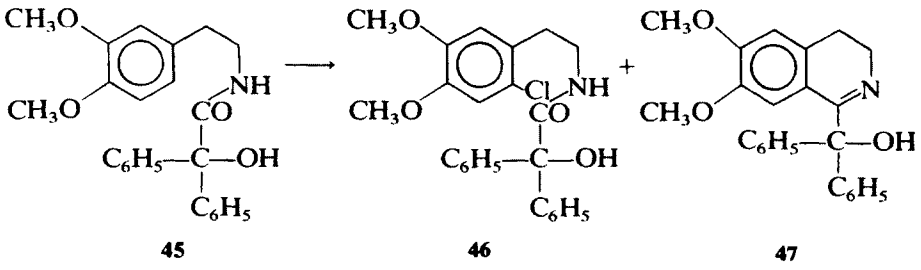
(12)

43, R^1, $R^2 = CH_2$; $R^3 = OCH_3$; $R^4 = OCH_2C_6H_5$
44, $R^1 = R^2 = CH_3$; $R^3 = NHCO_2C_2H_5$; $R^4 = H$

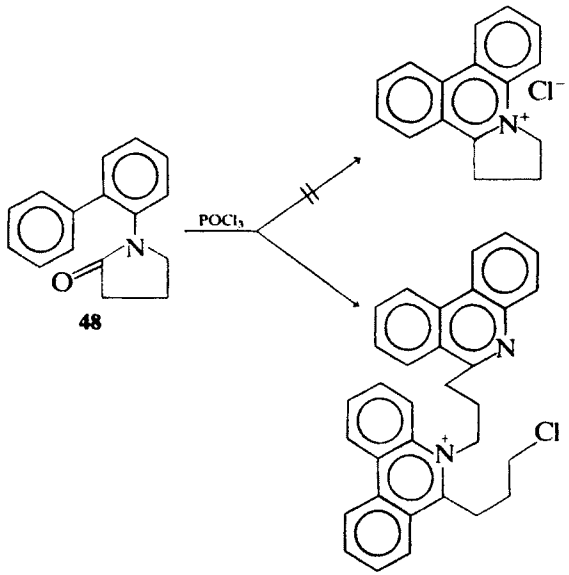
(iv) SIDE REACTIONS. In some Bischler–Napieralski reactions unexpected compounds are formed in addition to the cyclization products. Treatment of an amide **45** with phosphoryl chloride gave a mixture of the chlorinated product **46** and the 3,4-dihydroisoquinoline **47**.[46] Nagarajan and Shah[47] reported the isolation of an abnormal product from the attempted cyclization of **48**.

The amide **41** in which the aromatic ring is deactivated by a bromine atom has been found to undergo dehydration and cyclization, thus affording a mixture of the ketenimine **49** and small amounts of the 3,4-dihydroisoquinoline **42**.[37] Both were isolated as their respective reduction products.

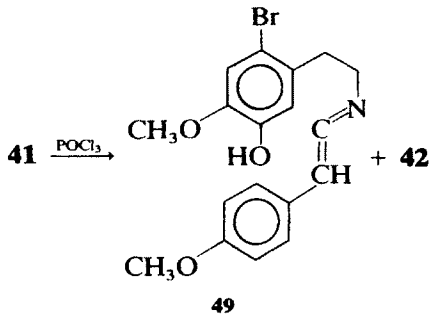
Although 1-alkyl- and 1-phenethyl-3,4-dihydroisoquinolines are stable in air, some 1-benzyl-3,4-dihydroisoquinolines tend to undergo air oxidation



45 46 47



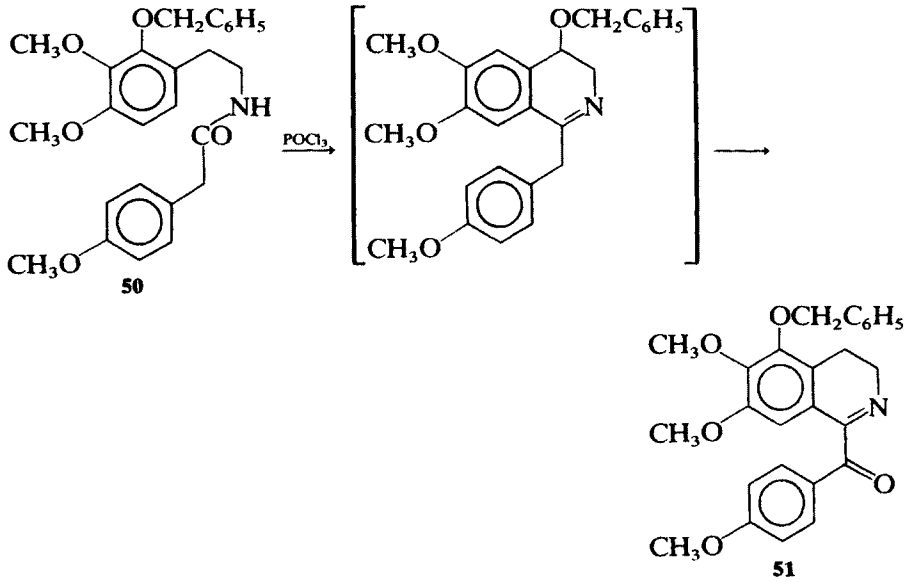
48



49

to 1-benzoyl-3,4-dihydroisoquinolines in neutral or alkaline solution, but usually not in acidic media. However, in the Bischler–Napieralski reaction of amide **50**, the oxidized product **51** was the only one isolated.[48] This type of oxidation occurs easily in the synthesis of 5-alkoxyisoquinolines.

Interesting phenomena were observed in the cyclization reaction of *N*-phenethylbenzocyclobutenecarboxamides. The hydrochloride of the product



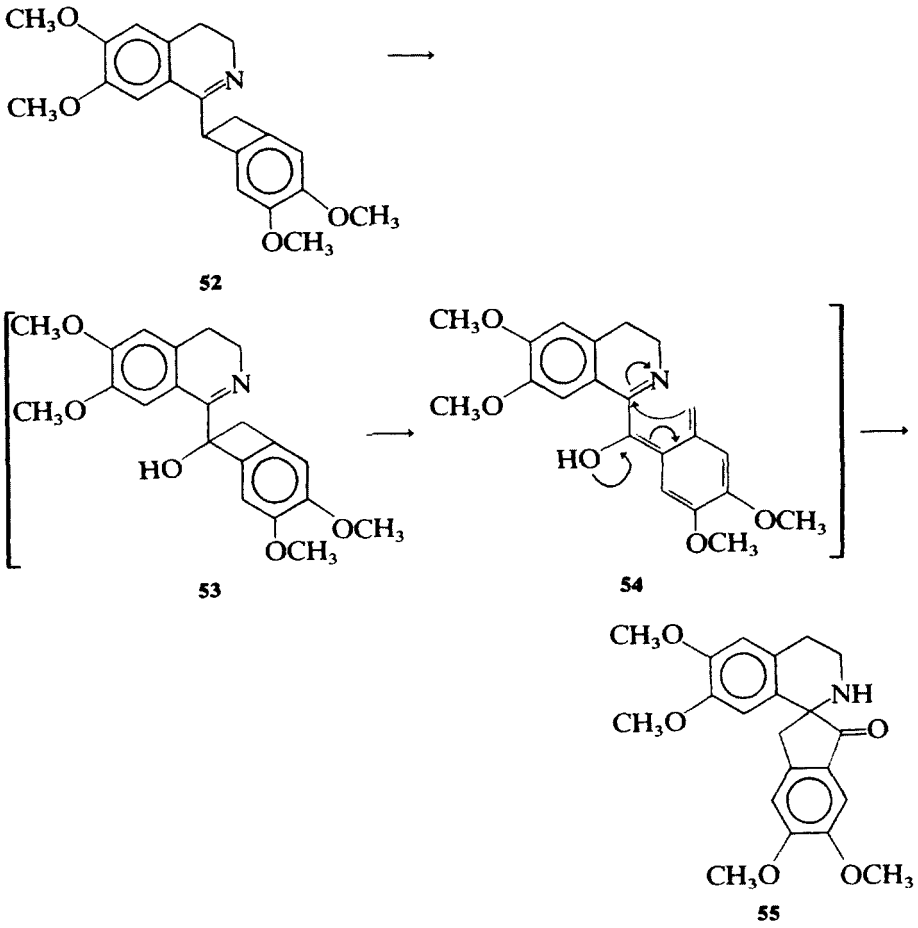
50 51

52 was stable at room temperature, but the free base again was unstable in air. A chloroform solution of **52** on standing at room temperature for 2 or 3 days was transformed, in good yield, into the ketospirobenzylisoquinoline **55**. The mechanism of this reaction can be explained by air oxidation of the benzocyclobutene **52** to the benzocyclobutenol **53**, followed by ring opening to the *o*-quinodimethane **54** and cyclization to give **55**.[49]

Moreover, the Bischler–Napieralski reaction of 1-methylbenzocyclobutene-1-carboxamide (**56**) with two molar equivalents of phosphoryl chloride did not yield the 3,4-dihydroisoquinoline **57** but afforded instead the spiroisoquinoline **60**. Probably, the 3,4-dihydroisoquinolinium salt **57** was initially formed but rearranged thermally by way of the *o*-quinodimethane **58** and the spiro compound **59** to the ochotensine-type compound **60** (Scheme 6).[50,51]

If the formation of the 3,4-dihydroisoquinoline in the Bischler–Napieralski reaction is prohibited because of a violation of Bredt's rule, a 1,2,3,4-tetrahydroisoquinoline containing a functional group at C-1 is obtained (Eq. 13).[52]

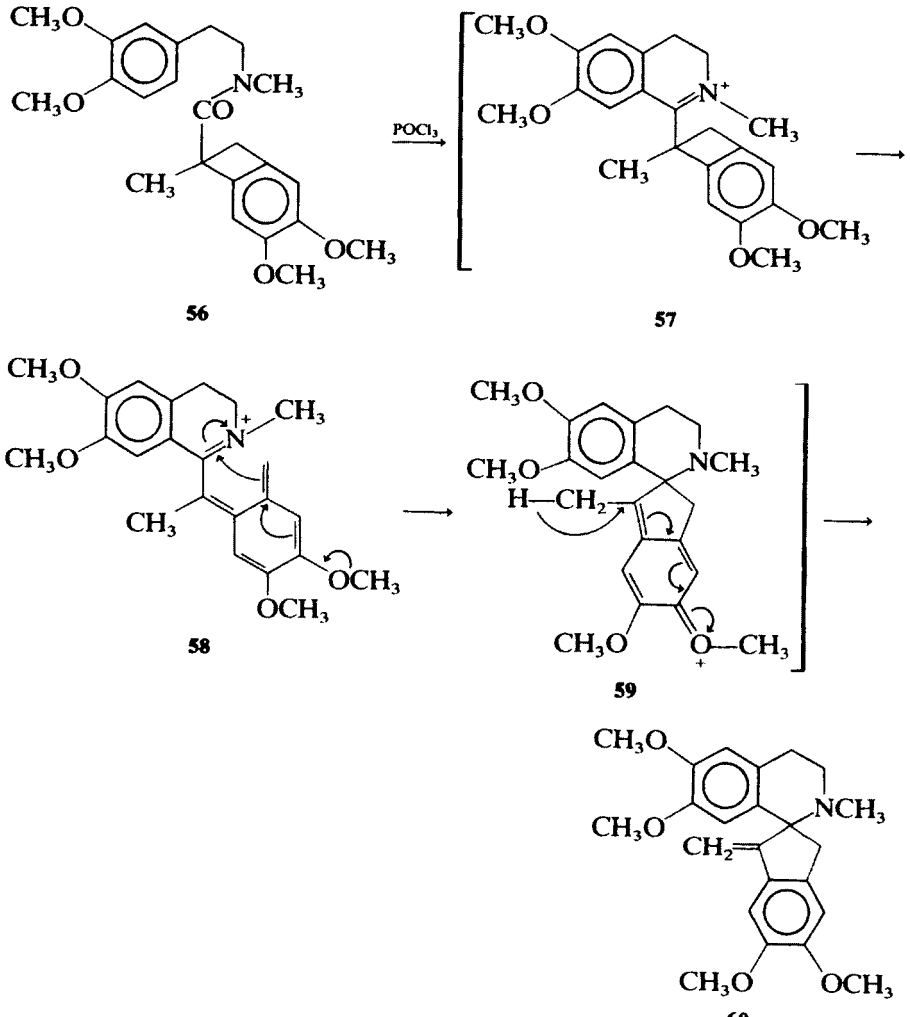
(v) Special Applications. The Bischler–Napieralski reaction has also been used for the preparation of octahydroisoquinolines from cyclohexenylamines (Eq. 14).[53] *N*-Phenethylpiperidones **61** are easily cyclized in the Bischler–Napieralski reaction to give the corresponding benzoquinolizidine derivatives **62**.[54] This method has been widely used for the synthesis of emetine and related alkaloids.[5,6] *N*-Phenethylpyridone such as **63** cannot be cyclized to the corresponding isoquinoline and gives instead the α-chloropyridine derivative **65**,[55] but the pyridone **64** having a carboxyl group at C-5 does



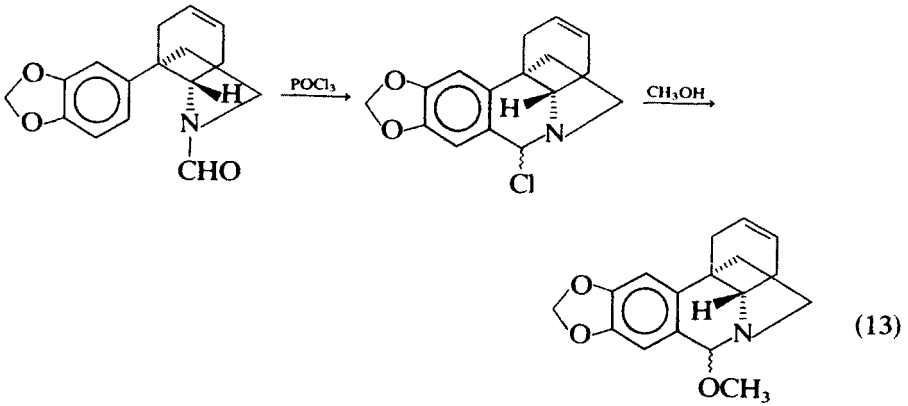
cyclize to afford the benzoquinolizidine **66**.[56] The successful Bischler–Napieralski reaction of certain *N*-phenethylimides has been achieved (Eq. 15),[57,58] but failures have also been reported.[59]

N-β-Phenylethylurea[7] and urethane derivatives[60] are useful for the synthesis of 3,4-dihydroisoquinolines having an amino or hydroxyl group at C-1. For example, urethane **67** yields the 3,4-dihydro-6,7,8-trimethoxyisocarbostyril (**68**), which is converted into anhalamine (**69**).[61] Torssell[62] reported a synthesis of the lycorane system (**71**) from a urethane precursor (**70**). A new modification of this cyclization has been reported by Tsuda et al.[63] The two-step treatment of the urethane **72** with phosphoryl chloride followed by stannic chloride gave the isocarbostyril **73** in better yields than previously obtained by polyphosphoric acid cyclization.[64] This method was conveniently applied to the preparation of hindered urethanes with complex structures.[63]

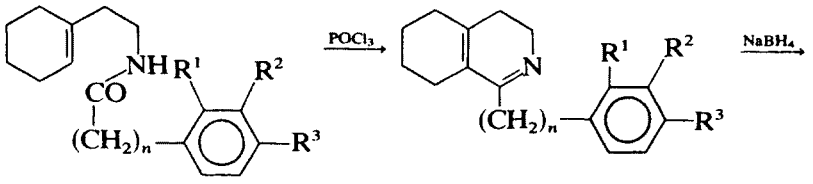
In some cases the amidine instead of the amide is used for the cyclization

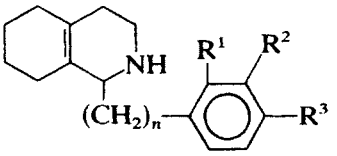


Scheme 6



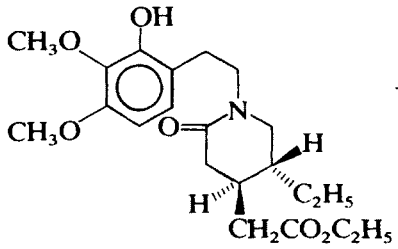
(13)



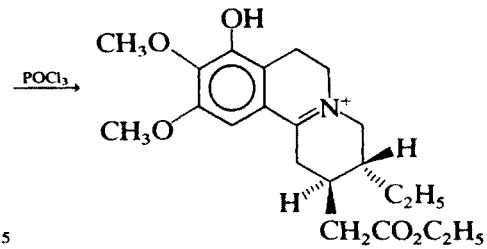


(14)

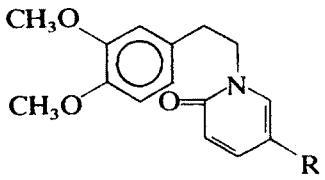
n	R^1	R^2	R^3	Yield (%)
1	OCH_3	H	H	30
2	H	H	H	54
2	H	OCH_3	H	42
2	H	OCH_3	OCH_3	51



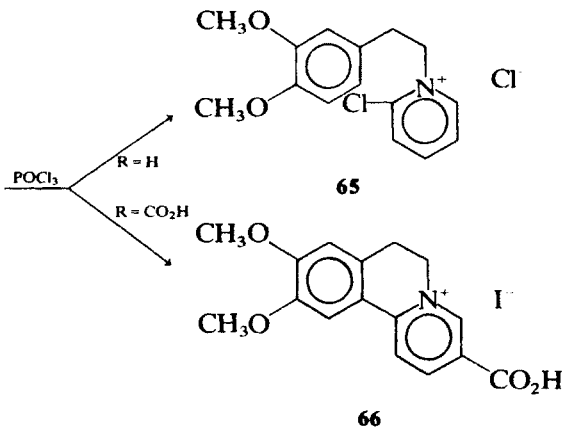
61



62

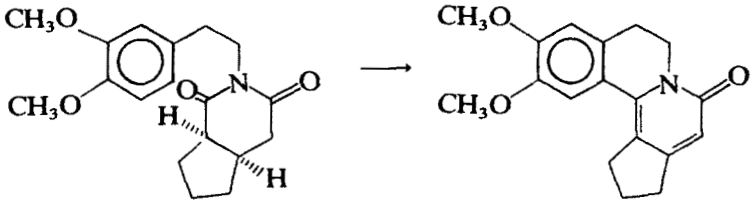


63, R = H
64, R = CO_2H

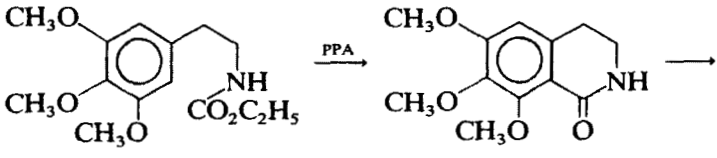


65

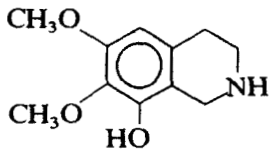
66



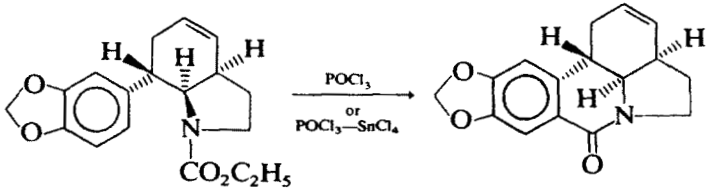
(15)



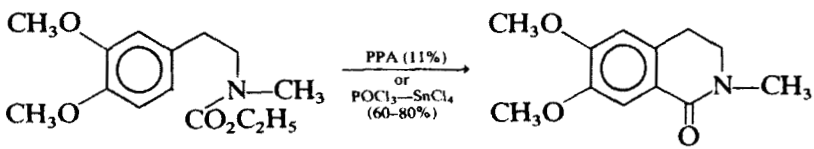
67 68



69

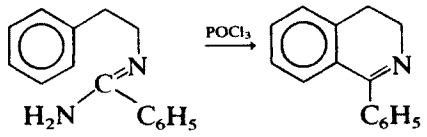


70 71

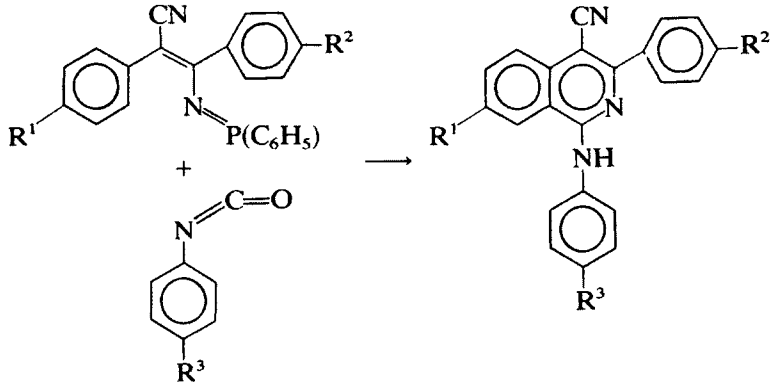


72 73

to give the isoquinoline derivatives in good yields.[7,65] Short and Brodrick[66] synthesized 3,4-dihydro-1-phenylisoquinoline by treatment of the corresponding amidine with phosphoryl chloride (Eq. 16). Phosphine *N*-(β-cyano-β-arylstyryl)imides afforded 3-aryl-1-arylaminoisoquinolines when treated with aryl isocyanates (Eq. 17).[67] The latter two methods lack generality to be of value for the synthesis of isoquinoline derivatives.



(16)

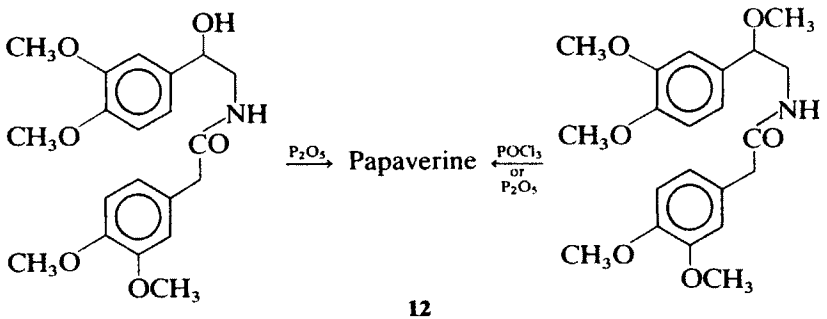


(17)

R^1	H	Cl	H	H
R^2	H	H	H	CH_3
R^3	H	H	Cl	H
Yield (%)	19	13	31	18

(b) *Pictet–Gams Reaction*

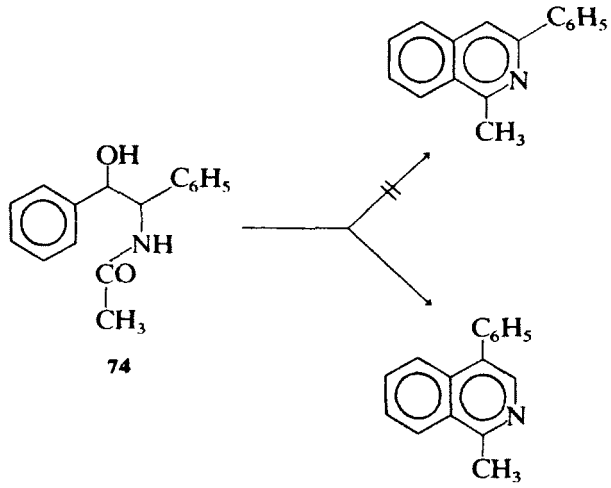
One of the most important modifications of the Bischler–Napieralski reaction was introduced by Pictet and Gams.[68] Cyclization of β-hydroxy- or β-methoxy-β-phenethylamides with Lewis acids[69] gives the isoquinoline derivatives instead of the 3,4-dihydro compounds, as shown for the synthesis of papaverine (**12**) (Eq. 18).[68,69]



(18)

12

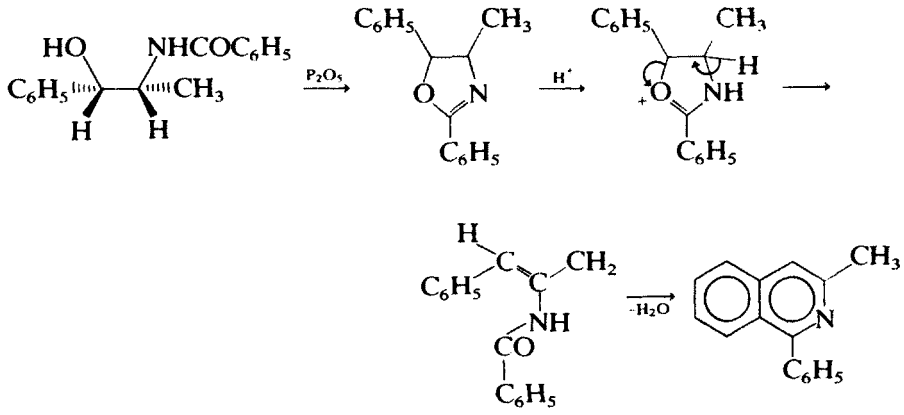
Many examples[70] have been reported for obtaining papaverine-type compounds by using this modification of the Bischler–Napieralski reaction. An Indian group[71] reported an aryl migration during the Pictet–Gams reaction of β-hydroxy-β-phenethyl-α-phenylamide (**74**). This result suggests that this reaction should only be used for the synthesis of isoquinolines without substituents at C-3 and C-4.



74

The mechanism of the Pictet–Gams reaction is shown in Scheme 7. *N*-Acyl derivatives of β-hydroxyphenethylamines cyclize either to oxazolines or isoquinolines, and since oxazolines are readily converted into isoquinolines, their intermediacy in the Pictet–Gams reaction has been postulated.[72]

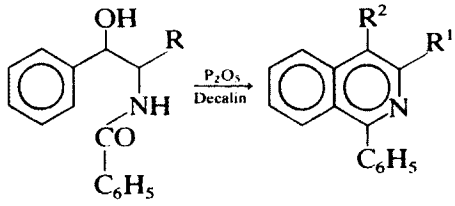
The oxazoline has also been reported[73] to be the intermediate in this reaction, and the ring closure of 2-benzamido-1-phenyl-1-propanol takes



Scheme 7

place only when the amide is heated with phosphorus pentoxide at the higher temperature of boiling decalin.

In 1977 Aldabilchi et al.[74] described the formation of rearranged isoquinolines when the amides were cyclized with phosphorus pentoxide and boiling decalin. While the amides (R = Me, Et) gave the normal 3-substituted isoquinolines, the third amide (R = *n*-Pr) yielded a mixture of the 3- and 4-substituted ones. Moreover, the other amides (R = *n*-Bu, Ph, Ch_2Ph) gave only the 4-substituted isoquinolines (Scheme 8). When



Starting Material, R	Product R^1	Product R^2
CH_3	CH_3	H
C_2H_5	C_2H_5	H
n-C_3H_7	*n*-C_3H_7	H
	H	*n*-C_3H_7
n-C_4H_9	H	*n*-C_4H_9
C_6H_5	H	C_6H_5
$C_6H_5CH_2$	H	$C_6H_5CH_2$

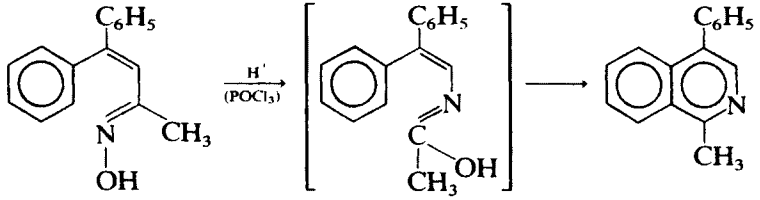
Scheme 8

milder cyclization conditions were used,[72] oxazolines were the main products, which on treatment with phosphorus pentoxide in boiling decalin yielded the corresponding 3-, 3- and 4-, and 4-substituted isoquinolines. The 3-substituted isoquinolines were shown not to rearrange in the preceding reaction conditions, and these results provide further support for the theory of oxazoline intermediacy in the Pictet–Gams reaction.

(c) *Beckmann Rearrangement and Related Reactions*

Oximes that can form *N*-acyl-β-phenethylamides by Beckmann rearrangement are also useful starting materials for the Bischler–Napieralski reaction. These oximes are converted directly into the corresponding isoquinolines or 3,4-dihydroisoquinolines without isolation of the intermediate amides (Eq. 19).[75]

The benzenesulfonyl ester of an oxime undergoes cyclization to the

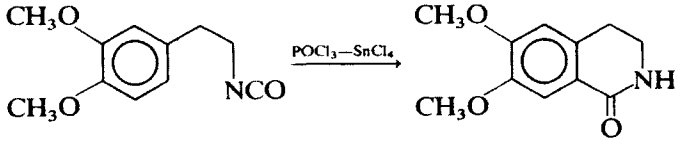


(19)

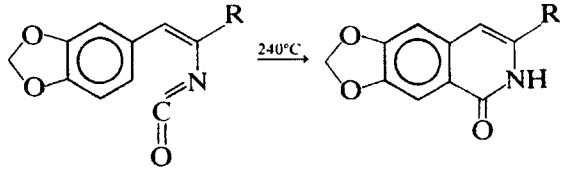
3,4-dihydroisoquinoline derivative by heating without adding any reagent.[7] However, this method has found only limited use in the synthesis of isoquinoline derivatives.

(d) *Curtius Rearrangement and Related Reactions*

Phenethyl isocyanates have been converted into isocarbostyrils with Lewis acids (Eq. 20)[63,76] or mineral acids.[74] Applications of the Curtius reaction in the total synthesis of haemanthidine and tazettine involving cyclization of the intermediate isocyanate with polyphosphoric acid[78] and with phosphoryl chloride–stannic chloride[63] have been reported recently. The use of the latter reagents provides good results and is applicable to hindered isocyanates. Isocyanates **75** were also converted into isocarbostyrils **76** under thermal[79] or photolytic conditions.[80] Transformation of thioisocyanates to the thioisocarbostyrils has been achieved with methyl fluorosulfonate or with Lewis acid (Eq. 21).[81]

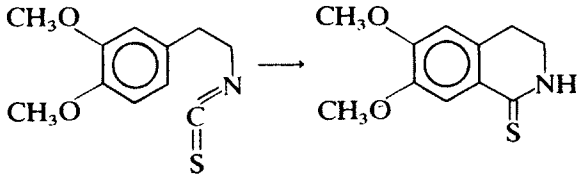


(20)

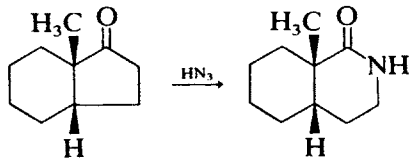


75 **76**

R = H, C_4H_9



(21)

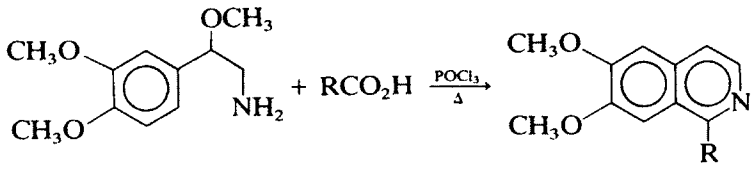


(22)

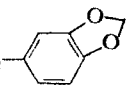
Schmidt rearrangement of properly annulated cyclopentanones has also been used for the synthesis of isocarbostyril derivatives (Eq. 22),[82] but this reaction has the disadvantage of affording a mixture of isocarbostyrils and undesired quinoline derivatives.

(e) *Sugasawa Method*

Sugasawa[83] has reported a simple synthetic method for the preparation of isoquinolines by heating a mixture of the β-methoxyphenethylamine with carboxylic acids in the presence of an excess of phosphoryl chloride (Eq. 23). This modified Pictet–Gams reaction gives isoquinolines in 50 to 70% yield and does not require the isolation of the intermediate amides.

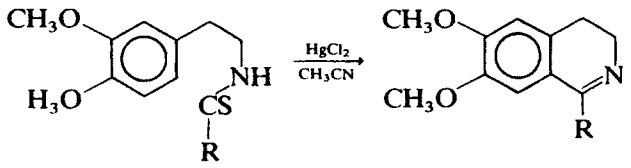


(23)

R	CH_3	$CH_3CH{=}CH$	C_6H_5	$C_6H_5CH{=}CH$	
Yield (%)	69.4	67.5	48	57.9	53

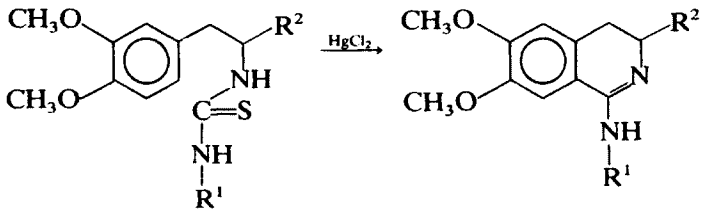
(f) *Cyclodesulfurization of Thioamides*

Thioamides **77** of homoveratrylamine on treatment with mercuric chloride in acetonitrile undergo cyclodesulfurization to give 3,4-dihydroisoquinolines **78**.[84] Phosphoryl chloride[85] can also be used as the condensation reagent in this variation of the Bischler–Napieralski reaction. Optimum yields of 3,4-dihydroisoquinolines are obtained when 3 moles of mercuric chloride are used for 1 mole of thioamide and the reaction is carried out in acetonitrile. Similarly, cyclodesulfurization of thiourea and *S*-alkylthiopseudourea derivatives with mercuric chloride or phosphoryl chloride gives 1-amino-3,4-dihydroisoquinolines (Eq. 24).[86] High yields and purity of products in these



77 78

R	CH_3	C_6H_5	$CH_2C_6H_5$
Yield (%)	70–82	72–90	78–92



(24)

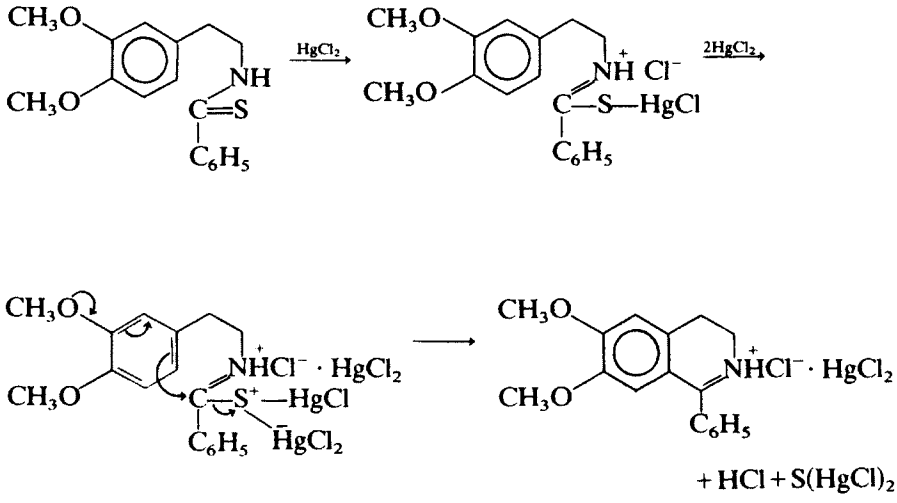
R^1	CH_3	C_6H_5	$CH_2C_6H_5$	o-$CH_3C_6H_4$	m-$CH_3C_6H_4$	p-$CH_3C_6H_4$	p-ClC_6H_4
R^2	H	H	H	H	H	H	H
Yield (%)	81.7	86.2	85–90	65.0–71.5	40.0–82.0	65.0–72.5	64.5

R^1	o-$CH_3C_6H_4$	m-$CH_3C_6H_4$	p-$CH_3C_6H_4$	C_6H_5	$CH_2C_6H_5$
R^2	CH_3	CH_3	CH_3	CH_3	CH_3
Yield (%)	76.0–86.0	56.5–82.0	83.0–94.0	76.0–89.0	65.0–79.0

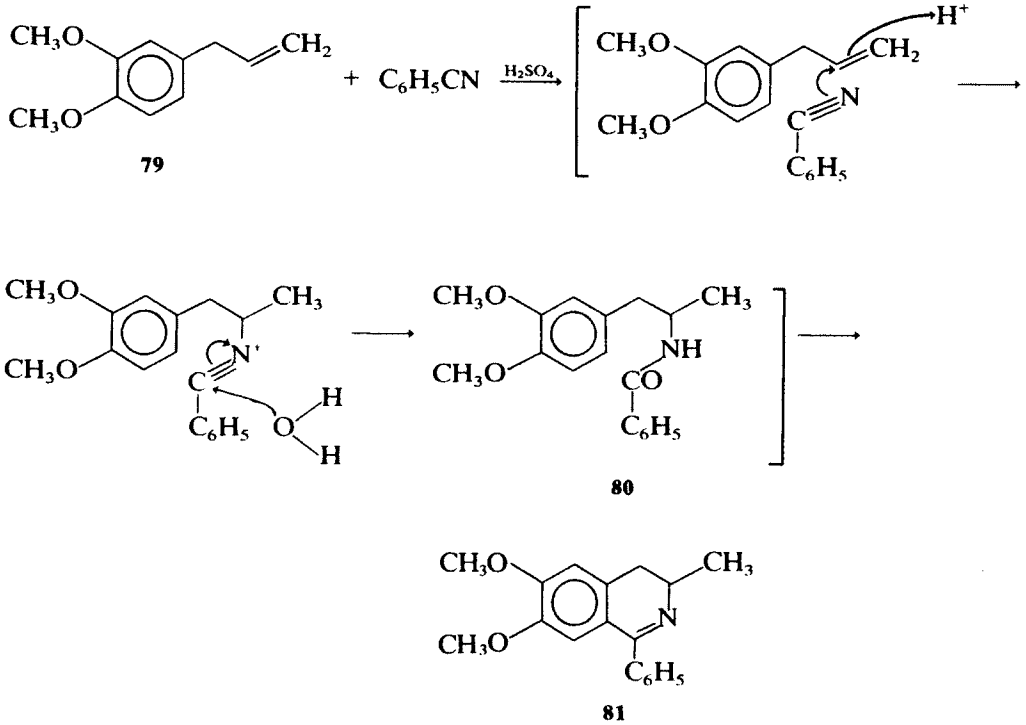
cyclizations attest to the high efficiency of mercuric chloride over phosphoryl chloride as cyclization agent. The proposed mechanism of this cyclodesulfurization is shown in Scheme 9.[84]

(g) *Ritter–Murphy and Related Reactions*

3-Alkyl-3,4-dihydroisoquinoline (**81**) has been synthesized in one step by heating a mixture of allylbenzene (**79**) and benzonitrile in the presence of sulfuric acid through α-alkyl-β-phenethylamide (**80**) as an intermediate.[87] In other examples a mixture of stannic chloride and halogen (Cl_2, Br_2) has been used as catalyst.[88] Certain isoquinolines are easily prepared by the Ritter–Murphy reaction, but the method fails for the synthesis of 3-unsubstituted isoquinoline derivatives.

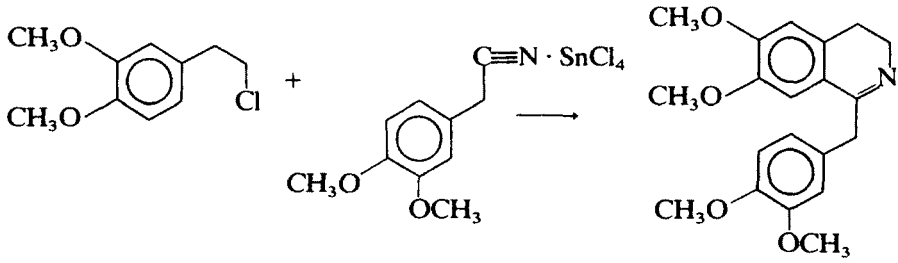


Scheme 9

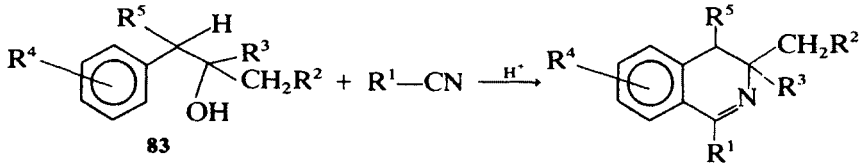


Lora-Tamayo et al.[89] have developed a synthesis of 3,4-dihydroisoquinolines on the basis of the intermediacy of nitrilium salts derived from the reaction of phenethyl halides with a nitrile–stannic chloride complex as exemplified in the preparation of compound **82**.[90] α-Alkyl-β-phenethyl alcohols (**83**) are reacted with nitriles to afford 3,4-dihydroisoquinolines **84**.[91] Hergrueter[92] recently reported a new synthesis of 3,4-dihydroisoquinolines of general utility. This approach employs a nucleophilic carbanionic species rather than a carbonium ion as the intermediate (Scheme 10).

N-Alkylnitrilium salts produced by the reaction of phenethyl azide with nitrile in the presence of nitrosonium salts, are easily converted into 3,4-dihydroisoquinolines (Eq. 25).[93] A method used only for the preparation of phenanthridines is the thermal decomposition of 2-biphenyldiazonium tetrafluoroborates (**85**) in the presence of aliphatic or aromatic nitriles (Eq. 26).[94]

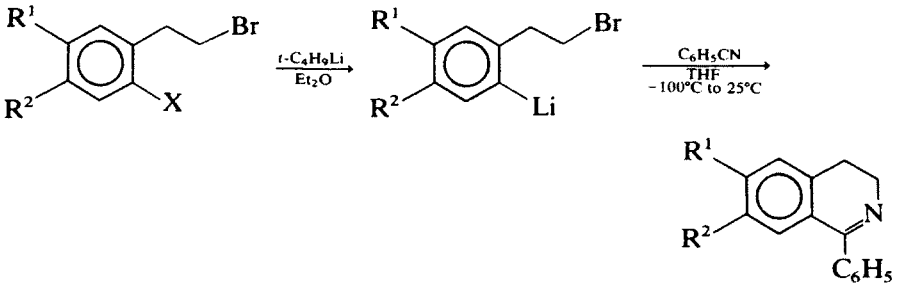


82



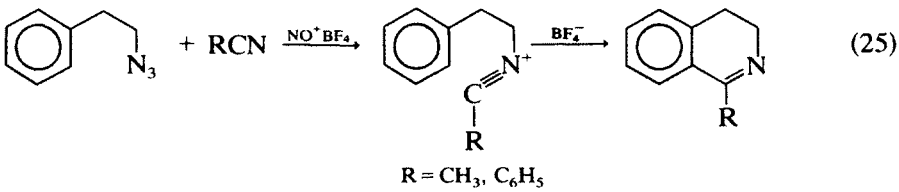
83 **84**

R^1	R^2	R^3	R^4	R^5	Yield (%)
4-C_5H_4N	H	CH_3	H	H	75
3-C_5H_4N	H	CH_3	H	H	72
2-C_5H_4N	H	CH_3	H	H	67
C_6H_5	H	CH_3	H	H	29
$C_6H_5CH_2$	H	CH_3	H	H	8
4-C_5H_4N	—$(CH_2)_3$	—	H	H	42
4-C_5H_4N	H	CH_3	H	CH_3	56
4-C_5H_4N	H	CH_3	7-CH_3	H	40



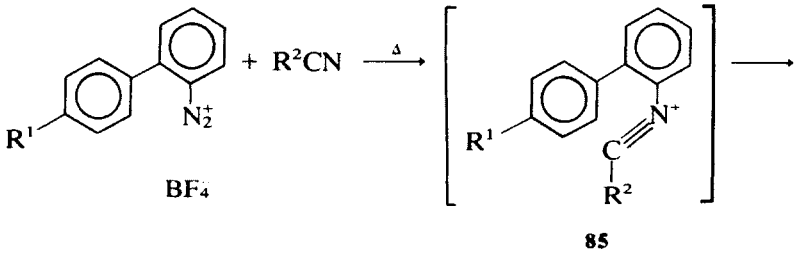
R^1	R^2	X	Yield (%)
H	H	Br	85
OCH_3	H	I	80
OCH_3	OCH_3	I	82
—OCH_2O—		I	96

Scheme 10

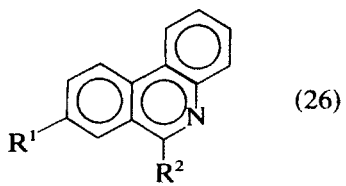


(25)

R = CH_3, C_6H_5



85

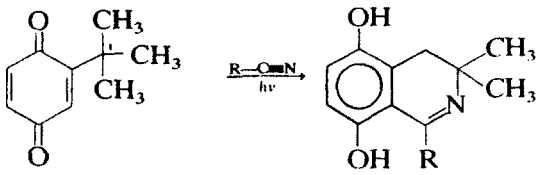


(26)

R^1	R^2	Yield (%)
H	CH_3	86
H	C_2H_5	43
H	n-C_3H_7	(71)[a]
H	C_6H_5	36(40)
H	SCH_3	52(53)[a]
NO_2	CH_3	33(35)[a]
NO_2	C_2H_5	9

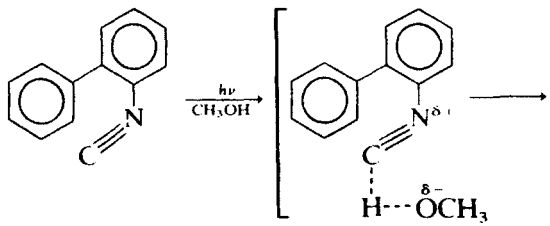
[a] Yield as picrate.

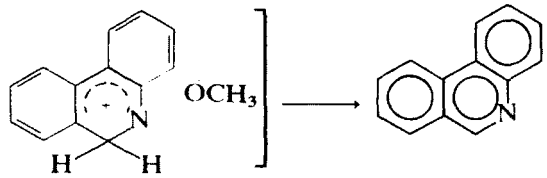
Photolysis of *tert*-butyl-*p*-benzoquinones in the absence of nitriles gives, in addition to other cycloaddition products, 1-substituted 5,8-dihydroxy-3,3-dimethylisoquinolines (Eq. 27),[95] and phenanthridine is formed by photolysis of *o*-phenylbenzoisonitrile (Eq. 28).[96] Both methods are only of limited synthetic value.



other products (27)

$R = CH_3, C_6H_5$





(28)

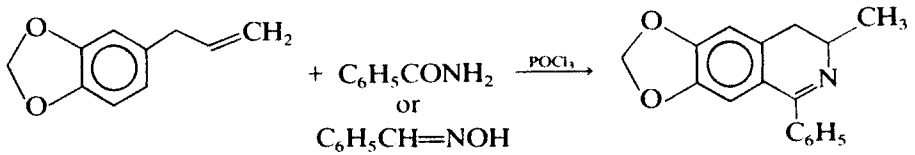
Kametani reported a simple synthesis of 3,4-dihydro-3-methylisoquinolines formed by the reaction of allylbenzenes with aromatic amides[97] or aldoxime[98] (Eq. 29). This variation of the Ritter–Murphy reaction has the disadvantage that the products always have an alkyl group at C-3 and that the reaction proceeds in poor yield.

B. Pictet–Spengler Reaction and Modifications

(a) *Pictet–Spengler Reaction*[8]

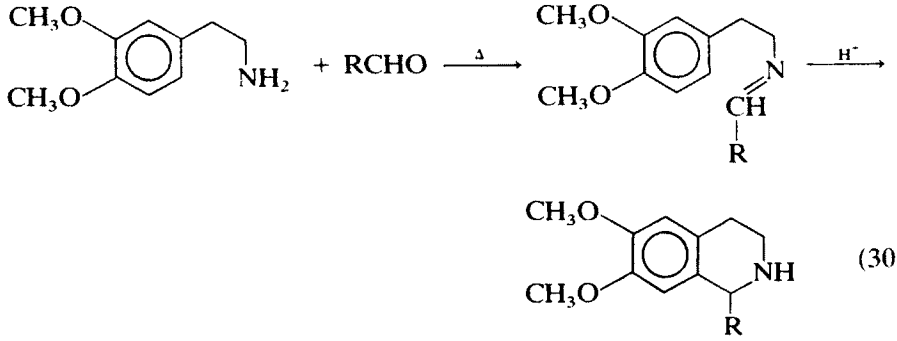
The condensation of β-phenethylamines with carbonyl compounds in the presence of an acidic catalyst to give 1,2,3,4-tetrahydroisoquinolines is called the *Pictet–Spengler reaction*, a special case of the Mannich reaction.

In 1911 Pictet and Spengler[99] reported the reaction of β-phenethylamine with methylal in the presence of concentrated hydrochloric acid to give 1,2,3,4-tetrahydroisoquinoline. The reaction was extended by Decker and



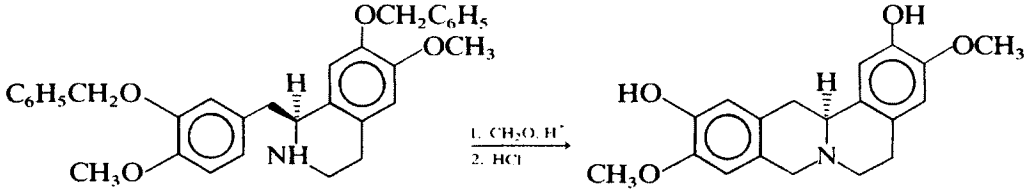
(29)

Becker[100] to the condensation of substituted phenethylamines with various aliphatic and aromatic aldehydes. The reactions were carried out in two steps (Eq. 30).



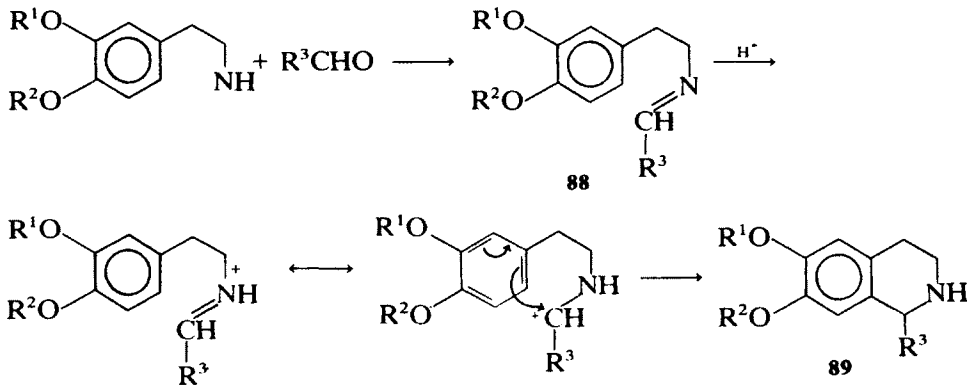
(30)

The Pictet–Spengler reaction has been used widely for the synthesis of a variety of 1,2,3,4-tetrahydroisoquinolines because of generally good yields and mild reaction conditions. Its application to the synthesis of berbine-type compounds[5,6] is exemplified by the conversion of (−)-*O*,*O*-dibenzylnorrecticuline (**86**) into coreximine (**87**).[101] The yohimbane system has also been obtained by this method.[102]

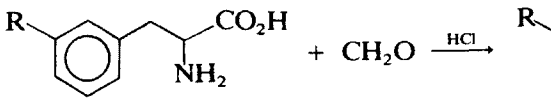


86 **87**

(i) MECHANISM. The probable mechanism of the Pictet–Spengler reaction is shown in Eq. 31. In support of this postulate, the intermediate Schiff base **88** has been isolated in some cases and subsequently cyclized to the isoquinoline derivative **89** by acid.[8] The electrophilic ring closure is facilitated by electron-donating substituents in the proper position, as illustrated by the cyclization of phenylalanine and its meta hydroxyl derivative to the corresponding tetrahydroisoquinoline by treatment with formalin and hydrochloric acid (Eq. 32).[103,104] The fact that even unactivated phenethylamines can be cyclized under these conditions suggests that only a low activation energy is required for this cyclization to occur.



(31)



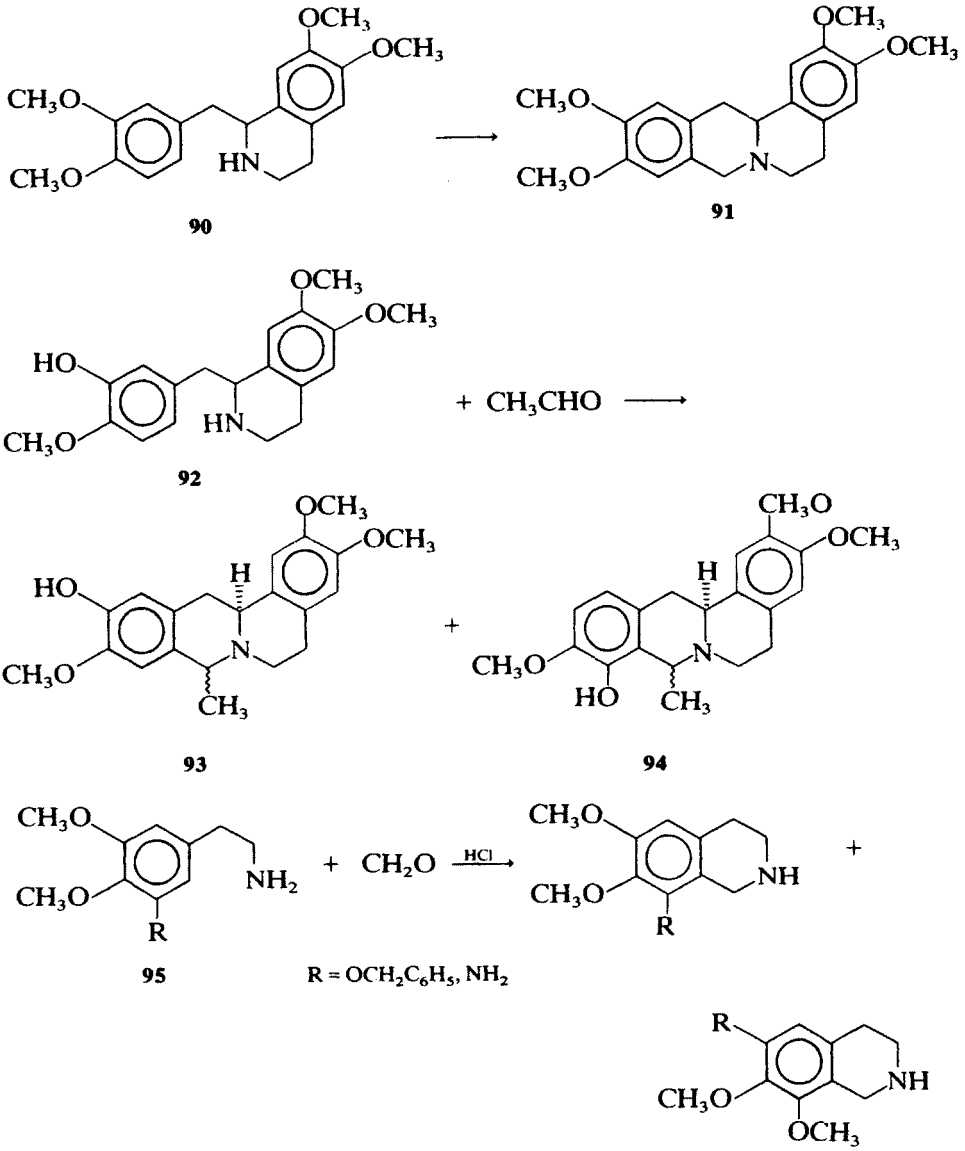
(32)

R	H	OH
Yield (%)	37	70

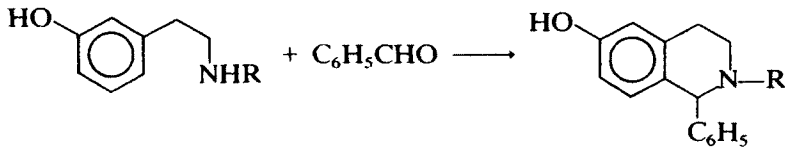
In general, alkoxyl groups direct the cyclization to the para position. Thus the reaction of 3-methoxyphenethylamine with formaldehyde yields only 1,2,3,4-tetrahydro-6-methoxyisoquinoline and no 8-methoxy compound[105]—the same result as that observed in the Bischler–Napieralski reaction. The products obtained by cyclization of many 3,4-dialkoxy-β-phenethylamines are always the 6,7-dialkoxy derivatives, and none of the possible 7,8-dialkoxy derivatives was found. This was also shown in the formation of xylopinine (**91**) from tetrahydropapaverine (**90**). However, Späth and Kruta[106] revealed that if the alkoxyl groups are replaced by hydroxyl groups, the orientation rule becomes invalid and the ring closure proceeds to both ortho and para positions with nearly equal facility. For example, treatment of the phenolic compound **92** with acetaldehyde afforded a mixture of products **93** and **94** in equal amounts.[107]

If both ortho positions are activated to the same extent, cyclization occurs in both directions to yield a mixture of the two possible tetrahydroisoquinoline derivatives. Condensation of phenethylamines **95** with formaldehyde gave a mixture of the two possible isomers in each instance.[108–110]

(ii) Conditions. Hydrochloric acid has been the most commonly employed dehydrating agent, but sulfuric acid and acetic acid have found occasional use.[111] Cyclization conducted in hydrochloric acid often does not require additional solvent if an excess of the reagent is used. Pictet–Spengler reaction under conditions of the Eschweiler–Clarke reaction using formic acid



and formalin has been reported;[104,111] this modification is suitable for the preparation of isoquinolines sensitive to strong acid. But undesired *N*-methylisoquinolines are formed as minor products in this reaction if primary amines are the starting materials. An interesting example is the Pictet–Spengler reaction in basic medium.[37,112] Condensation of *N*-methyl-3′-hydroxyphenethylamine (**96**) (R = CH_3) with benzaldehyde in the presence of pyridine or triethylamine gives the tetrahydroisoquinoline (**97**) (R = CH_3). This method is also suitable for the synthesis of acid-sensitive isoquinolines.

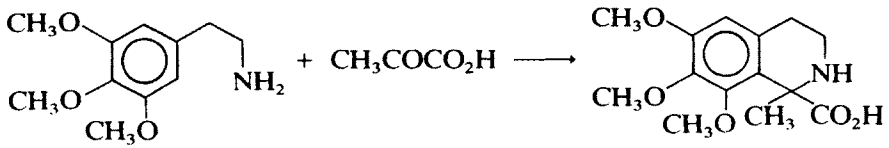


96 **97**

R	Reagent	Yield (%)
H	HCl	48.7
H	Pyridine	69.4
H	Triethylamine	52.4
H	—	66.0
CH_3	HCl	53.0
CH_3	Pyridine	77.1
CH_3	Triethylamine	63.2
CH_3	—	82.2

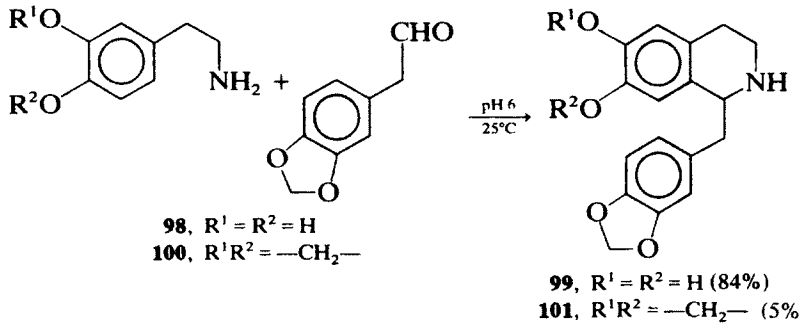
Formaldehyde, most frequently employed as the carbonyl compound in the Pictet–Spengler reaction,[8] generally gives the product in excellent yield and is used preferably to methylal or sodium hydroxymethanesulfonate.[113] For instance, tetrahydropapaverine (**90**) was cyclized to xylopinine (**91**) in 46% yield using methylal, whereas it was obtained with formaldehyde in 60% yield under otherwise identical conditions.[8] The reaction with aldehydes other than formaldehyde needs more drastic conditions and gives poor results.[104]

(iii) APPLICATIONS. Pyruvic acid reacts much more easily than do aldehydes (Eq. 33).[114] In 1911 Pictet and Spengler suggested that this type of reaction constitutes a biogenetic route of isoquinoline alkaloids in plants[99]



(33)

(Chapter IV). In the synthesis of tetrahydroisoquinolines in nature it is unlikely that a catalyst of the strength of concentrated hydrochloric acid is involved, and so the condensation under possible physiological conditions was examined. In 1934 Schöpf carried out a Pictet–Spengler reaction at the same temperature, concentration, and acidity as those in plants. For example, the reaction of β-(3,4-dihydroxyphenyl)ethylamine (**98**) with homopiperonal at pH 4 to 7 and 25°C[115] gave an isoquinoline (**99**). Hahn proved that the ether derivative reacted in the same way as the phenolic base, but its reaction rate was found to be slower. For example, a mixture of homopiperonylamine (**100**) and homopiperonal at pH 5 for 8 days at 25°C

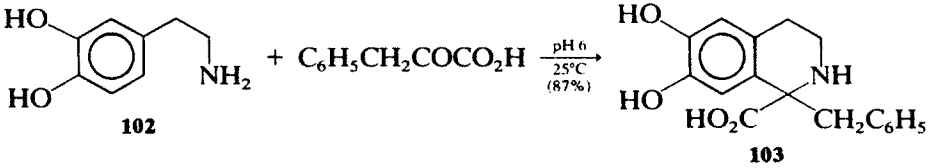


98, $R^1 = R^2 = H$
100, $R^1R^2 = —CH_2—$

99, $R^1 = R^2 = H$ (84%)
101, $R^1R^2 = —CH_2—$ (5%)

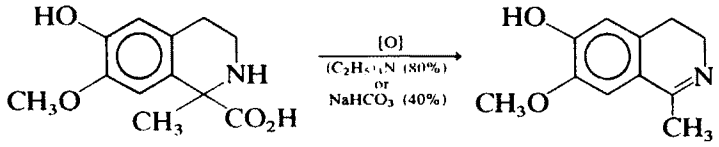
gave a small amount of the corresponding isoquinoline base (**101**).[116] This fact suggests that a very active nucleus, having an increased electron density at the cyclized position, is necessary if the reaction is to be carried out under physiological conditions.[117]

It is well known that naturally occurring phenylacetaldehyde is probably derived from its appropriate α-amino acid through the corresponding phenylpyruvic acid. Hahn has proposed that the α-keto acids are the actual precursors in the biogenesis of isoquinoline alkaloids in nature.[118] His suggestion was supported by the synthesis of the 1-carboxy-1,2,3,4-



102 **103**

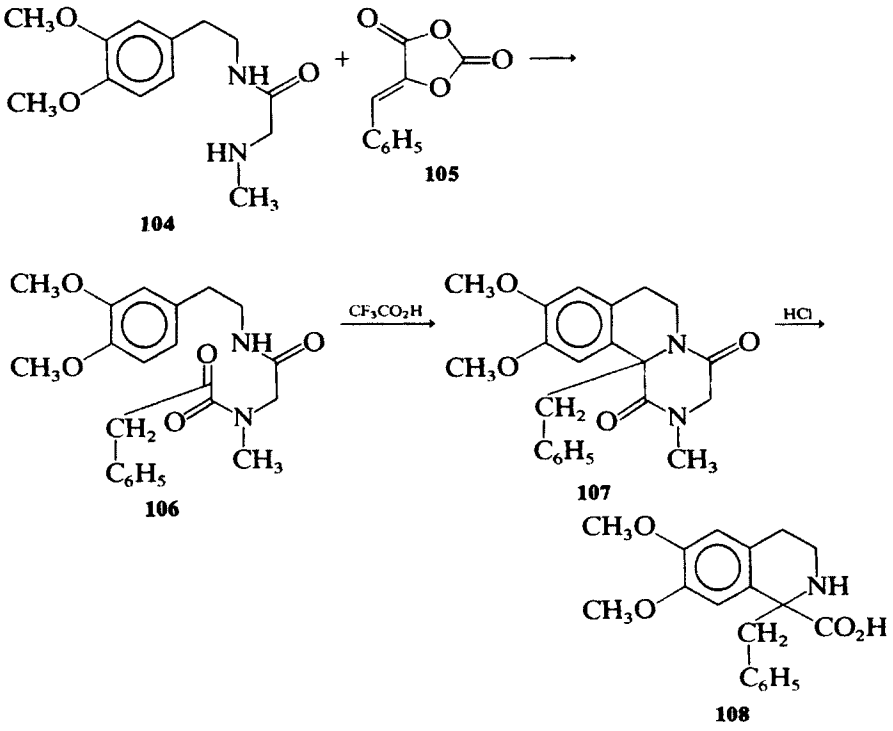
tetrahydroisoquinoline **103** from **102** under biologically plausible conditions, but the reaction with pyruvic acid was slower than that with aldehyde. Furthermore, decarboxylation of the 1-carboxy-1,2,3,4-tetrahydroisoquinoline under mild conditions could not be realized. However, this decarboxylation has been recently achieved in phenolic tetrahydroisoquinolines by Bobbitt.[119] When stirred in air under basic conditions in the presence of sodium bicarbonate, triethylamine or sodium methoxide, 1-carboxy-1,2,3,4-tetrahydroisoquinolines containing at least one free phenol group in the aromatic ring are decarboxylated oxidatively to yield 3,4-dihydroisoquinolines (Eq. 34).



(34)

In support of a suggestion that the biosynthesis of isoquinoline alkaloids involves peptide chains, a model sequence designed to simulate this process has been investigated. The peptide analog **104** was treated with the masked

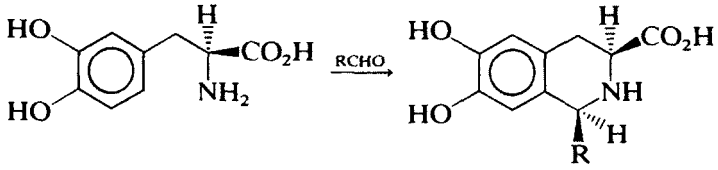
phenylpyruvate **105** to give a diamide **106**, which cyclized easily to the tetrahydroisoquinoline **107**, the hydrolysis of which gave the amino acid **108**. Presumably, if nature does indeed take a course analogous to this



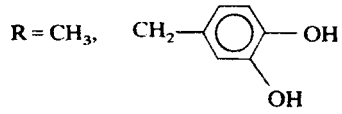
laboratory model, 1-benzyl-1-carboxyisoquinoline derivatives may well exist in benzylisoquinoline-producing plants.[120]

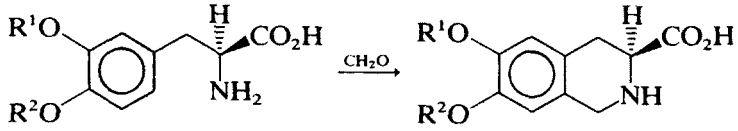
A biogenetically patterned asymmetric synthesis of (+)-laudanosine from (−)-dopa has been reported by Yamada et al. (Eq. 35).[121] Similar results were reported by Brossi (Scheme 11),[122] and a stereospecific isoquinoline synthesis has also been achieved from amino acids (Scheme 12).[123]

Most of the protoberberine alkaloids belong to the 2,3,9,10-oxygenated series, and there have been many attempts to synthesize these alkaloids by a Pictet–Spengler reaction, but only few successful examples in which the usual method was used have been reported. Since the cyclization of *m*-hydroxyphenethylamines gives a mixture of ortho- and para-cyclized products[124,125] as mentioned previously, 2,3,10,11-oxygenated berbines are obtained in addition to the desired 2,3,9,10-oxygenated derivatives.[126] But under controlled pH conditions 2,3,9,10-oxygenated berbines can be obtained from 1,2,3,4-tetrahydro-1-(3-hydroxybenzyl)isoquinolines as major products;[127–129] for example, nandinine **111** is synthesized from the phenolic tetrahydroisoquinoline **109** in 71% yield at pH 1.2 but only in 5.1% and 3.3% yield at pH 6.0 and 7.2, respectively. In these runs the 2,3,10,11-



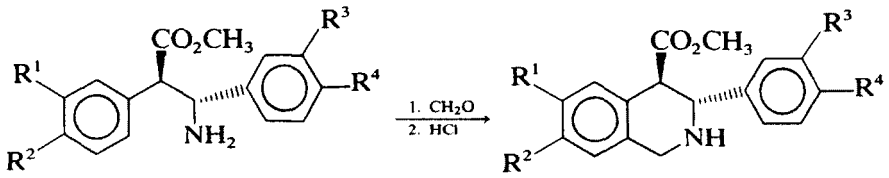
(35)





R^1	R^2	Yield (%)
H	H	87
CH_3	H	27
H	CH_3	85

Scheme 11

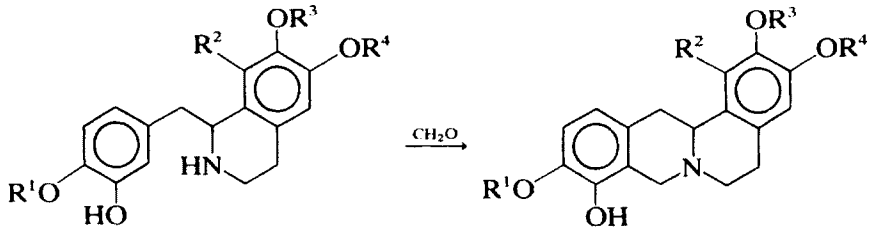


R^1	R^2	R^3	R^4	Yield (%)
OCH_3	OCH_3	—OCH_2O—		49
OCH_3	OCH_3	OCH_3	OCH_3	72
OCH_3	OCH_3	H	H	63
—OCH_2O—		H	H	29

Scheme 12

oxygenated isomer is always formed in about 18% yield.[129] Similarly, Pictet–Spengler reaction of the hydrochloride of the isoquinoline **110** gives only the 2,3,9,10-oxygenated berbine **112**, but reaction at pH 6.4 forms a mixture of **112** and its 2,3,10,11-oxygenated isomer.[128,129]

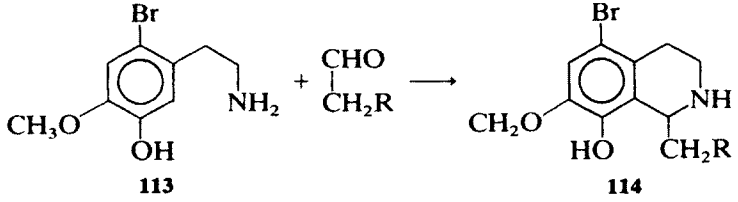
Another method for achieving regiospecificity in the Pictet–Spengler synthesis of 7,8-dioxygenated isoquinoline was developed by Kametani. The normal cyclization position is blocked with bromine, and the methoxyl group



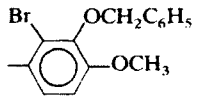
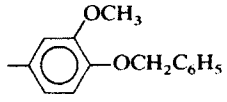
	R^1	R^2	R^3	R^4	Yield (%)
109	CH_3	H	$-CH_2-$		
110	$CH_2C_6H_5$	$OCH_2C_6H_5$	CH_3	CH_3	
111	CH_3	H	$-CH_2-$		71
112	$CH_2C_6H_5$	$OCH_2C_6H_5$	CH_3	CH_3	44

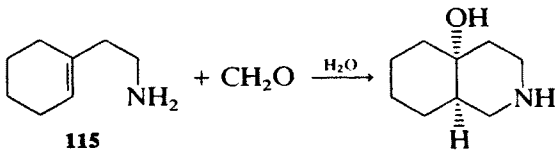
is replaced by hydroxyl to offset the inactivation of the nucleus caused by the *I* effect of the bromine atom. These manipulations were anticipated to promote ring closure ortho to the hydroxyl group. Indeed, reaction of the bromophenethylamine **113** with aldehyde and hydrochloric acid gave the expected 1,2,3,4-tetrahydro-8-hydroxy-7-methoxyisoquinoline **114**.[131] This type of reaction is now widely used for protoberberine alkaloid synthesis.[5,6,101,132] Pictet–Spengler reaction of 3,4,5,6-tetrahydrophenethylamine (**115**) under nonaqueous conditions gives the corresponding octahydroisoquinoline,[133] whereas ring closure with formalin in aqueous medium leads to the *cis*-decahydroisoquinoline **116** in a stereospecific manner.[134]

Mollov has reported a new synthesis of 2-acyl-1-aryl-1,2,3,4-



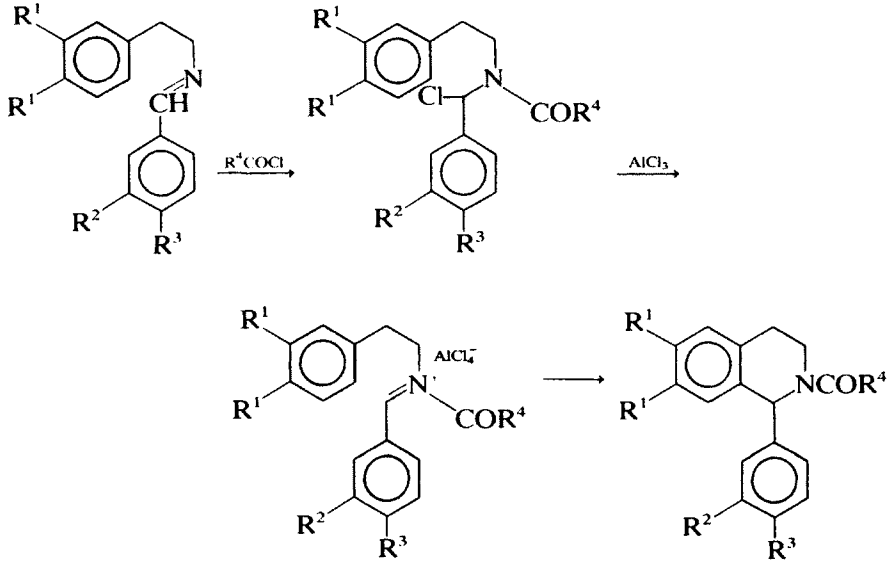
113 **114**

R		
Yield (%)	25	49



115 **116**

tetrahydroisoquinolines by a reaction of *N*-benzalphenethylamines with acyl chlorides in the presence of aluminum chloride. In this reaction cyclization proceeds smoothly by heating without aluminum chloride when an electron-donating group is present on the benzene ring of the phenethylamines (Scheme 13).[135]

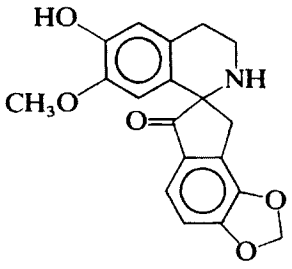


				Yield (%)	
R^1	R^2	R^3	R^4	With $AlCl_3$	Without $AlCl_3$
H	H	H	CH_3	40	—
H	H	H	C_6H_5	48	—
OCH_3	H	H	CH_3	56	50
OCH_3	H	H	C_6H_5	63	54
OCH_3	OCH_3	OCH_3	CH_3	35	21
OCH_3	OCH_3	OCH_3	C_6H_5	40	28
OCH_3	H	NO_2	C_6H_5	90	78

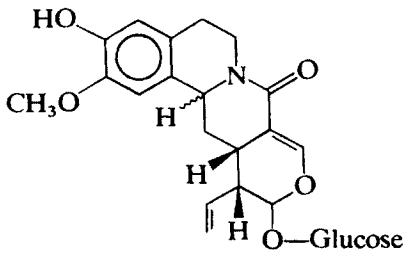
Scheme 13

The Pictet–Spengler reaction has been applied to the synthesis of alkaloids of the spirobenzylisoquinoline **117**[125,136] and the benzoquinolizidine **118**[137] types and to Amaryllidaceae **119**[138] and Erythrina alkaloids **120**[139] as well as the protoberberine alkaloids described earlier.

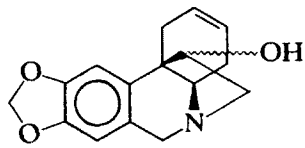
(iv) SIDE REACTIONS. Several side reactions occurring during the Pictet–Spengler cyclization have already been summarized by Whaley and Govindachari.[8] In two recently reported side reactions hydroxymethylation occurred after cyclization in the aromatic ring activated by a hydroxyl group (Eq. 36),[129] and in the other reaction, which involved a less reactive starting material, *N*-methylation without cyclization was observed (Eq. 37).[132]



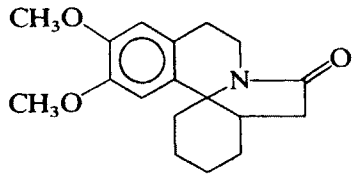
117



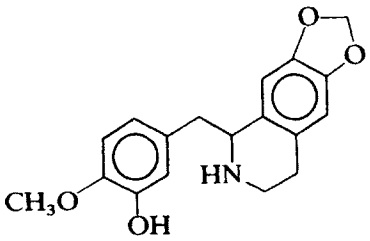
118



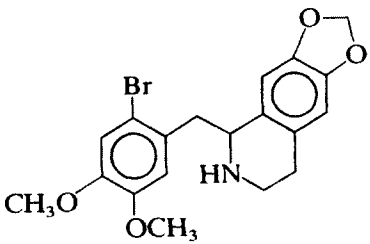
119



120



(36)

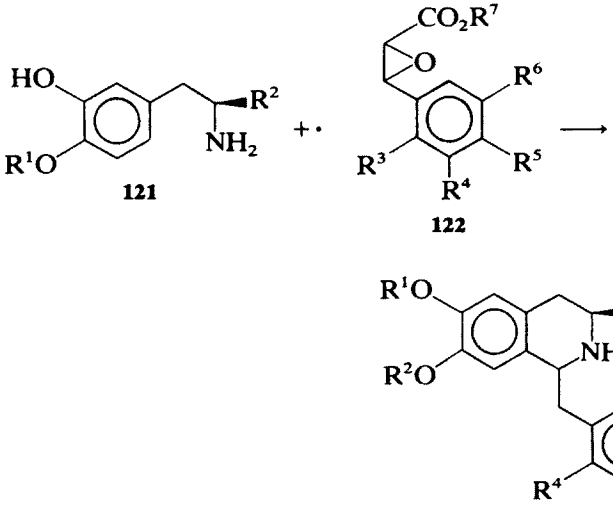


(37)

(b) *Modified Pictet–Spengler Reactions*

(i) Reactions with Chemical Equivalents of Carbonyl Compounds. As the Pictet–Spengler reaction is carried out in an acidic medium, the carbonyl compound can be generated *in situ* from a suitable substrate under these conditions and react with phenethylamines to give 1,2,3,4-tetrahydroisoquinolines.

A typical example is the reaction of the glycidate **122** with the phenethylamine **121**,[140,141] a biogenetically modeled synthesis of benzylisoquinoline alkaloids (Eq. 38).[142] This reaction gives better results than



121 **122**

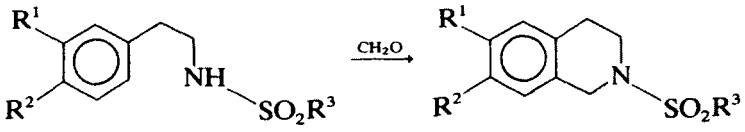
(38)

R^1	R^2	R^3	R^4	R^5	R^6	R^7	Yield (%)
H	CO_2CH_3	H	OCH_3	OCH_3	H	Na	87.0
$C_6H_5CH_2$	CO_2CH_3	H	OCH_3	OCH_3	H	Na	17.0
H	H	OCH_3	H	H	H	Na	7.0
H	H	OCH_3	OCH_3	OCH_3	H	Na	3.8
H	H	H	OCH_3	H	H	Na	18.8
H	H	H	OCH_3	H	OCH_3	Na	32.8
H	H	H	OCH_3	OCH_3	OCH_3	H	31.6

does the reaction with phenylacetaldehydes because the latter are sensitive to acid. Acetals,[143] enol ethers,[143] and chloromethyl methyl ethers[144] are also used as chemical equivalents of carbonyl compounds. *N*-Sulfonylphenethylamines are also used as starting materials for a synthesis of the corresponding tetrahydroisoquinolines by reaction with formalin in the presence of acid (Eq. 39).[145]

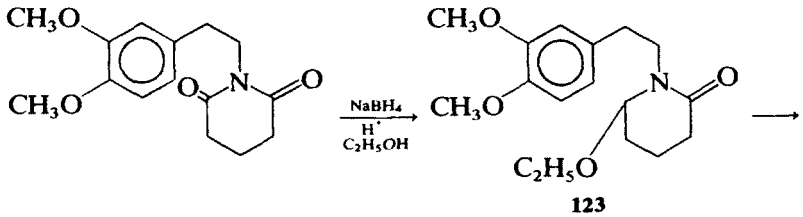
(ii) Cyclization of α-Amino Alcohols. Mild acid treatment of α-aminoalcohols **123**[146] gives the corresponding isoquinolines by cyclodehydration (Eq. 40). Cyclization of an amide alcohol, in which the aryl nucleus is activated by an electron-donating group, was carried out with *p*-toluenesulfonic acid in boiling benzene to form the corresponding ring-closed product (Eq. 41).[147].

(iii) Cyclization of Enamines and Related Compounds. *N*-Vinylphenethylamine **124** is cyclized with polyphosphoric acid to give the

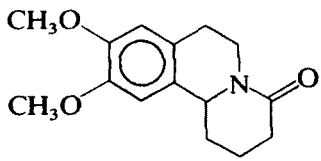


(39)

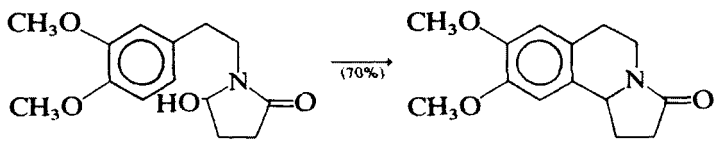
R^1	R^2	R^3	Yield (%)
H	H	CH_3	60.8
H	H	p-$CH_3C_6H_4$	57.8
H	H	p-$NO_2C_6H_4$	60.4
OCH_3	OCH_3	p-$CH_3C_6H_4$	70.9
—OCH_2O—		p-$CH_3C_6H_4$	53.9



123



(40)

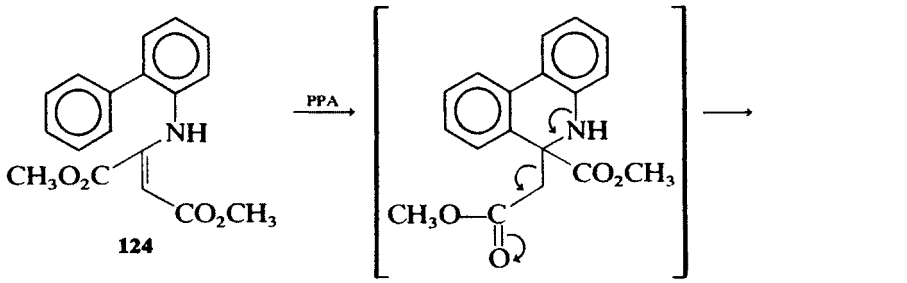


(41)

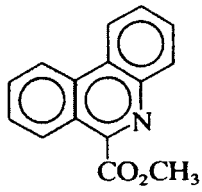
isoquinoline **125**.[148] This type of ring-closure reaction has been widely used for the synthesis of pavine-type isoquinoline alkaloids **126**[5,6,149] and for the elaboration of the Erythrina ring system **127**.[5,6,138,150] However, the yields are generally low because of the severe reaction conditions. Similarly, *N*-phenethyl-3,4-dihydroisoquinoline **128** afforded the dibenzoquinolizidine **129**.[151]

C. Phenolic Cyclization[152]

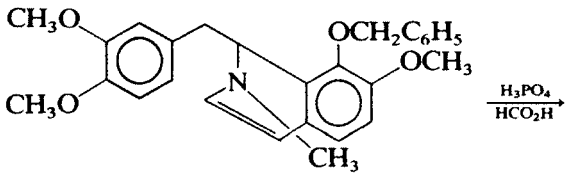
The reaction of 3-hydroxyphenethylamines with various carbonyl compounds under nonacidic conditions gives the corresponding 1,2,3,4-

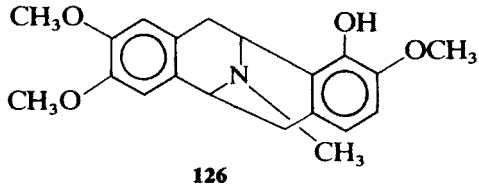


124

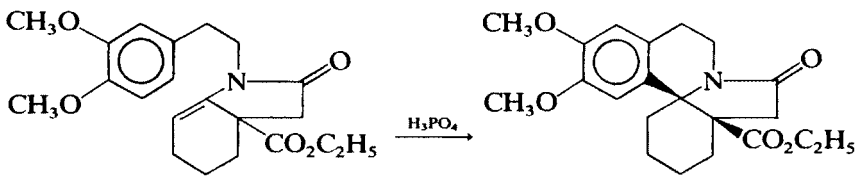


125

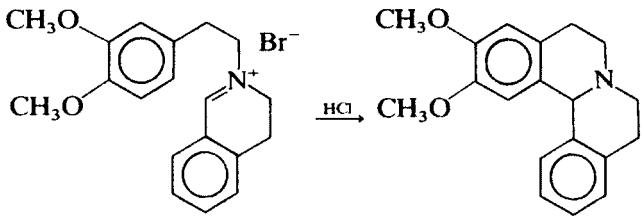




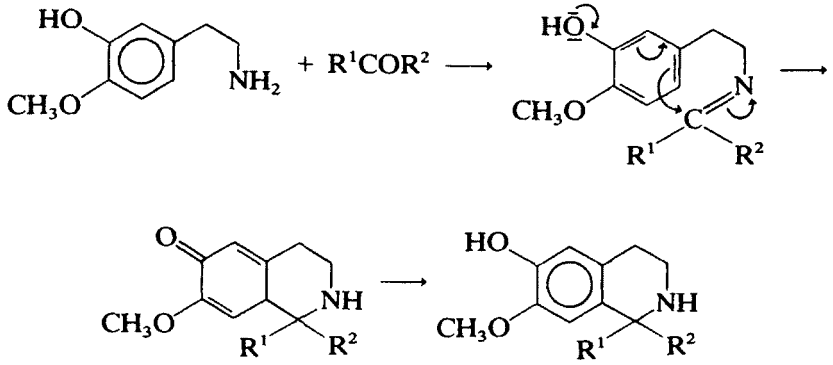
126



127



128 **129**



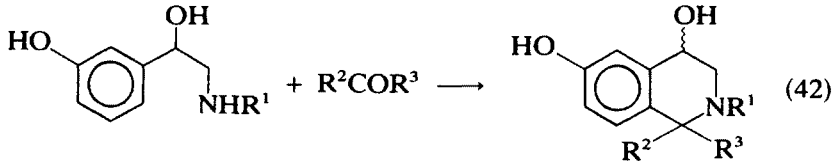
R^1	R^2	Yield (%)
CH_3	H	17
CH_3	CH_3	25
CH_3	CO_2H	28.6
$-(CH_2)_5-$		31
$-(CH_2)_4-$		36
p-HOC_6H_4	H	80
p-$PhCH_2OC_6H_4$	H	72.5
$C_6H_3(OH)(OMe)$-3,4	H	80
$C_6H_3(OMe)(OCH_2Ph)$-3,4	H	80
$C_6H_3(OCH_2Ph)(OMe)$-3,4	H	80
p-$PhCH_2OC_6H_4CH_2$	H	36–60
$CH_2C_6H_3(OMe)(OCH_2Ph)$-3,4	H	36–60

Scheme 14

tetrahydroisoquinolines (Scheme 14). Condensation is carried out by fusion of a mixture of 3-hydroxyphenethylamine and carbonyl compound or by refluxing both components in alcohol in a current of nitrogen with no acidic and basic catalyst for several hours. This reaction closely resembles the Pictet–Spengler reaction, except that isoquinoline formation occurs without acidic catalysts. Kametani has proposed to call this reaction *phenolic cyclization* because of the importance of the phenolic hydroxyl group in the reaction.[153] Because of the neutral conditions the phenolic cyclization reaction is very well suited for the preparation of isoquinolines with acid-sensitive functional groups such as a hydroxyl group (Eq. 42).[152]

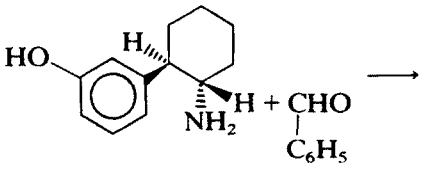
Interestingly, the reaction of *trans*-2-(3-hydroxyphenyl)cyclohexylamine **130** with benzaldehyde gave the two products **132** and **133**, cyclized ortho and para, respectively, to the hydroxyl group. The formation of **133** can be explained by an interaction of the phenolic hydroxyl group with the π-electrons of the benzene ring in the intermediate Schiff base **131**.[36]

Many other examples such as 1-benzylisoquinolines, 1,1-spiroisoquinolines, protoberberines, and benzophenanthridines have been synthe-

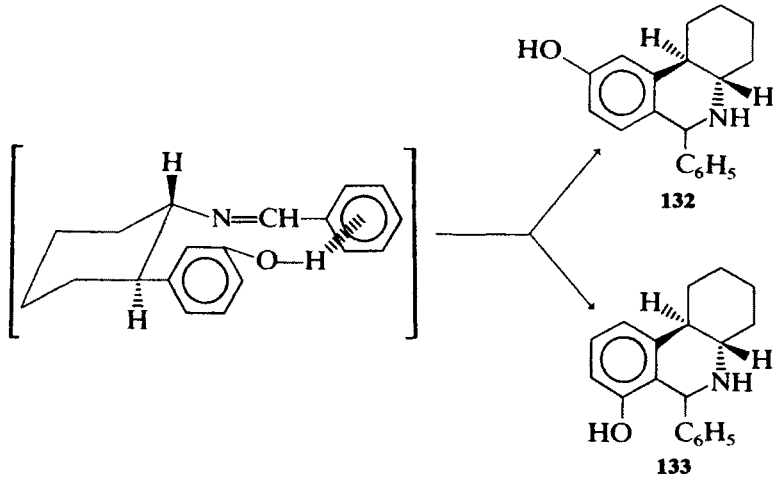


(42)

R^1	R^2	R^3	Yield (%)
H	C_6H_5	H	47
H	CH_3	C_2H_5	41
H	CH_3	C_6H_5	28
H		$-(CH_2)_5-$	22
H		$-(CH_2)_4-$	54
H	$-CH_2CH_2N(CH_2C_6H_5)CH_2CH_2-$		69
H	$-CH_2CH_2N(CH_3)CH_2CH_2-$		96
H	$-CH_2CH_2OCH_2CH_2-$		51
H	$-CH_2CH_2SCH_2CH_2-$		38
H	CO_2H	H	87
H	CO_2CH_3	H	65
H	CO_2H	C_2H_5	80
CH_3	CH_3	CH_3	32
CH_3		$-(CH_2)_4-$	22
CH_3	C_6H_5	H	46
CH_3	p-ClC_6H_4	H	34
CH_3	$C_6H_5CH_2CH_2$	H	47
CH_3	CO_2H	H	73



130



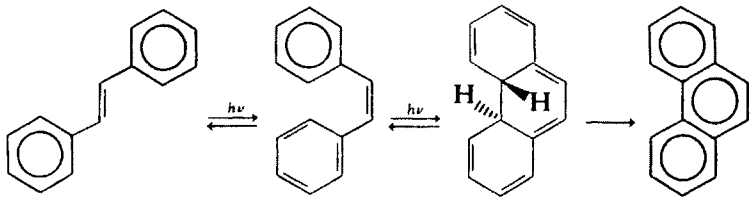
132

133

sized by this method.[152] Moreover, this cyclization has been extended to a synthesis of the benzazepine ring system.[154]

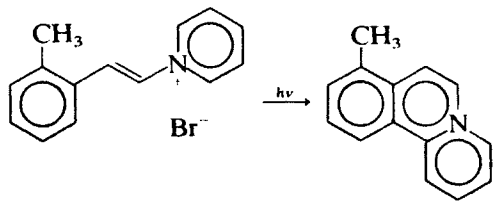
D. Photochemical Isoquinoline Synthesis

Conjugated polyene systems often undergo photolytic electrocyclization. Thus *trans*-stilbene **134** undergoes a rapid cis–trans isomerization under the influence of ultraviolet (uv) light to *cis*-stilbene **135**, which then cyclizes to the *trans*-dihydrophenanthrene **136** on further irradiation. Mild oxidation of the latter with air or iodine produces phenanthrene **137**.[155] This type of



134 **135** **136** **137**

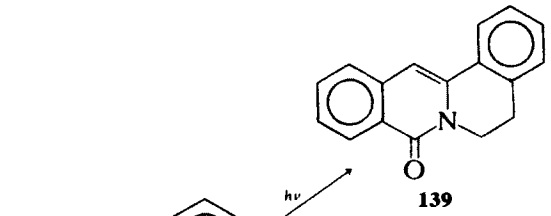
hexatriene–cyclohexadiene isomerization has been widely applied to the synthesis of several types of isoquinoline and isoquinoline alkaloid.[156] Although this reaction cannot be used for the preparation of simple isoquinolines, benzoquinolizidine and dibenzoquinolizidine systems are synthesized in low yield by a photochemical reaction (Eq. 43).[157]



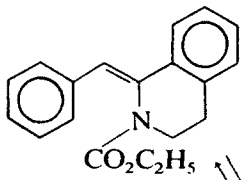
(43)

Molecular orbital calculations for 1-benzylidene-2-ethoxycarbonylisoquinoline (**138**) call for localization of electron density at the ortho position of stilbene in the excited state. The aromatic system is thus activated in the excited state, and intramolecular acylation occurs. In fact, irradiation of the urethane **138** gave the dehydroprotoberberine **139** in 65% yield in addition to the dehydroaporphine **140** (10 to 21%).[158]

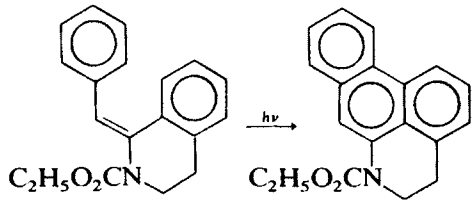
The same protoberberine-type compounds were obtained by Cava and Havlicek[159] and Lenz and Yang[160] in good yield. Lenz and Yang[160] proposed the following mechanism: protonation of the amide group of **141** to the iminium alcohol **142**, thereby increasing the carbon–nitrogen double-bond character, is followed by irradiation of the newly formed hexatriene system to form the berbine **143**.



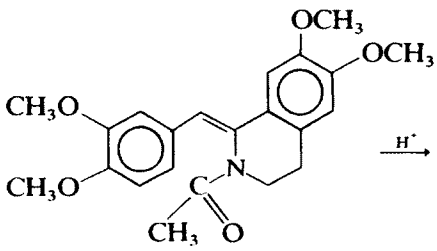
139



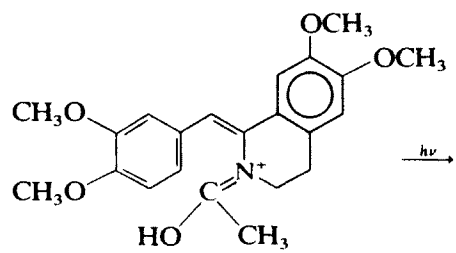
138



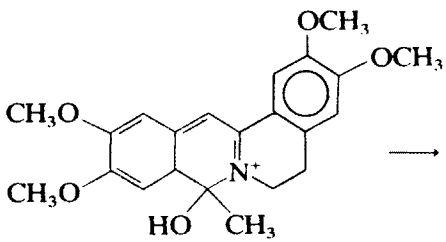
140



141



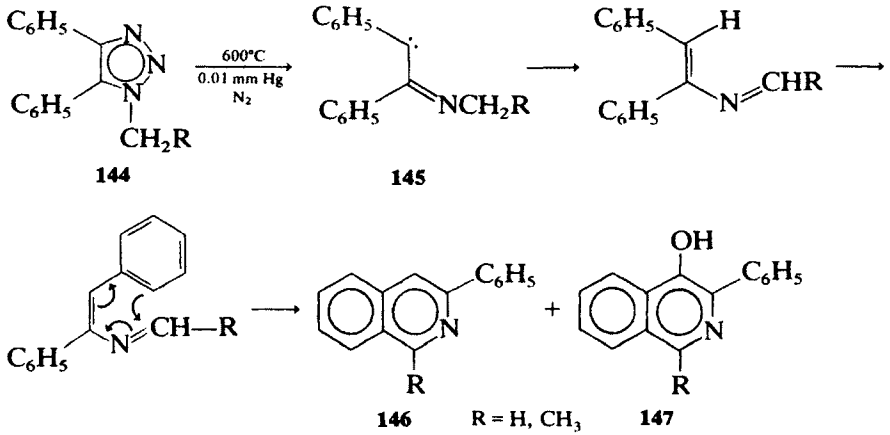
142



143

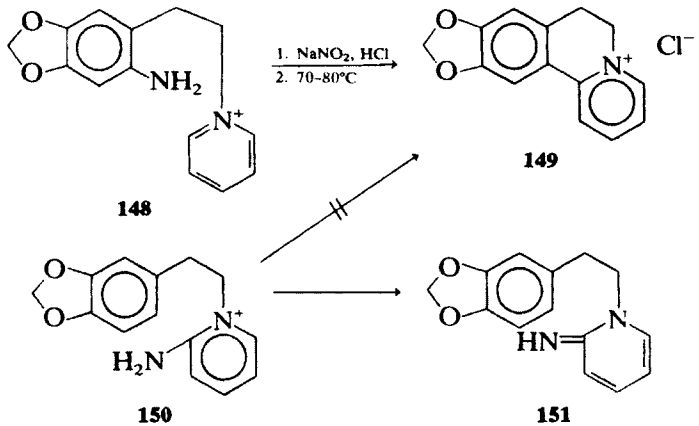
E. Pyrolysis of Triazoles and Pschorr Reaction

An abnormal formation of isoquinolines by pyrolysis of triazoles has been reported.[161] When 1-alkyl-4,5-diphenyltriazoles **144** are pyrolyzed in the vapor phase, nitrogen is extruded and the remaining imino carbene **145** reacts by 1,4-hydrogen transfer from the alkyl group, followed by cis-trans isomerization and electrocyclic ring closure and oxidation, leading to the 3-phenylisoquinolines **146** and **147**.



144 **145** **146** R = H, CH_3 **147**

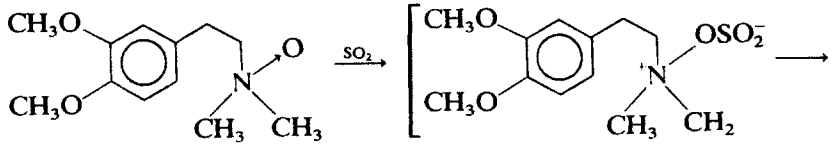
Pschorr reaction of *N*-(*o*-aminophenethyl)pyridinium chlorides proceeds smoothly to give the corresponding benzoquinolizidine derivatives; for example, a diazotization of the amine **148** at 0 to 5°C, followed by thermal decomposition of the resulting diazonium salt at 70 to 80°C, affords **149** in 84% yield. However, 2-amino-*N*-phenethylpyridinium salt **150** does not form **149** but gives the 2-amino-*N*-phenethylpyridine **151** instead.[162] This cyclization is a general method for the preparation of benzoquinolizidines, and many compounds have been obtained by the Japanese group.[162]



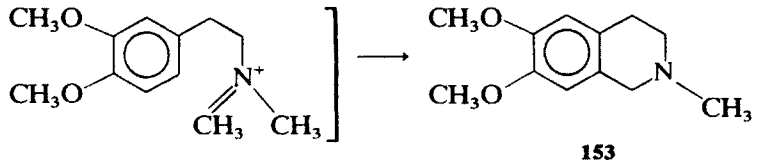
148 **149** **150** **151**

F. Oxidative Coupling

Synthesis of the tetrahydroisoquinoline **153** by sulfur dioxide dehydrative cyclization of *N,N*-dimethylphenethylamine *N*-oxide **152** along a Polonovsky reaction was reported by Bather et al.[163] This reaction has been used for the synthesis of xylopinine from laudanosine *N*-oxide.



152



153

The Erythrina ring system is synthesized in one step by the phenolic oxidative coupling of the diphenolic bisphenethylamine along the biogenetic route.[164,165] Thus oxidation of the bisphenethylamine **154** with potassium ferricyanide at room temperature gives erythrinadienone **155** in 35% yield. This is a special application of phenolic oxidative coupling, and not a general synthesis of isoquinoline derivatives.

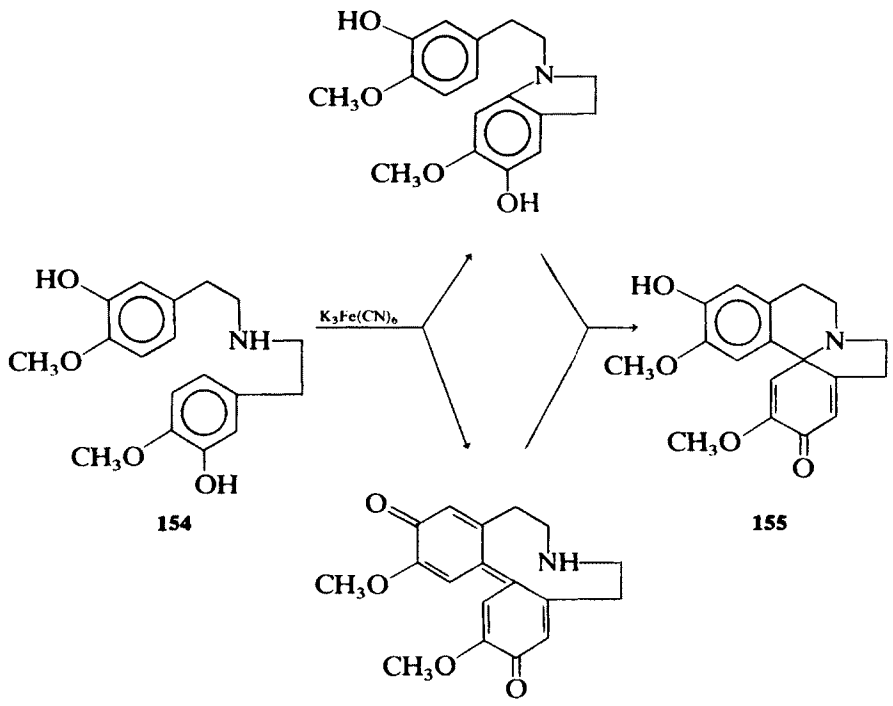
G. Isoquinoline Synthesis by Palladium-Catalyzed Insertion of Carbon Monoxide

Dihydroisocarbostyril has recently been prepared by palladium-catalyzed amidation. The insertion of carbon monoxide into *o*-bromophenethylamine to form the isoquinolone easily occurs under mild condition such as an atmospheric pressure of carbon monoxide at 100°C by use of a catalytic amount of palladium acetate and triphenylphosphine in the presence of *n*-tributylamine. In this reaction *o*-bromophenethylamine is directly converted into the isoquinolone in good yield, and the cyclization takes place at the initial position of the halogen atom in the aromatic ring (Eq. 44).[166]

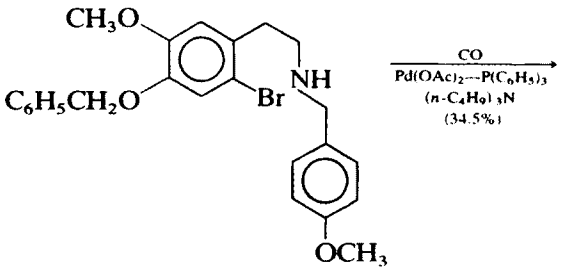
As an extension of this method, sendaverine has been synthesized.[166]

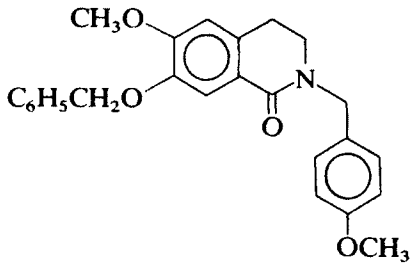
III. TYPE 2 SYNTHESES

The type 2 synthesis consists of bond formation between the C-1 and the nitrogen atom. Most of these reactions are intramolecular condensations of


HO
CH3O
N
CH3O
OH
HO
CH3O
NH
CH3O
OH
K3Fe(CN)6
HO
CH3O
N
CH3O
O
O
CH3O
NH
CH3O
O

154 **155**


CH3O
C6H5CH2O
NH
Br
OCH3
CO
Pd(OAc)2—P(C6H5)3
(n-C4H9)3N
(34.5%)


CH3O
C6H5CH2O
N
O
OCH3

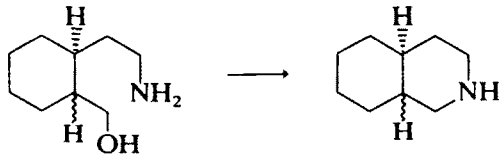
(44)

β-arylethylamines having an appropriate functional group in the ortho position. Although the isoquinoline syntheses from isocoumarins and benzopyrylium salts could be interpreted as type 2 synthesis, they are described in Section IV.

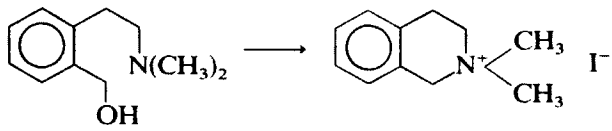
A. Syntheses from β-Phenethylamines

(a) *Syntheses from o-Hydroxymethylphenethylamines and Related Compounds*

Heating of *o*-hydroxymethylphenethylamines or treating this type of amine with thionyl chloride or tosyl chloride in the presence of pyridine causes cyclodehydration to give the corresponding isoquinoline derivative, as exemplified by the conversion of amine **156** into the decahydroisoquinoline **157**.[167] Similarly, *o*-hydroxymethyl-*N*,*N*-dimethylphenethylamine (**158**), obtained by hydroxymethylation of *N*,*N*-dimethylphenethylamine, was easily transformed into the 2,2-dimethyl-1,2,3,4-tetrahydroisoquinolinium salt **159**.[168] This type of cyclization has been used advantageously for the synthesis of lycorine-type alkaloids[169] and protoberberine alkaloids.[170–172]

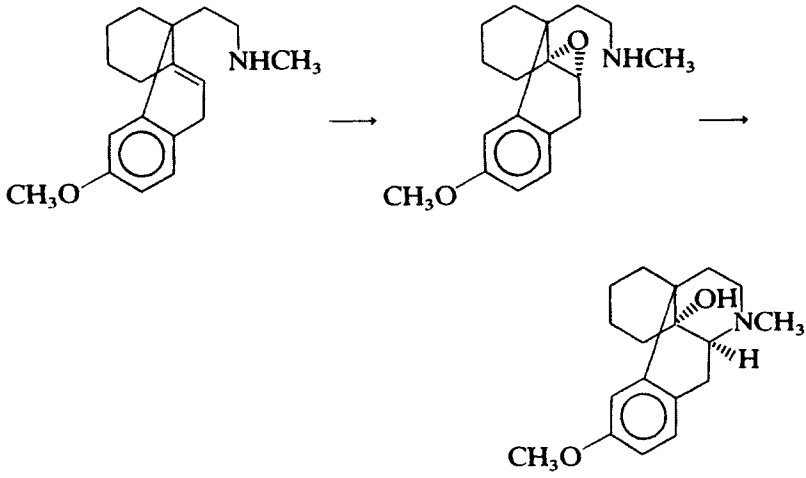


156 **157**



158 **159**

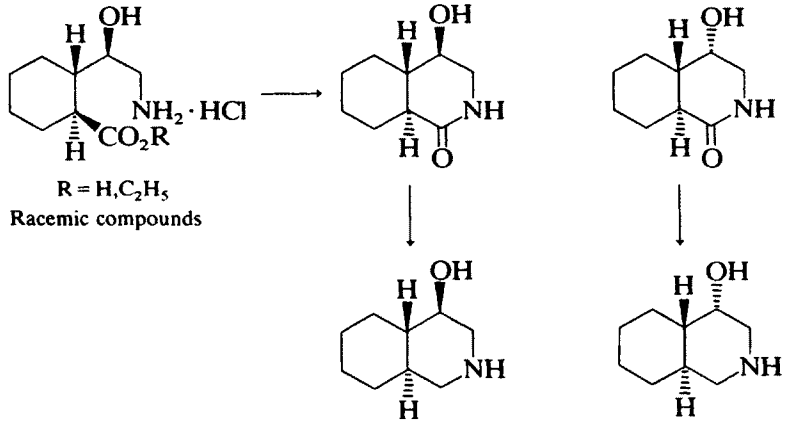
Many isoquinolines of the morphinan type have been prepared by a type 2 synthesis that consisted of a nucleophilic attack of the nitrogen of the phenethylamine at an epoxide representing the hydroxymethyl group (Eq. 45).[173] In general, syntheses belonging to this category constitute an effective method for the preparation of isoquinoline derivatives when *o*-phenethylamino alcohols or *o*-phenethylamino aldehydes are easily available.



(45)

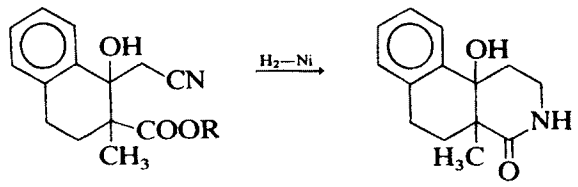
(b) *Syntheses from o-Carboxyphenethylamines and Related Compounds*

The hydrochlorides of δ-amino acids and their corresponding esters are stable compounds, but the free bases derived from these amines are labile and change into lactams by intramolecular cyclodehydration.[174] Kimoto et al.[175] prepared many decahydroisoquinolines by this reaction, as exemplified by the synthesis of isomeric *trans*-4-hydroxydecahydroisoquinolines (Scheme 15). Similarly, appropriate γ-cyano esters are converted into



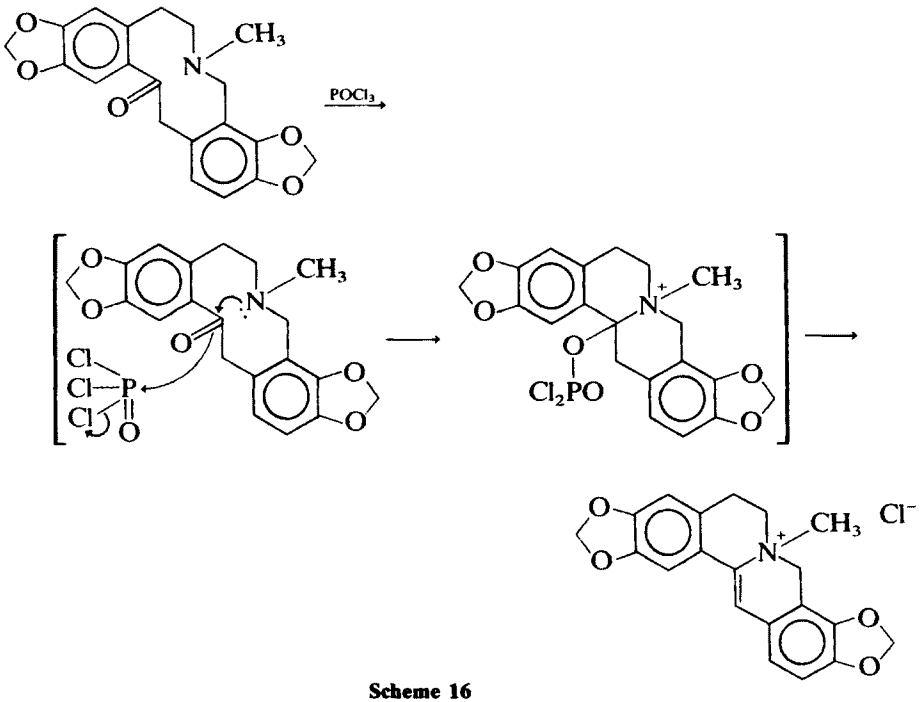
Scheme 15

isocarbostyrils after catalytic reduction to the corresponding δ-amino esters (Eq. 46).[176] These reactions provide a general synthesis of isocarbostyrils because the starting amino esters or their respective precursors are readily



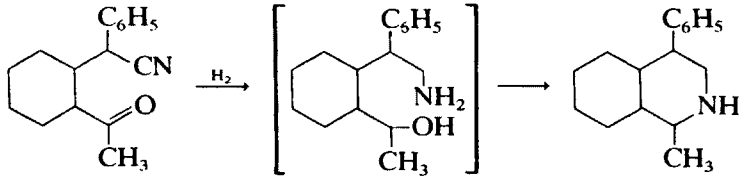
(46)

available and can be transformed into the products under simple and mild conditions in good yield. In a variation of this method, protoberberins have been synthesized by a transannular reaction (Scheme 16).[177]



Scheme 16

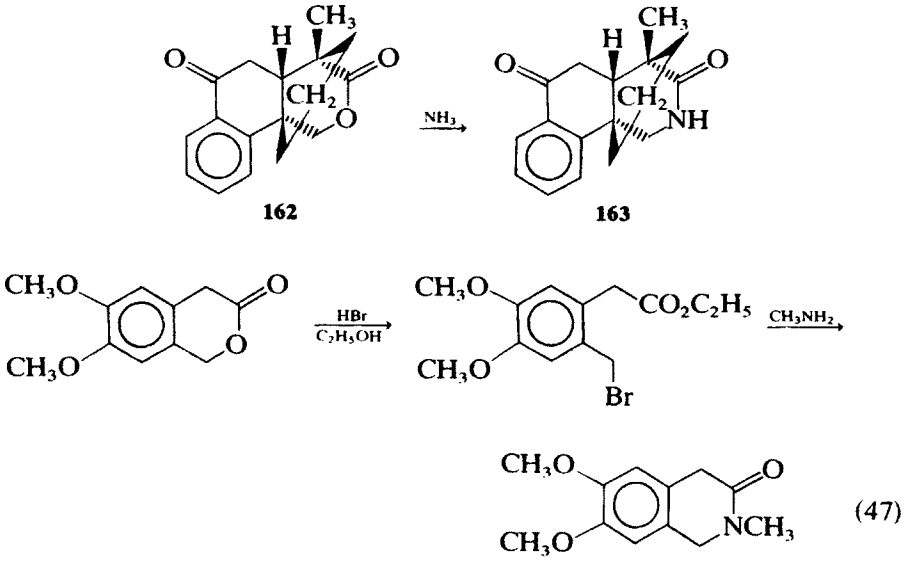
Furthermore, the reductive condensation of α-(2-acetylcyclohexyl)benzyl cyanide (**160**) on copper chromite in ethanol was carried out successfully to afford a mixture of the two stereoisomers of the isoquinoline **161**.[178] This method was applied to a synthesis of the key intermediate in the synthesis of morphine.[179]



160 **161**

B. Syntheses from Lactones

Ammonolysis of the lactone **162** proceeds smoothly to give the isoquinolin-3-one derivative **163**.[180] In some cases, the starting isochromanones are first converted into the *o*-bromomethylphenylacetates, which are then transformed to the isoquinolinones (Eq. 47).[181] Similar



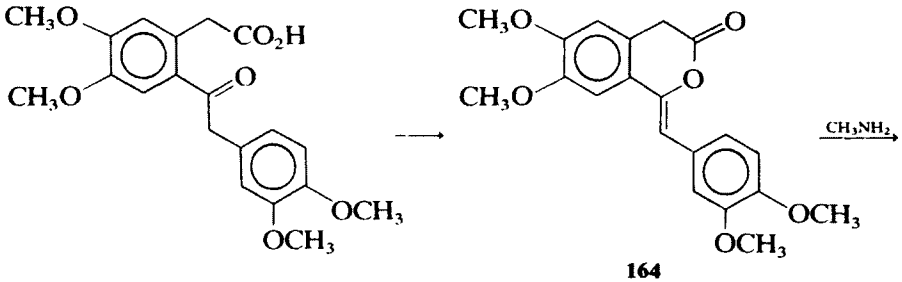
(47)

modifications of this indirect method are reported by many groups[182] because the starting materials can be easily obtained by hydroxymethylation of phenylacetic acid derivatives.

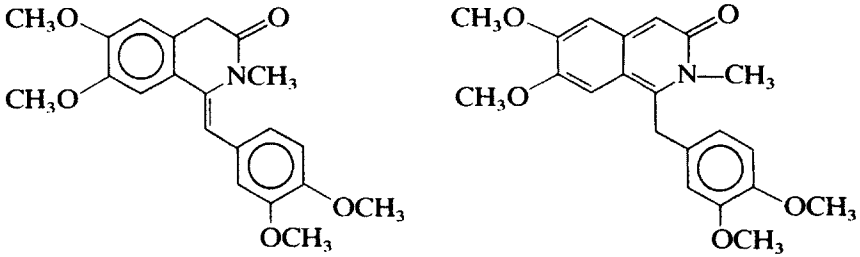
Enolic lactones **164**, obtained from *o*-acylphenylacetic acids, form the isoquinolin-3-ones **165** in good yield by treatment with ammonia or amines.[183] Elliot has proposed the quinonoid structure **166** for the end product.[183] Since *o*-acylphenylacetic acids can be prepared easily by the Friedel–Crafts reaction of phenylacetic acids with appropriate carboxylic acids, this method has also been used for the synthesis of benzylisoquinoline alkaloids of the laudanosine type.[184]

C. Syntheses from *o*-Acyl-*N*-acylphenethylamines

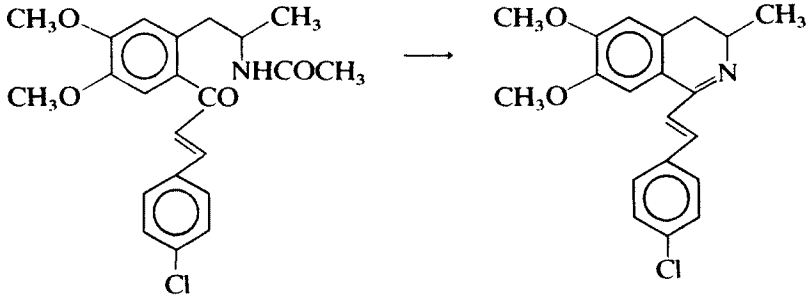
Acidic treatment of *o*-acyl-*N*-acylphenethylamines affords 3,4-dihydroisoquinolines by hydrolysis of the amide group and subsequent cyclodehydration between the amino group and the carbonyl function.[185] For example, the 3,4-dihydro-1-styrylisoquinoline **168** is synthesized in 70% yield by reaction of the amide **167** with hydrochloric acid.[186] Winterfeldt et al.[187] have prepared indoloquinolizidine derivatives by this method.



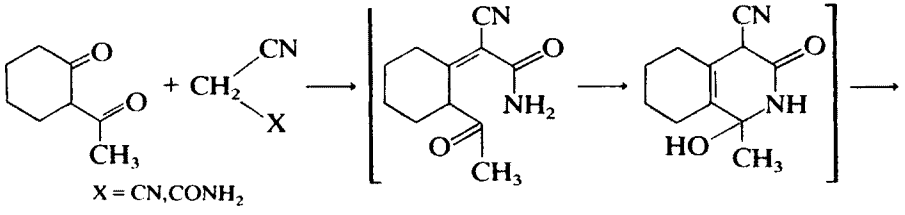
164



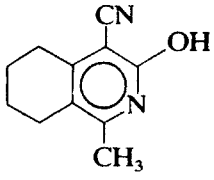
165 **166**



167 **168**



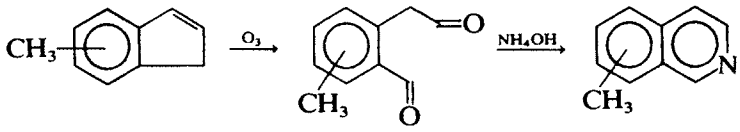
169 **170**



171

Knoevenagel reaction of α-acetylcyclohexanone **169** with malononitrile or cyanoacetamide has been shown to proceed through the amido ketone **170** to yield the isoquinoline derivative **171**.[188] Because of the mild reaction conditions, numerous applications have been reported by several groups.[189]

A new synthesis of isoquinolines has been developed that is particularly applicable to compounds containing alkyl or deactivating groups (e.g., nitro or halo groups) on the isoquinoline ring. The general sequence involves ozonolysis of an indene derivative followed by treatment with ammonia to directly give the isoquinoline in 60 to 90% yield (Eq. 48).[190]



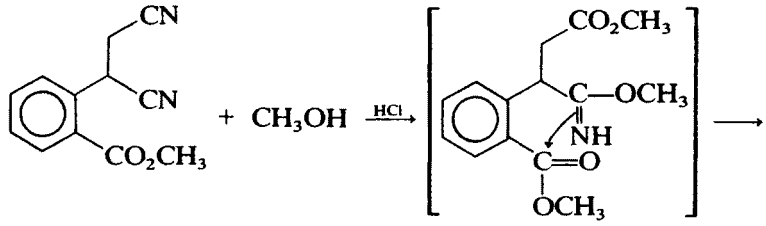
(48)

D. Synthesis from Benzyl Cyanides

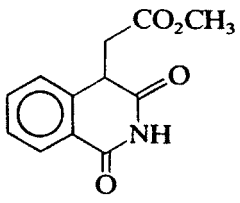
Isoquinoline derivatives in which the nitrogen atom formed part of an imino group can readily be obtained by cyclization of the appropriate benzoic acid derivatives.[191] Very often these imino derivatives are generated *in situ*, most notably from benzyl cyanides. For example, treatment of the *o*-carboxybenzyl cyanides **172** and **175** with methanolic hydrogen chloride[192] or phosphorus pentachloride[193] afforded the isoquinoline derivatives **174** and **177** through the intermediate imino ether **173** or imino chloride **176**, respectively. The *o*-alkoxycarbonylbenzyl cyanide **178** is converted into the isocarbostyril **180** under conditions of the Reformatsky reaction.[194] The imine **179** has been postulated as the reactive intermediate. The imino chloride **182** has been proposed as an intermediate in the formation of isoquinolines **183** from benzyl cyanides **181** by Vilsmeier reaction.[195] Although this synthesis gives 3-chloroisoquinolines, many compounds have been obtained by this method because the starting materials are easily available, and the procedure is simple.[196]

E. Ammonolysis of Homophthalic Acid and Derivatives

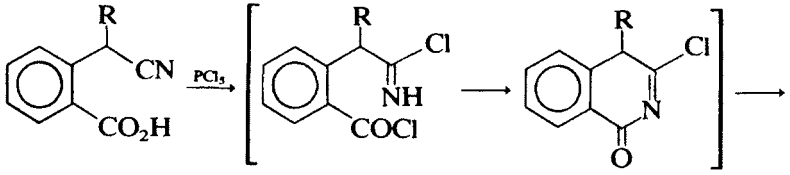
Reaction of homophthalic acid with ammonia gives homophthalimide, 1,2,3,4-tetrahydro-1,3-diketoisoquinoline, which on heating with zinc powder or phosphoryl chloride and hydriodic acid affords isoquinoline (Eq. 49).[197] This reaction has been applied to various homophthalic acid derivatives. For example, treatment of compound **185**, obtained from the homophthalic acid derivative **184** and ammonia in 89% yield, with phosphoryl chloride gave compound **186** in 95% yield. The latter was hydrogenated in the presence of nickel catalyst at 80 atm to give the tetrahydroisoquinoline **187** in 95% yield.[198] Tahara et al.[199] have applied this reaction to



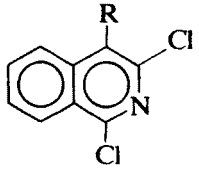
172 173



174

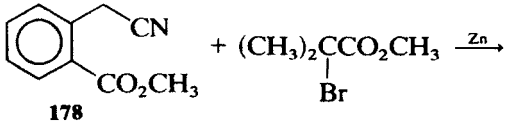


175 176

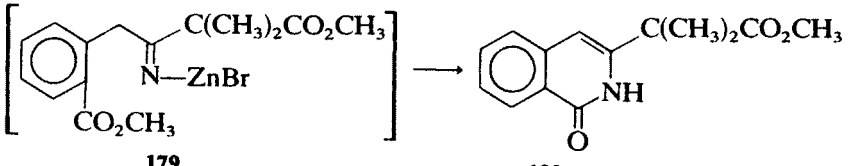


177

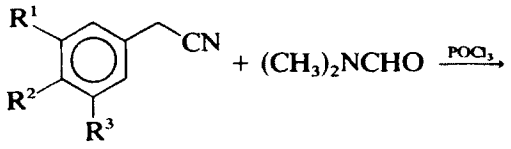
R = H, C_2H_5, C_4H_9, $CH_2C_6H_5$



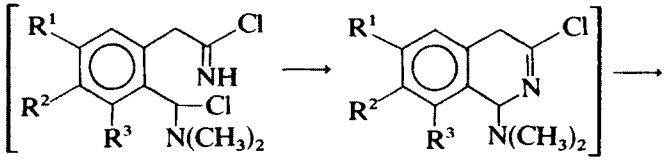
178



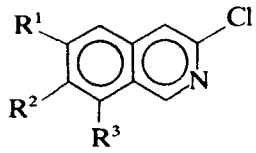
179 180



181

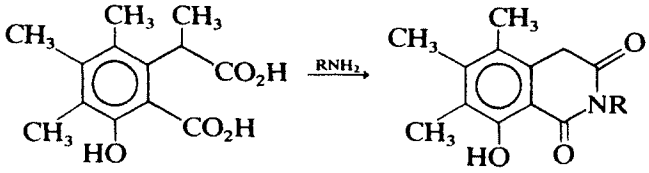


182



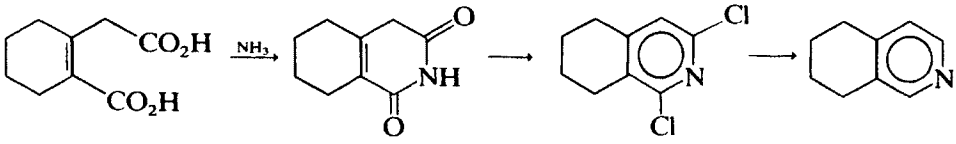
183

R^1	R^2	R^3	Yield (%)
OCH_3	H	OCH_3	62
OCH_3	OCH_3	H	7.5
—OCH_2O—		H	6.1
OCH_3	OCH_3	OCH_3	8
CH_3	H	CH_3	3
OCH_3	H	H	4



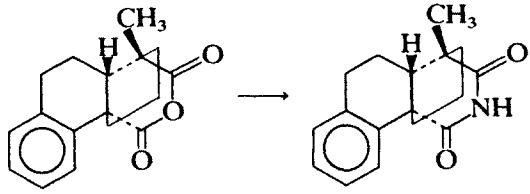
(49)

R	Yield (%)
H	46
C_6H_5NH	15.5
$NHCONH_2$	30



184 **185** **186** **187**

the synthesis of the basic skeleton of diterpene alkaloids (Eq. 50). Since the diacid has two carboxylic acid groups situated closely in 1,3-diaxial relation-



(50)

ship, the formation of an acid anhydride bridge was easily performed under reflux in acetic anhydride. Heating the product or the diacid with urea gave the imide, which on usual reduction with lithium aluminum hydride gave the isoquinoline derivative. In a special case, this reaction has been utilized for the synthesis of 5,6,7,8-tetrahydro- or octahydro- and decahydroisoquinolines.

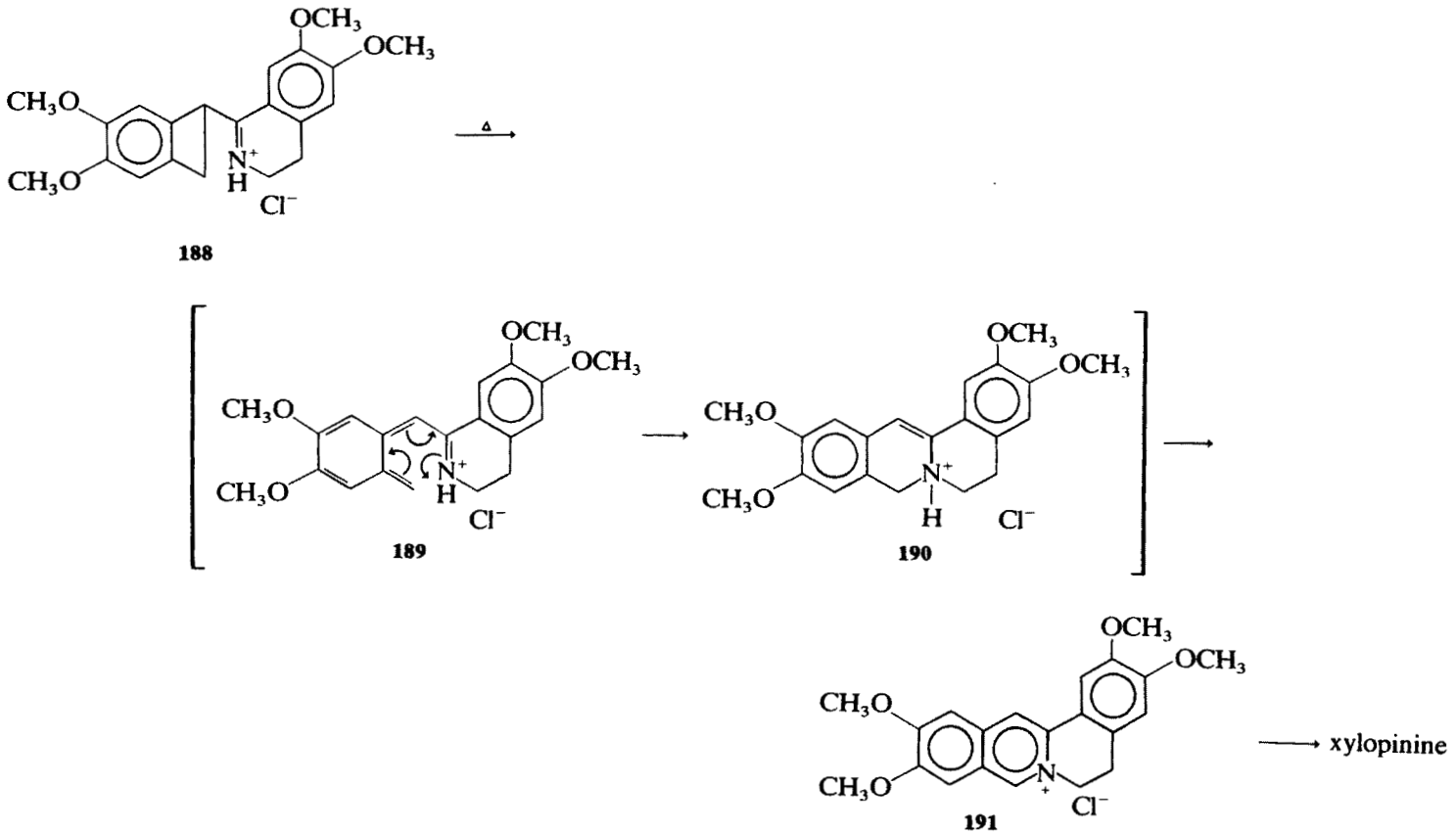
F. Electrocyclic Reaction

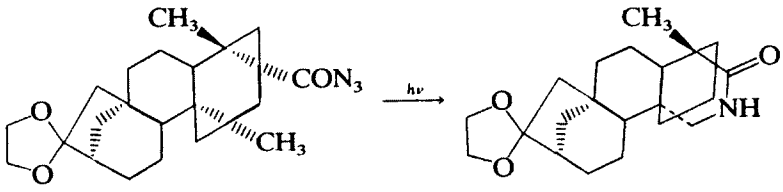
On the basis of the Woodward–Hoffmann rules[200] directing the formation of cyclohexadiene from hexa-1,3,5-triene, a new isoquinoline synthesis has been developed involving an electrocyclic reaction of an imine system with an *o*-quinodimethane generated *in situ* by thermolysis of benzocyclobutene derivatives.[201–203]

The benzocyclobutene **188** was subjected to thermolysis in bromobenzene at 150–170°C for 20 min in a current of nitrogen to furnish, presumably by cyclization of the *o*-quinodimethane **189** to the unstable dihydroprotoberberine **190** followed by dehydrogenation, the protoberberine **191** in 90% yield. Catalytic reduction of this protoberberine gave (±)-xylopinine.[204] Although this reaction has not been applied as yet to the synthesis of a simple isoquinoline system, discretine,[205] coreximine,[206] and hexadehydroyohimbane[207] have been synthesized by this method in good yield.

G. Photolysis of Azides

Photolysis of 2-methylcyclohexylacetyl azides gives the corresponding decahydroisoquinolin-3-one derivatives by insertion of the intermediate nitrene into the methyl group.[208,209] For example, Masamune irradiated the azide **192**, prepared by reaction of the hydrazide with nitrous acid, with a Hanovia 450-W mercury lamp at −10 to −15°C to obtain the isoquinoline **193**, which was converted into garryine.[208] This reaction has been used for the preparation of isoquinolines incorporated into complicated ring systems.[209]


OCH3
OCH3
CH3O
CH3O
N+
H
Cl−
Δ
188
189
190
191
xylopinine



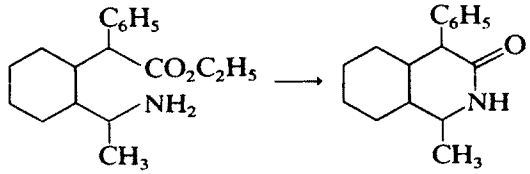
192 193

IV. TYPE 3 SYNTHESES

Isoquinoline syntheses belonging to this category, in which a bond is formed between the nitrogen atom and C-3, are of little value as general synthetic methods. The preparation of isoquinolines from isocoumarins and indanones is used in special cases.

A. Synthesis from Benzylamines

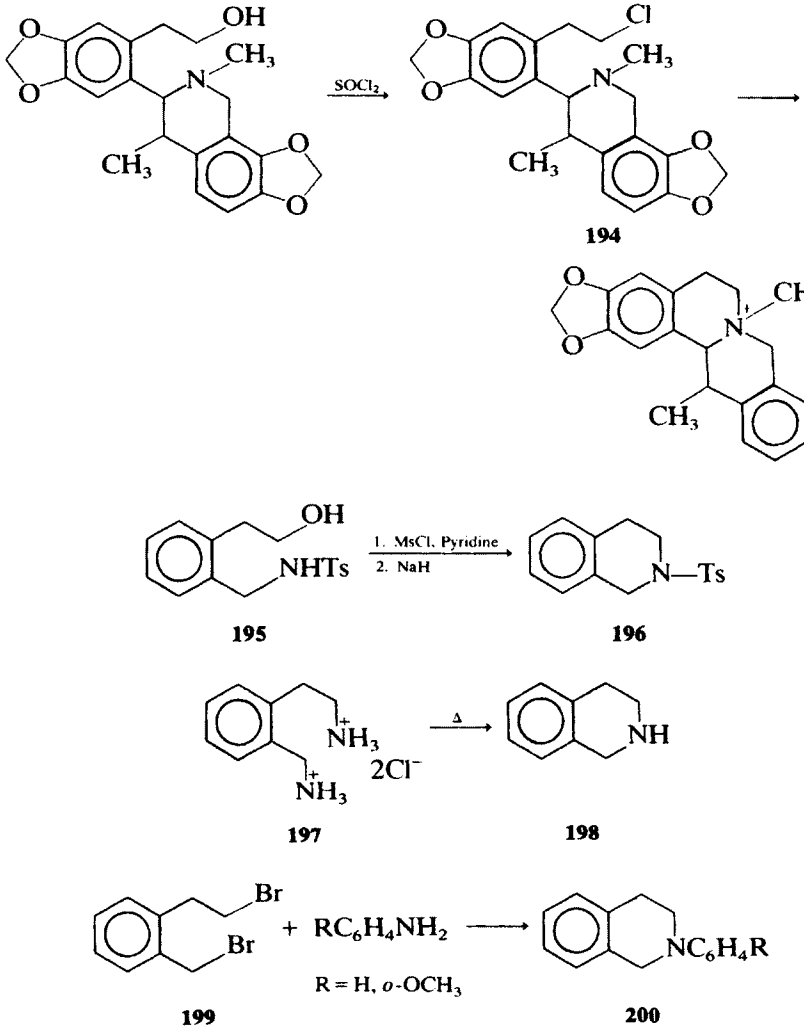
Benzylamines that have β-hydroxyethyl, carbonylmethyl, or alkoxycarbonylmethyl groups at the ortho position cyclize smoothly to form isoquinoline derivatives (Eq. 51). This is similar to the formation of isoquinolines from ortho-substituted phenethylamines in a type 2 synthesis.



(51)

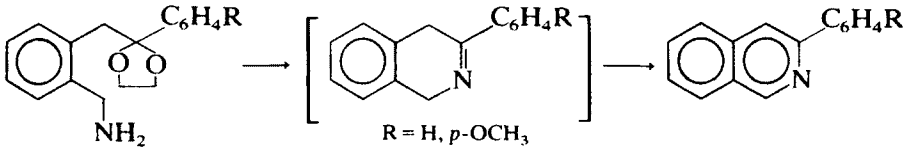
Nonaka et al.[210] reported a protoberberine synthesis by cyclodehydrohalogenation of the ε-halo alcohol **194** obtained from the corresponding phenethyl alcohol. An interesting example is the preparation of the isoquinoline derivative **196** by first treating the *o*-hydroxyethylbenzylamine *N*-tosylate **195** with mesyl chloride and pyridine and then cyclizing the resulting mixture with a strong base.[211]

The distillation of hydrochlorides of α,ω-diamino compounds, proceeds with elimination of ammonia to give piperidine derivatives. Helfer[212] applied this method to the synthesis of 1,2,3,4-tetrahydroisoquinoline (**198**) by distilling the hydrochloride of β-(2-aminomethylphenyl)ethylamine (**197**). Das and Basu[213] reported the conversion of homoxylene dibromide (**199**) to 1,2,3,4-tetrahydro-2-phenylisoquinoline (**200**) through the intermediate aniline hydrobromides. The use of dimethylamine instead of aniline resulted in the isolation of the bromide of the quaternary isoquinoline derivative.[214]

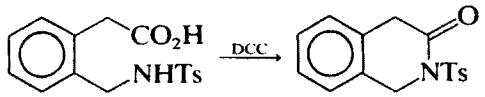


An isoquinoline synthesis from the amino ketone derivative **201** is reported,[215] and dehydration of an amino acid with dicyclohexyl carbodiimide (DCC)[216] (Eq. 52) or intramolecular cyclization of the amino ester **202** by heating gives the corresponding isoquinolin-3-ones.

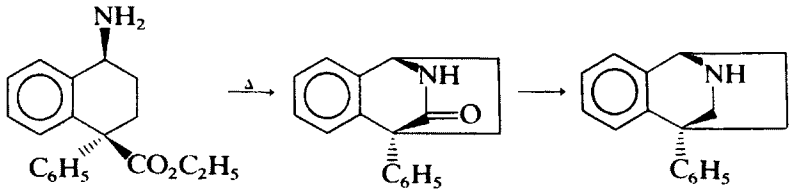
The amino group of the required ortho-substituted benzylamines can also be generated *in situ*. Reduction of the nitriles **203** and **204**[217,218] and of the tertiary amine **205**[219] and hydrolysis of the amide **206**[220] is immediately followed by cyclization of the generated amine with a carbonyl or carboxyl function to give the isoquinoline derivatives in good yield (this type of synthesis is limited to a few special cases). Hydrolysis of amides similar to **206** has been applied widely by Wiesner for the preparation of intermediates in the synthesis of diterpene alkaloids.[221]



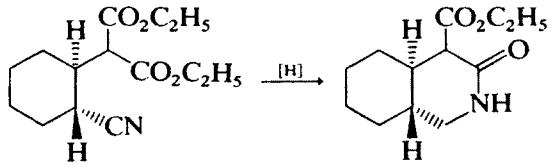
201



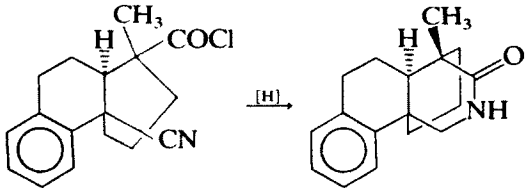
(52)



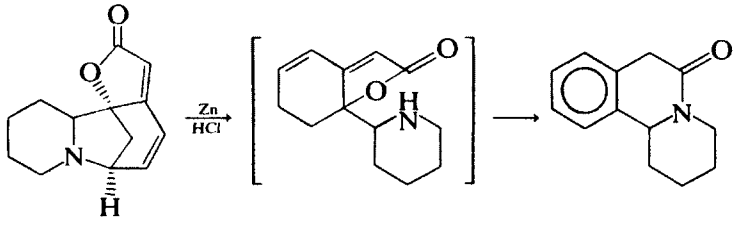
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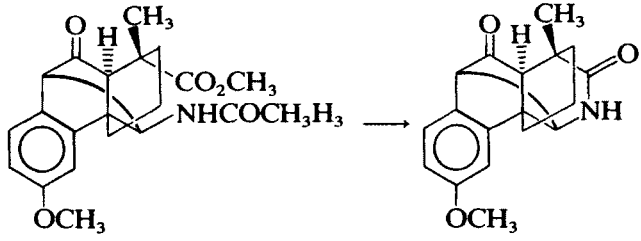
203



204



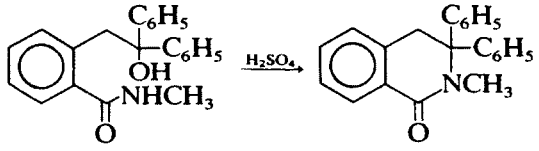
205



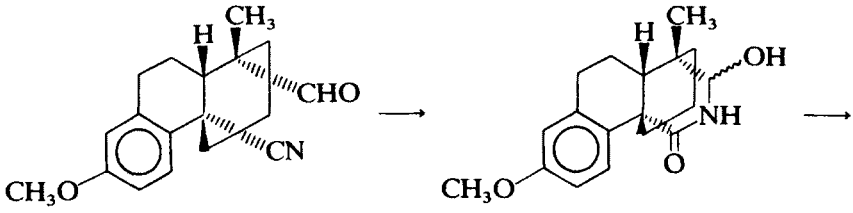
206

B. Syntheses from Benzamides

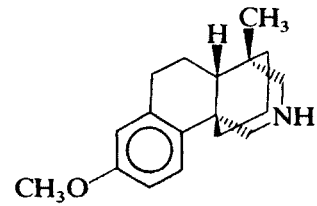
Acidic treatment of *o*-hydroxyethylbenzamides causes intramolecular dehydration to give tetrahydroisocarbostyrils.[222] For example, the benzamide **207** is converted into the isocarbostyril **208** with sulfuric acid at 0°C.[223] In similar fashion Nagata et al.[224] prepared the complex isoquinoline derivative **210**, a precursor of the diterpene alkaloid atisine, by partial hydrolysis of the nitrile **209** to the amide, followed by cyclization and reduction of the intermediate lactamol.



207 208

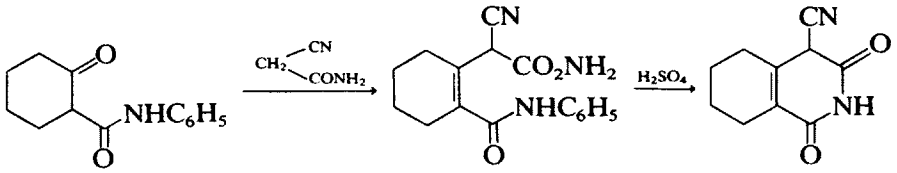


209



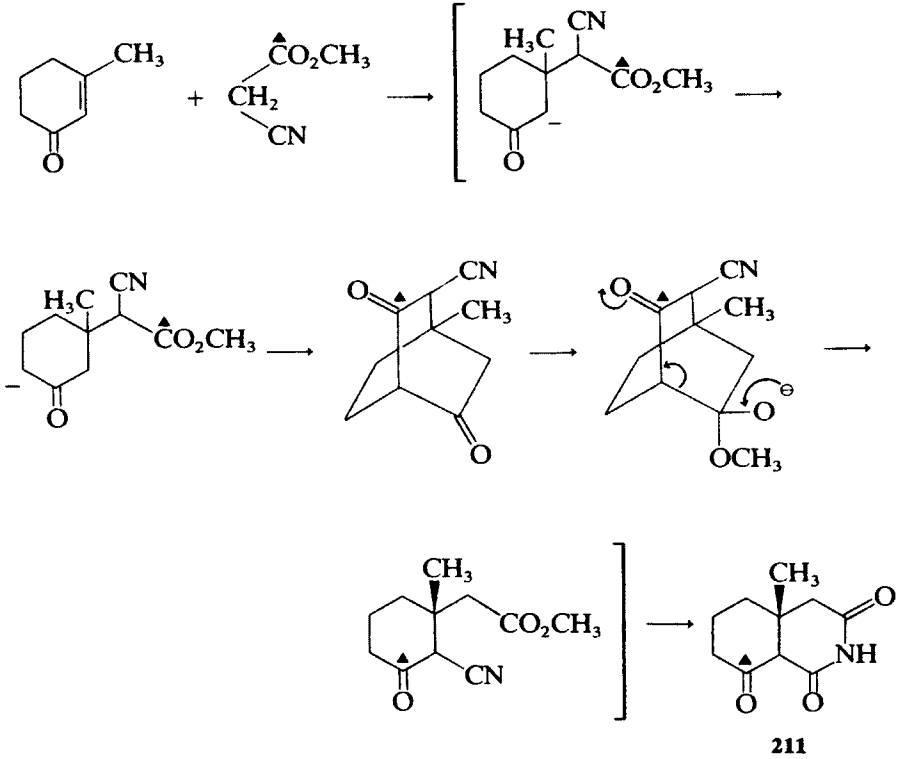
210

An intramolecular condensation of two amide functions gives homophthalimide derivatives, which can be converted into isoquinolines by reduction. Condensation of an amido ketone with cyanoacetamide in the presence of acetic acid and ammonium acetate gives a diamide, which is then cyclized to the isoquinoline derivatives by sulfuric acid (Eq. 53).[225]



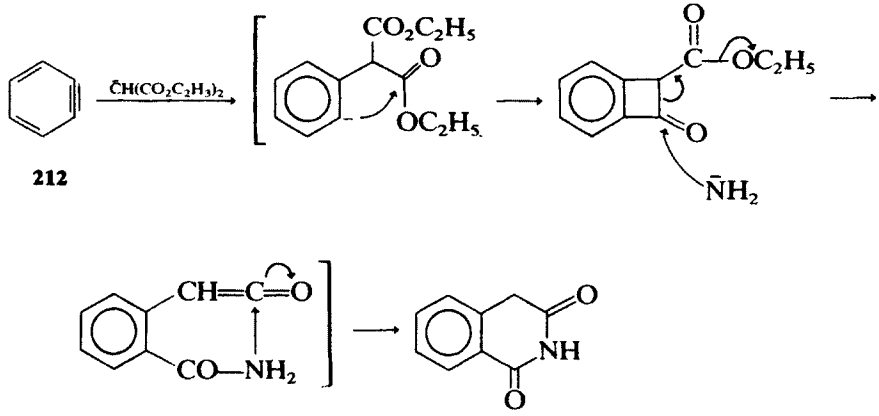
(53)

Some unusual reactions involving intermediate benzylamides have been reported. Reaction of 3-methylcyclohexenone with methyl cyanoacetate gives the isoquinoline-1,3,8-trione **211** through an intermediate cyano ester (Scheme 17).[226] Similarly, benzyne **212** reacts with ethyl malonate to afford the isoquinolone derivative **213**.[227]



211

Scheme 17

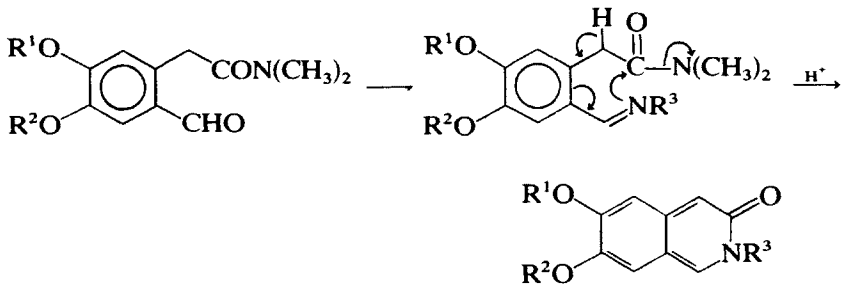


212

213

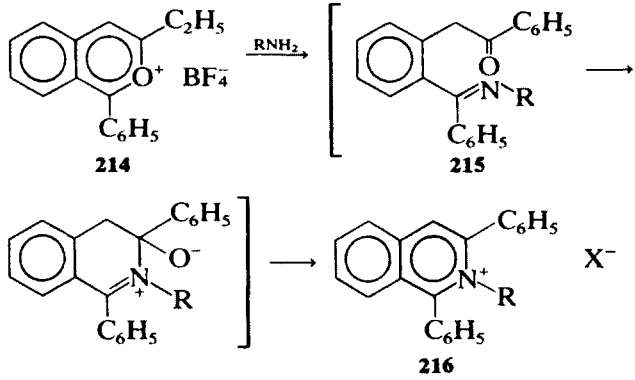
C. Syntheses from Imines

Schiff bases react with properly situated carbonyl,[228] carboxyl,[229] and amide[230] functions to give isoquinoline derivatives by intramolecular condensation. In most cases the imino derivatives are not isolated (Eq. 54).[230] For example, isochromylium salts **214** are easily transformed into the isoquinoline derivatives **216** by reaction with ammonia or primary amines through the intermediate imino derivative **215**.[228]



(54)

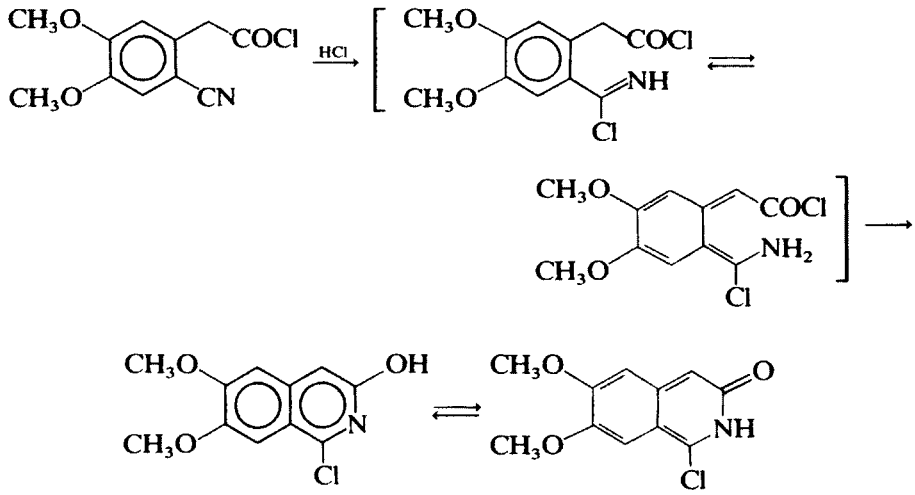
R	R	R	Yield (%)
CH_3	CH_3	CH_3	73
CH_3	CH_3	OH	80
CH_3	CH_3	NH_2	80
CH_3	CH_3	H	97
—CH_2—		CH_3	85
—CH_2—		$CH_2C_6H_5$	83
—CH_2—		OH	84
—CH_2—		NH_2	85
—CH_2—		H	quant.



214 215 216

R	Yield (%)
H	86
CH_3	45
C_2H_5	38
C_6H_5	45
p-HOC_6H_4	52

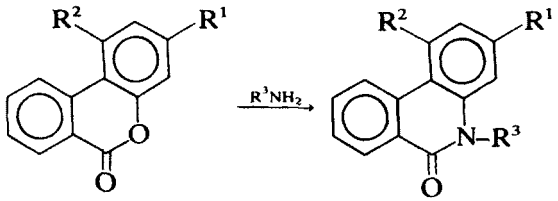
Iminochlorides, formed as intermediates in the reaction of nitriles with anhydrous hydrogen halide, react readily and intramolecularly with another imino group[231] or with a carboxylic acid or acid derivative[232] to afford isoquinoline derivatives. Simchen[232] prepared a large number of 1-chloro-3-hydroxyisoquinoline derivatives in excellent yield from *o*-cyanophenylacetyl chlorides by reaction with anhydrous hydrogen chloride (Scheme 18). This method is generally applicable to the preparation of 1-chloro-3-hydroxyisoquinolines.



Scheme 18

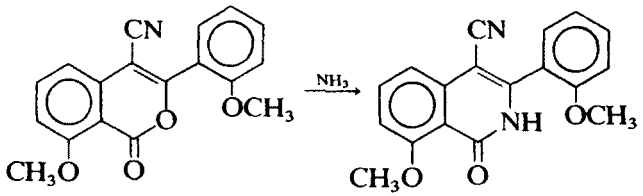
D. Syntheses from Isocoumarins

In 1885 Gabriel[233] reported the conversion of 3-phenylisocoumarin into 3-phenylisocarbostyril with ammonia. This reaction has been widely used since for the preparation of various isocarbostyril derivatives. Instead of ammonia,[234] urea[235] and ammonium formate[236] have been used. Reaction of primary amines with isocoumarins affords *N*-alkylisocarbostyrils,[237] as exemplified by the preparation of phenanthridinones (Eq. 55)[238] and 3-phenylisocarbostyryls (Eq. 56).[239] This general synthetic method has also been applied to the synthesis of the benzophenanthridine alkaloid chelerythrine[240] and recently to the synthesis of an isomer of narciprimine (Eq. 57).[241]

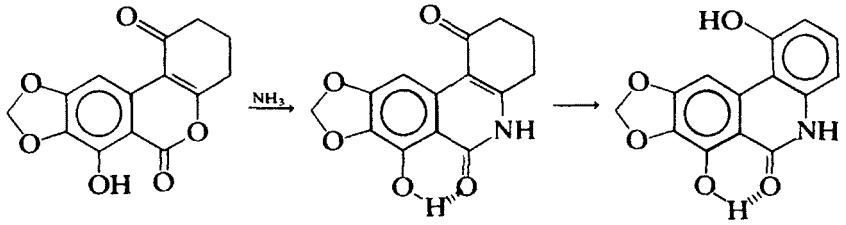


(55)

R^1	R^2	R^3	Yield (%)
OH	H	CH_3	80
CH_3	OH	H	50
CH_3	OH	CH_3	80
CH_3	OH	C_2H_5	47
C_5H_{11}	OH	CH_3	70



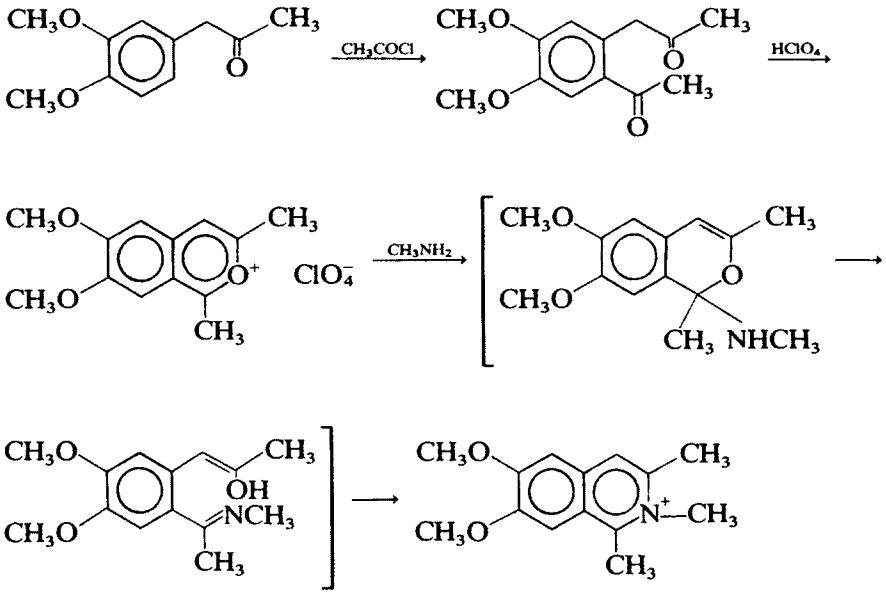
(56)



(57)

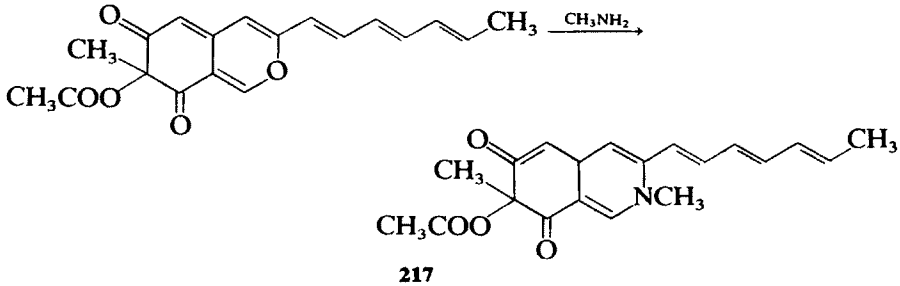
E. Syntheses from Benzopyrylium Salts

The reaction of benzopyrylium salts with ammonia or amines leading to isoquinolines was studied in detail by Kuznetsov et al.[242] The reaction mechanism is thought to proceed through the imine that is formed by ring opening of the pyrylium salt by nucleophilic attack of an amine (Scheme 19).[243] As the benzopyrylium salts can be prepared easily by acidic treat-



Scheme 19

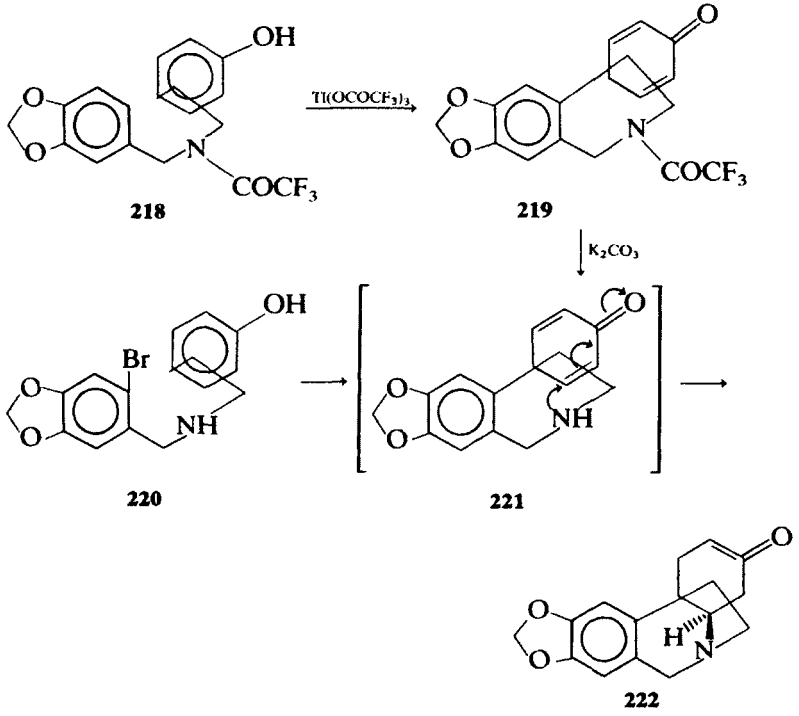
ment of *o*-acylbenzyl alkyl ketones derived from benzyl alkyl ketones by Friedel–Crafts acylation, this method offers a convenient synthesis of 1,2,3-trisubstituted isoquinolines. Benzopyrone derivatives are also converted into the corresponding isoquinoline derivatives,[244] as shown in the reaction of chrysodin (**217**) with methylamine.[245]



217

F. Synthesis by Michael Addition

Primary and secondary amines add to α,β-unsaturated ketones in a Michael-type reaction. An application of this reaction toward the synthesis of isoquinolines has been reported by many groups.[246] For example, oxocrinane (**222**) is obtained from the amido ketone **219** by hydrolysis with potassium carbonate through the intermediate **221**.[247] The ketone is easily synthesized by oxidation of the phenolic amide **218**. The intermediate **221** has also been invoked in the photolytic cyclizations of the phenolic



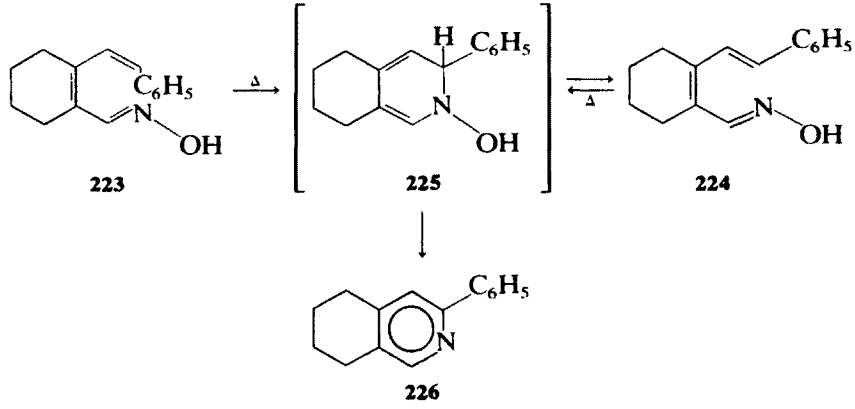
218 **219** **220** **221** **222**

bromoamine **220**.[248] Many similar reactions have been reported by Kametani et al.[249] Uyeo synthesized the crinan ring system by using a Michael addition of an amido nitrogen to an α,β-unsaturated ketone in the presence of an acidic catalyst.[250] This method, although not of general use for the synthesis of isoquinolines, provides a nice technique for the synthesis of Amaryllidaceae alkaloids.

G. Synthesis by Electrocyclic Reaction

Heating of azomethines derived from *o*-vinylbenzaldehydes affords isoquinolines by an electrocyclic reaction. The unsaturated oximes **223** and **224**

undergo cis–trans isomerization through the cyclized product **225**, which forms the isoquinoline derivative **226** on dehydration.[251] Similar cyclizations have been reported by other investigators.[252–254] This reaction is especially convenient for the synthesis of 5,6,7,8-tetrahydroisoquinolines because of its simplicity.



223 **225** **224** **226**

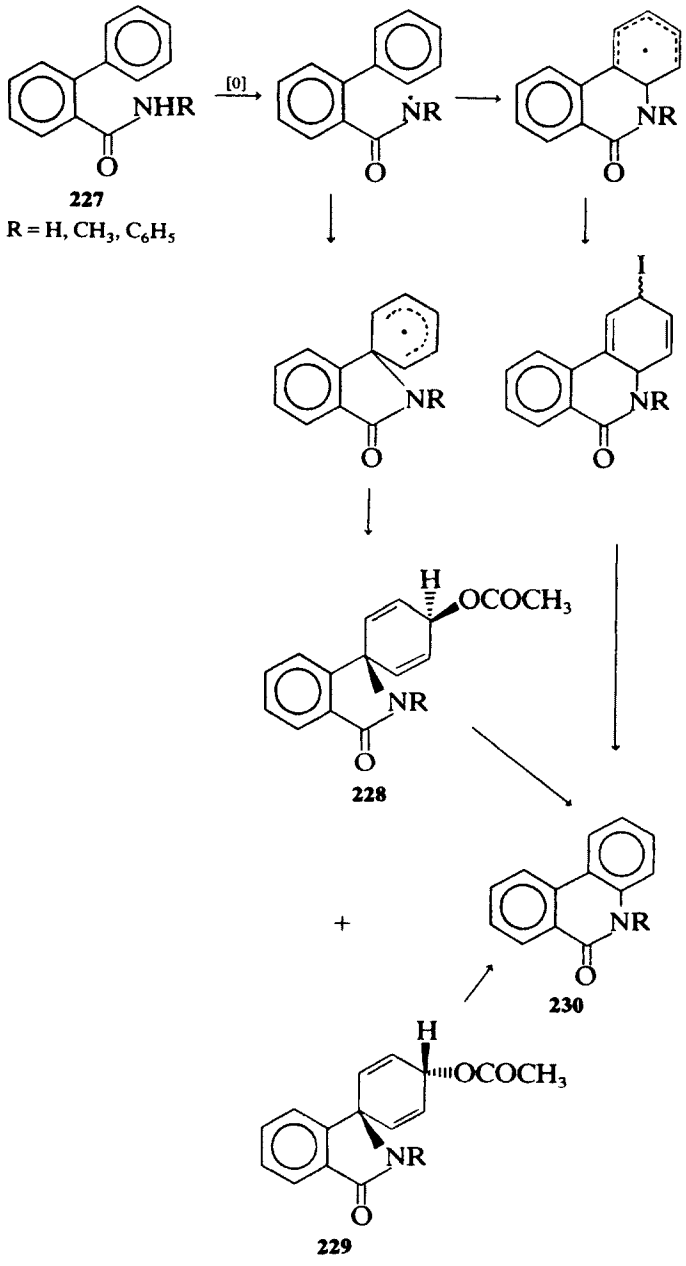
H. Synthesis by Radical Coupling

Although there is no report on the synthesis of simple isoquinolines by radical pairing, phenanthridone derivatives have been synthesized by a radical coupling reaction of biphenyl-2-carboxamides.[255,256]

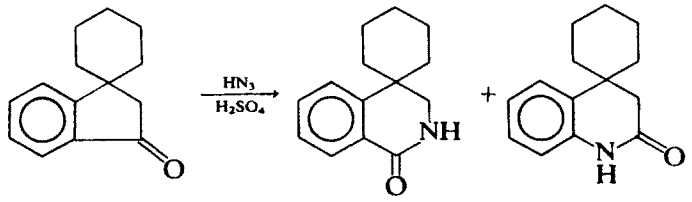
Oxidation of the carboxamide **227** ($R = CH_3$) with lead tetraacetate and iodine gives a mixture of the *cis*- and *trans*-3-oxoisoindoline-1-spirocyclohexa-2′,5′-dienes **228** ($R = CH_3$) and **229** ($R = CH_3$), which were easily hydrolyzed to the *N*-methylphenanthridone **230** ($R = CH_3$).[255] When the oxidation was carried out with *tert*-butyl hypochlorite and iodine in *tert*-butanol containing potassium *tert*-butoxide, the phenanthridone **230** was obtained in addition to the 1-spirocyclohexadienes.[255,256] The reaction mechanism is shown in Scheme 20. Similar coupling reactions of biphenyl-2-carboxamides were carried out with potassium persulfate[257,258] and under photolytic conditions.[257]

I. Beckmann and Schmidt Rearrangements and Related Rearrangements

The isoquinolone ring system is prepared from indanone by ring enlargement using the Beckmann or the Schmidt rearrangement. These reactions proceed smoothly and in good yield in some cases, but their disadvantage is that the products usually consist of a mixture of the expected isocarbostyril

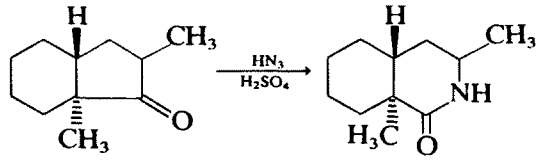


Scheme 20

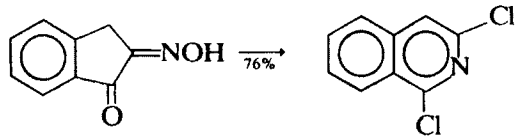


(58)

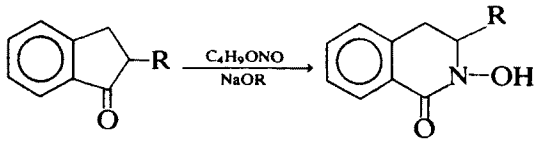
and the undesired carbostyril (Eq. 58).[259] Typical examples of the application of the Schmidt rearrangement[260] and the Beckmann reaction[261,262] to the preparation of isoquinoline derivatives are shown in Eqs. 59, 60, and 61,



(59)



(60)

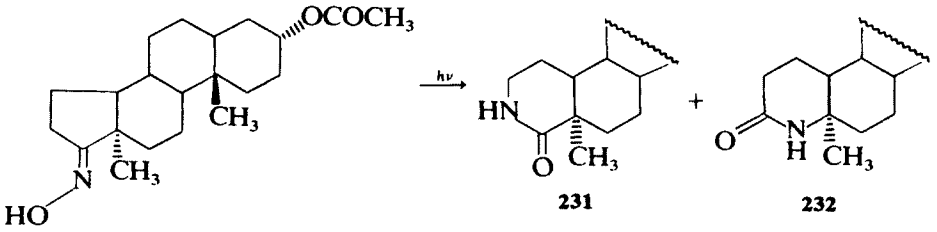


(61)

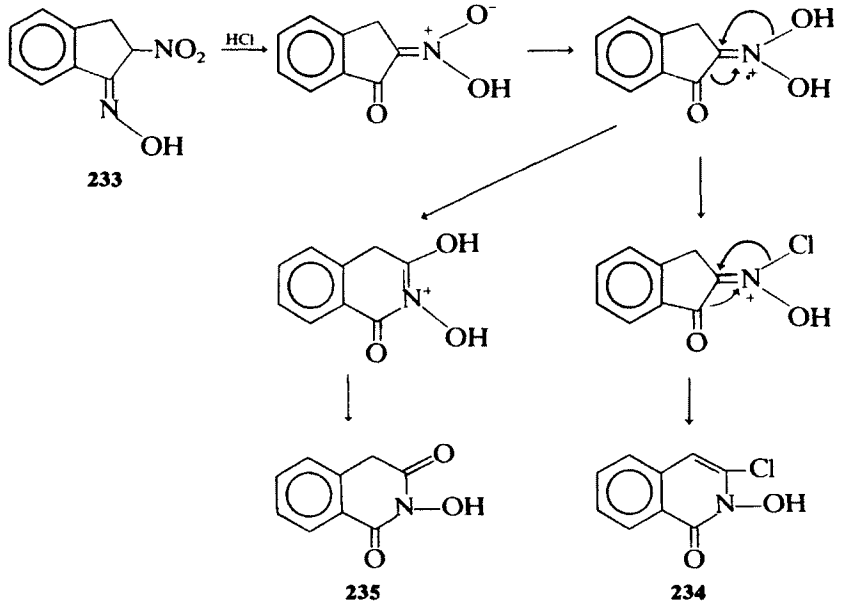
R	Yield (%)
CH_3	71 (92)[a]
C_2H_5	71 (94)[a]
n-C_3H_7	74 (95)[a]
i-C_3H_7	81 (96)[a]
n-C_4H_9	91 (93)[a]
t-C_4H_9	96 (96)[a]

[a] Based on recovered starting material.

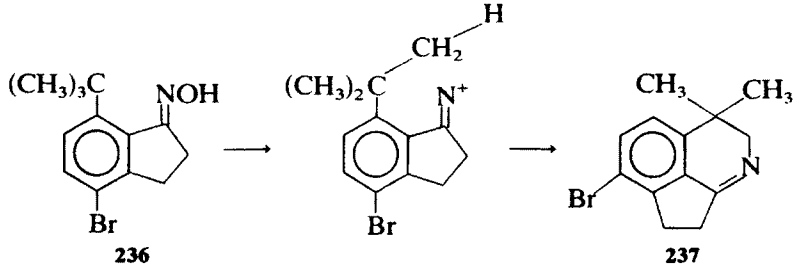
respectively. These rearrangements constitute a general synthesis of isocarbostyrils; the basic skeletons of the lycorine system,[263] of diterpene alkaloids,[264] and of azasteroids[264] have been prepared by this way. Usually, the Beckmann rearrangement is carried out in the presence of a Lewis acid. Two groups[265,266] recently reported a synthesis of the azasteroids **231** and **232** by a photochemical Beckmann rearrangement. Isoquinoline formation by the abnormal rearrangement of oximes is also reported. On treatment with ethanolic hydrochloric acid, 2-nitro-1-indanone oxime (**233**) undergoes



a novel isomerization to give 3-chloro-2-hydroxyisocarbostyril (**234**) and *N*-hydroxyhomophthalimide (**235**).[267]



The oxime **236** is converted into the isoquinoline **237** with polyphosphoric acid as a result of bond insertion to the electron-deficient nitrogen. *D*-Labeling studies have shown that an iminium cation, rather than a vinyl nitrene, is the attacking electrophile;[268] however, these reactions are of little value for the synthesis of isoquinolines.

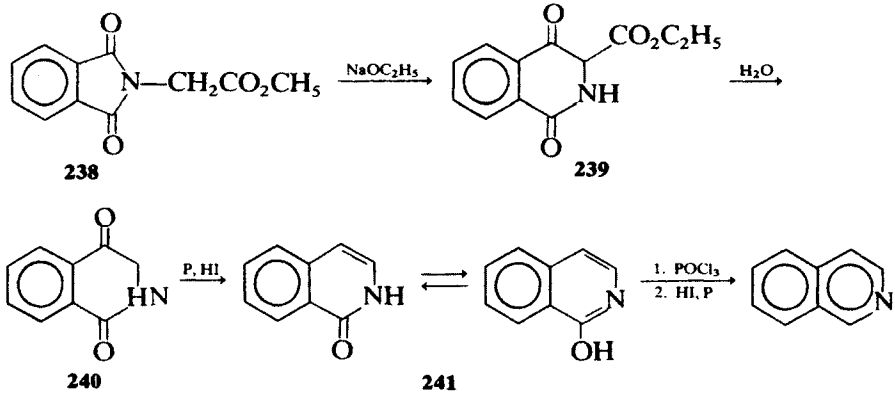


V. TYPE 4 SYNTHESES

This type of isoquinoline synthesis is characterized by bond formation between C-3 and C-4 and has been used only sparingly.

A. Gabriel–Colman Method

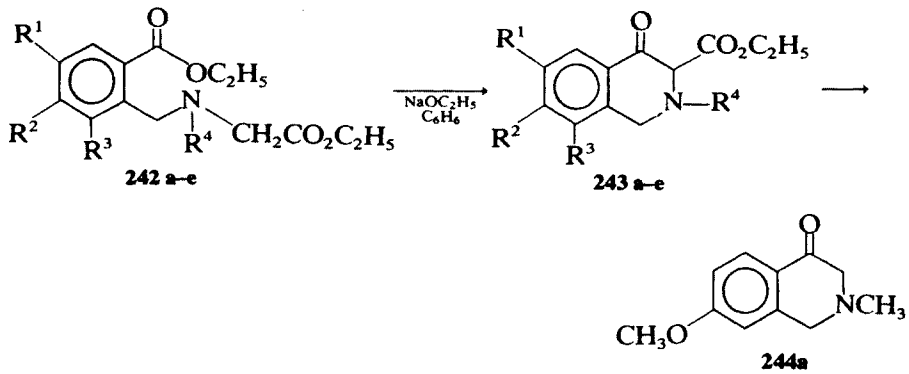
The rearrangement of phthalylglycine esters is a typical type 4 synthesis. In this reaction, first reported by Gabriel and Colman[269] in 1900, ethyl phthalylglycinate (**238**) is heated with sodium ethoxide in ethanol to give 3-ethoxycarbonyl-4-hydroxyisocarbostyril (**239**). Hydrolysis, followed by decarboxylation and reduction of 4-hydroxyisocarbostyril (**240**) with hydriodic acid and phosphor, gave the expected compound **241**. The isocarbostyril can



then be converted by standard procedures to isoquinoline. As this reaction includes several steps and the yields are poor, it is not used as a general method for the synthesis of isoquinolines.

B. Dieckmann Condensation

Dieckmann reaction of the amino diester **242a** gave the β-keto ester **243a**, which was converted into the 4-ketoisoquinoline **244a**.[270] Several 3-ethoxycarbonyl-2,3-dihydro-4(1H)-isoquinolones (**243b** through **g**) and their corresponding ketones have been prepared by this method.[271,272] The advantage of this method is that the isoquinolones **244**, which because of their substitution pattern are difficult to synthesize by other methods such as the Bischler–Napieralski or the Pictet–Spengler reaction, can be prepared in reasonable yields in a few steps.



242 a–e

243 a–e

244a

	R^1	R^2	R^3	R^3	Yield (%)[a]
a,	H	H	H	CH_3	—
b,	H	OCH_3	H	$CH_2C_6H_5$	68
c,	OCH_3	OCH_3	H	CH_3	35[b]
d,	OCH_3	OCH_3	H	$CH_2C_6H_5$	71[b]
e,	H	OCH_3	OCH_3	$CH_2C_6H_5$	59[b]
f,	H	Cl	H	$CH_2C_6H_5$	—
g,	H	H	H	$CH_2C_6H_5$	56

[a] Yield of **243**.
[b] Isolated as hydrochloride.

C. Miscellaneous Methods

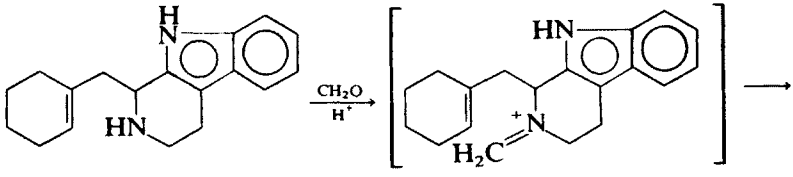
Winterfeldt et al.[273] prepared the yohimbane system **246** from the 1-allyl-1,2,3,4-tetrahydro-β-carboline **245** by [3,3]sigmatropic rearrangement and subsequent cyclization.

The basic skeleton **248** of the diterpene alkaloids was obtained by Wiesner from compound **247** by ring closure involving electrophilic attack of the isocyanate function at an active methine group.[274]

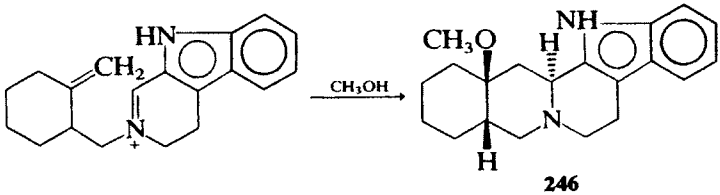
Oppolzer and Keller[275] obtained the benz[*c*]phenanthridine **251** by thermal rearrangement of the benzocyclobutene derivative **249** and subsequent intramolecular cyclization of the intermediate *o*-quinodimethane **250**. In a general approach to the preparation of the lycorine skeleton, Ganem[276] prepared the tricyclic compound **253** from the unsaturated ketone **252** by Michael addition.

VI. TYPE 5 SYNTHESES

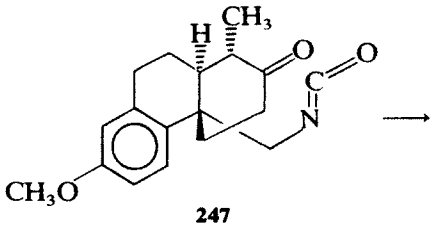
The synthetic methods discussed in this section involve cyclization between C-4 and C-4a of the isoquinoline nucleus. The Pomeranz–Fritsch



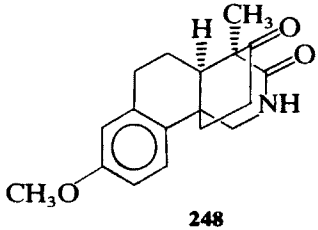
245



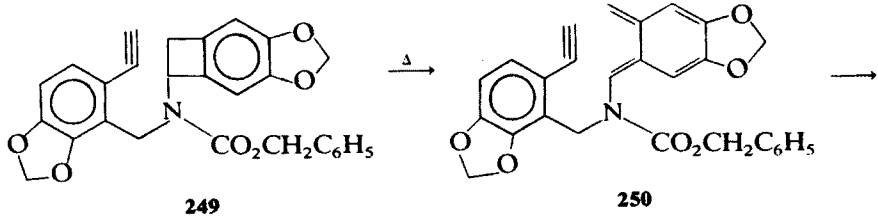
246



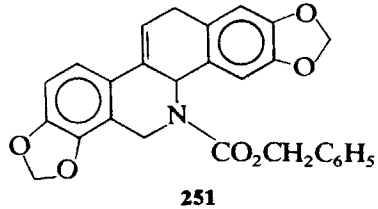
247



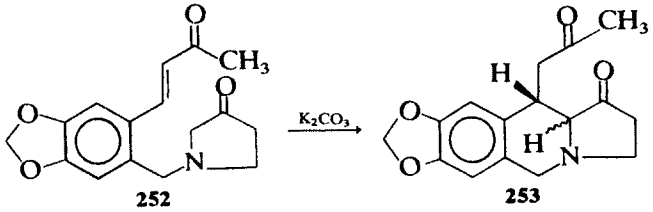
248



249 250



251

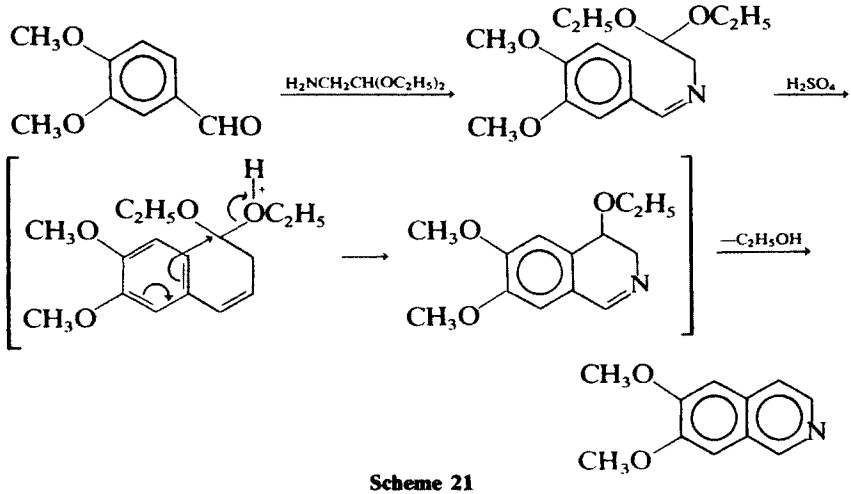


252 253

reaction is typical of these methods; it has been extensively studied, and several modifications have been reported. Recently, the bond formation between C-4 and C-4a has been achieved by photochemical and benzyne reactions.

A. Pomeranz–Fritsch Reaction[9]

The cyclization of benzalaminoacetals in the presence of acid to yield isoquinolines is called the *Pomeranz–Fritsch reaction.*[277,278] This reaction proceeds in two stages; the first involves the formation of the benzalaminoacetal, and the second entails the acid catalyzed cyclization to the isoquinoline. The Pomeranz–Fritsch reaction is an intramolecular electrophilic aromatic substitution,[279] and the ease of cyclization depends on the susceptibility of the benzene ring to electrophilic attack (Scheme 21). Thus



Scheme 21

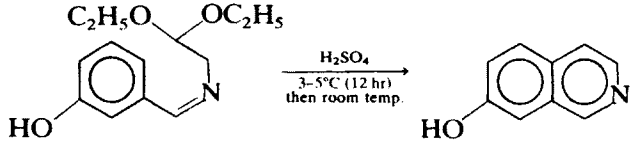
compounds with groups donating electrons to the cyclization site will react under relatively mild conditions, whereas unsubstituted and halogen-substituted derivatives will require higher temperatures and more acidic media for the cyclization. Nitrobenzalaminoacetal does not react at all.

Schiff base formation from aromatic aldehydes and aminoacetals occurs easily and in good yield, and the product can be used for the cyclization either directly or after purification. In general, the condensation proceeds smoothly when a mixture of aldehyde and aminoacetal is kept aside at room temperature or on the steam bath.

Cyclization of the benzalaminoacetals is effected with sulfuric acid, which has been used in concentrations ranging from fuming acid to approximately 70% sulfuric acid or in admixture with such reagents as hydrogen chloride, acetic acid, phosphorus pentoxide, and phosphoryl chloride.[9] Other reagents

used in this cyclization are polyphosphoric acid,[280] super polyphosphoric acid,[281] boron trifluoride,[282] and chlorosulfonic acid.[283]

The yields of isoquinolines are remarkably affected by the concentration of the sulfuric acid (Eq. 62).[284] A small deviation from the optimum acid

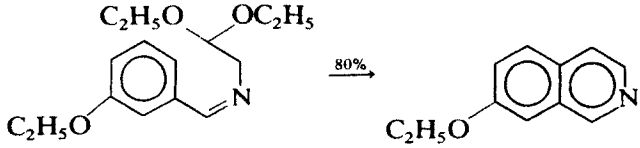


(62)

Concentration of H_2SO_4 (%)	84	82	80	78	76	62
Yield (%)	31	44	64	59	43	30

concentration results in a substantial decrease in yield. Variation of the yields with acid concentration may be attributed, at least in part, to the fact that competitive hydrolytic cleavage of the Schiff base may occur under conditions of the cyclization. The cyclization has been carried out at temperatures from 0°C or below in the case of alkoxy- or hydroxybenzalamines to 150 to 160°C in the case of halobenzalaminoacetals.

Cyclization of unsymmetrically substituted benzalaminoacetals such as 3-ethoxybenzalaminoacetal **254** may be expected to lead to either a 5-ethoxy- or a 7-ethoxyisoquinoline, depending on the direction of ring closure. Experimentally, only 7-ethoxyisoquinoline (**255**) is obtained in

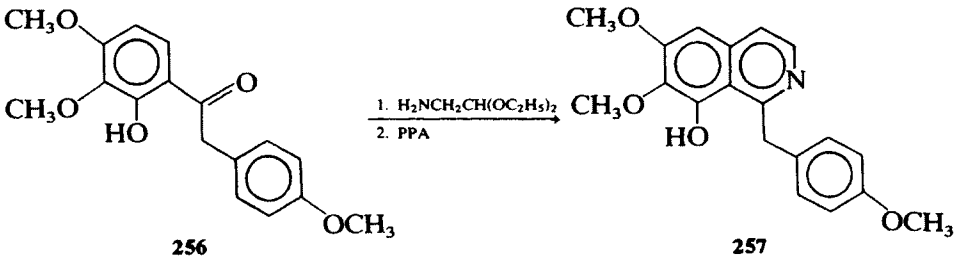


254 **255**

more than 80% yield.[285] Similarly, 3,4-methylenedioxybenzalaminoacetal affords only 6,7-methylenedioxyisoquinoline, and 3,4-dimethoxybenzalaminoacetal yields 6,7-dimethoxyisoquinoline.[286] However, 3-hydroxybenzalaminoacetal is transformed into a mixture of 7-hydroxy- and 5-hydroxyisoquinoline containing the former as the main product.[287]

The use of ketones instead of aromatic aldehydes in the Pomeranz–Fritsch reaction yields 1-substituted isoquinolines. For instance, 1-methylisoquinolines are obtained from acetophenones and aminoacetals in the presence of boron trifluoride and trifluoroacetic anhydride[282] or super polyphosphoric acid.[281] The 1-benzylisoquinoline **257** is formed from the ketone **256**,[288] but an extension of this reaction usually results in poor yields, possibly because of difficulties encountered in the condensation of the ketones with aminoacetals to form the Schiff bases.

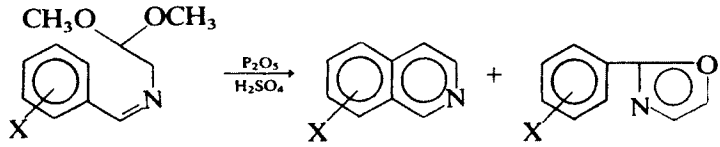
Application of the Pomeranz–Fritsch synthesis as a preparative method



256 257

for isoquinolines is often limited by low yields. Although the yields vary from 0% to more than 80%, they are mostly below 50%. In the case of 3-alkoxy-, 3-hydroxy-, and 3-halobenzalaminoacetals, satisfactory results are obtained, whereas 2- or 4-alkoxy (or hydroxy) derivatives either do not react or afford the isoquinolines only in low yield. But the Pomeranz–Fritsch reaction offers the possibility of preparing substituted isoquinolines that would be otherwise difficult to obtain by the Bischler–Napieralski or the Pictet–Spengler reaction. For example, 8-substituted and 7,8-disubstituted isoquinolines are best prepared by the Pomeranz–Fritsch method, whereas the Bischler–Napieralski reaction and the Pictet–Spengler reaction are better suited for the preparation of 5,6- and 6,7-disubstituted isoquinolines. Furthermore, the Pomeranz–Fritsch method yields fully aromatized isoquinolines, whereas partially or fully hydrogenated isoquinolines are obtained by the two methods using phenethylamines.

As mentioned earlier, the Pomeranz–Fritsch reaction has been used for the preparation of a number of isoquinolines, and the yield varies from quite good with certain methoxy substituents to zero with nitro groups; in the latter case, the products are oxazoles (Scheme 22). Brown has reported a competition between isoquinoline and oxazole formation in this reaction.[289]

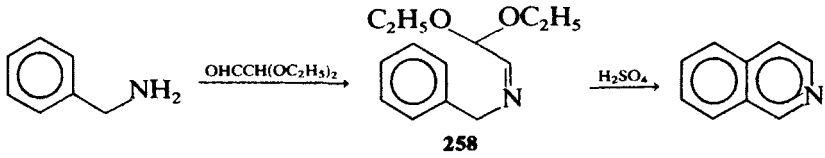


Starting Benzaldehyde	Total Yield (%)	Oxazole–Isoquinoline
o-CH_3	18	3–97
m-CH_3	21	6–94
p-CH_3	22	6–94
o-Cl	9	36–64
m-Cl	25–50	61–39
p-Cl	14	23–77
o-NO_2		100–0
m-NO_2		100–0
p-NO_2		100–0

Scheme 22

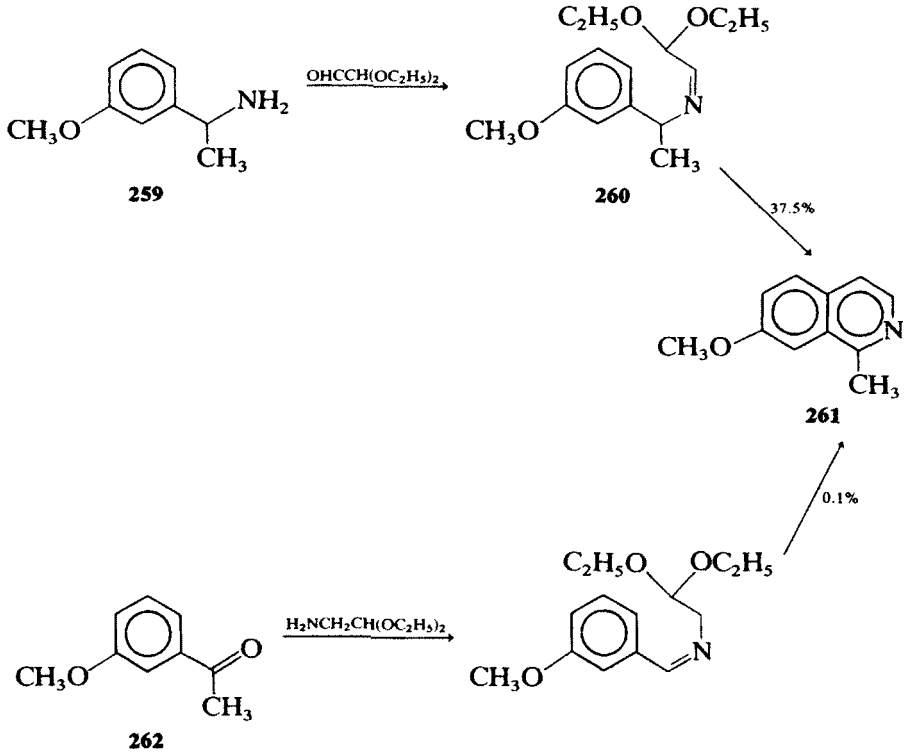
B. Variation of Pomeranz–Fritsch Reaction

An alternative method reported by Schlittler and Müller[290] is available in the reaction of benzylamine with glyoxal semiacetal. Cyclization of the product **258** so obtained with sulfuric acid gives the same isoquinoline as



258

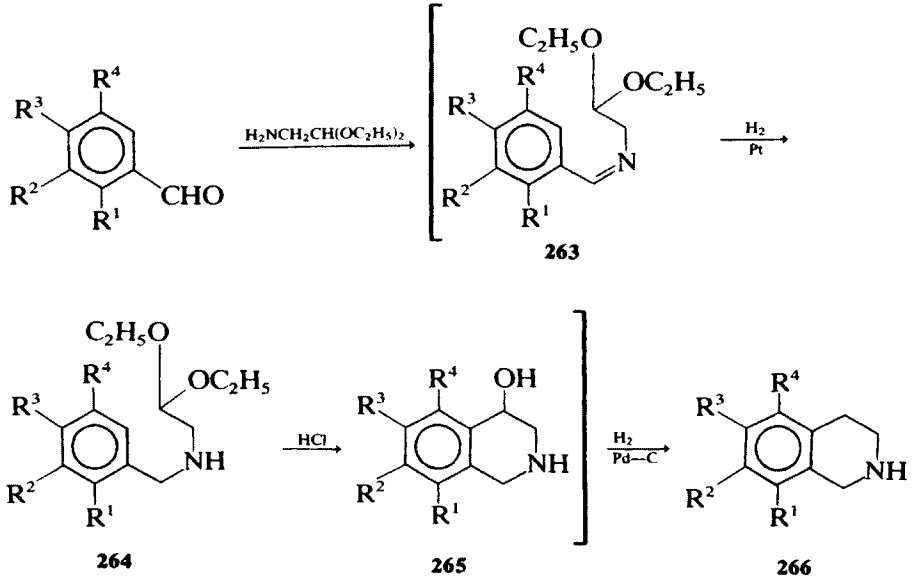
that obtained from the Schiff base derived from the aromatic aldehyde and aminoacetal. This variation is especially useful for the synthesis of 1-substituted isoquinolines. Compared with the difficulty of condensing an aminoacetal with a ketone, the formation of the Schiff base from benzylamine is relatively facile. α-Phenylethylamine **259** was first reacted with glyoxal semiacetal to give the Schiff base **260**, which on treatment with concentrated sulfuric acid afforded 1-methylisoquinoline **261** in 38% yield. This was a large improvement over previous yields in the reaction between acetophenone **262** and aminoacetal.[290]



259 **260** **261** **262**

C. Bobbitt's Modification of Pomeranz–Fritsch Reaction

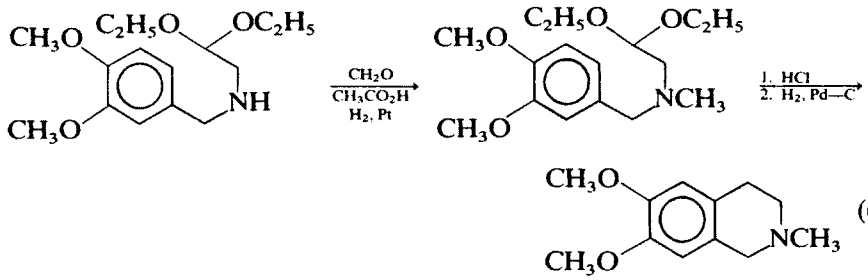
The modifications introduced by Bobbitt et al.[291] in 1965 gave 1,2,3,4-tetrahydroisoquinoline derivatives in good yield. In this variation of the Pomeranz–Fritsch reaction the Schiff base **263** obtained from the aromatic aldehyde and the aminoacetal is first hydrogenated over platinum oxide to the secondary amine **264**, which is then immediately cyclized with 6*N* hydrochloric acid. The resulting 1,2,3,4-tetrahydro-4-hydroxyisoquinoline **265** is hydrogenolyzed over 5% palladium–carbon to afford the 1,2,3,4-tetrahydroisoquinoline **266**. 2-Alkyl-1,2,3,4-tetrahydroisoquinolines are



R^1	R^2	R^3	R^4	Yield (%)
H	OH	OCH_3	H	67
H	OCH_3	OH	H	71
OH	OCH_3	H	H	75
H	OCH_3	OCH_3	OCH_3	78
H	OCH_3	OCH_3	H	68
H	OCH_3	H	H	58

also available by this modification by subjecting the secondary amine to reductive alkylation with formalin before cyclization and catalytic hydrogenation (Eq. 63).[292]

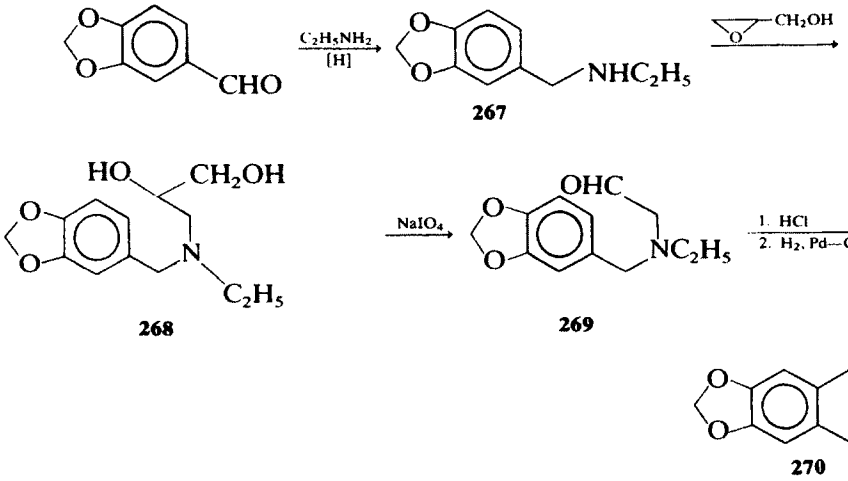
Because of the mild reaction conditions, the simple procedure, and the generally good yields, Bobbitt's modification is now widely used as a general procedure for the preparation of 1,2,3,4-tetrahydroisoquinolines having



(63)

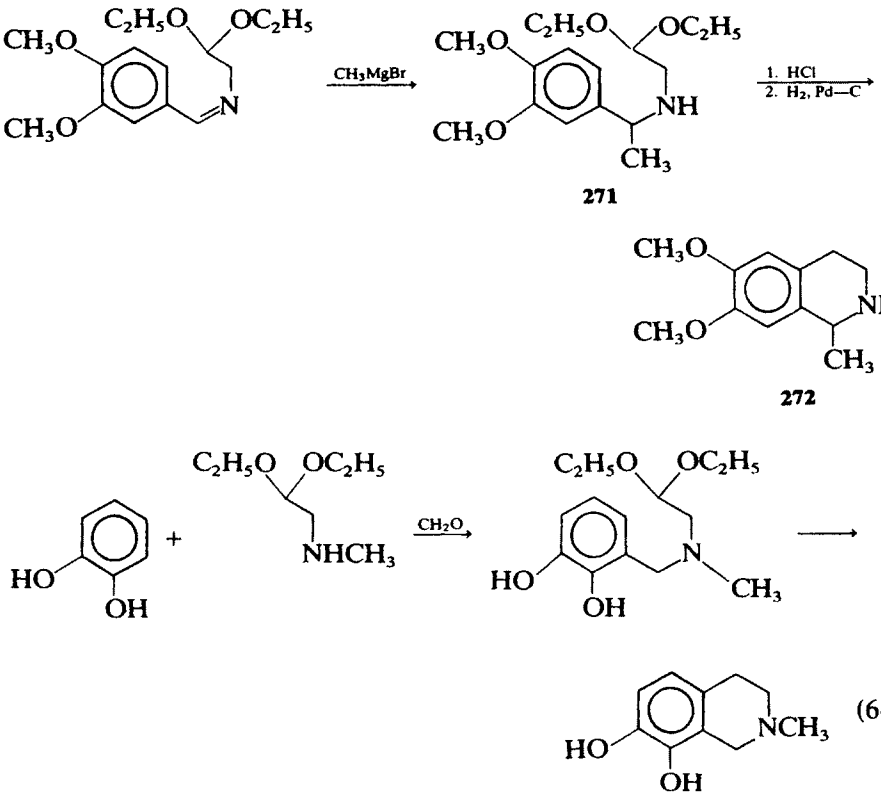
substituent(s) at C-1, N, C-5, C-6, C-7, and C-8. The scope of the reaction has been broadened considerably by the introduction of many recently reported variations.

Reductive condensation of an aromatic aldehyde with an alkylamine, followed by *N*-alkylation of the secondary amine **267** with glycidol, gave the tertiary amine **268**, which was converted into the unstable α-aminoaldehyde **269** with sodium metaperiodate. Cyclization of this compound with hydrochloric acid and subsequent catalytic hydrogenation as usual afforded the 2-alkyl-1,2,3,4-tetrahydroisoquinoline **270**.[292]

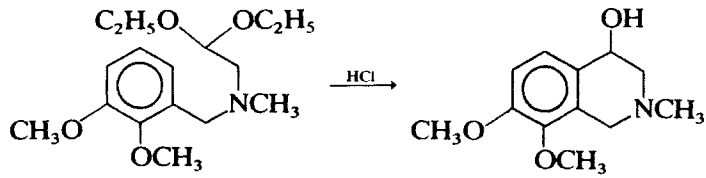


The Schiff base can be treated with an alkyl Grignard reagent, and the resulting secondary amine **271** is then cyclized and reduced to afford the 1-alkyl-1,2,3,4-tetrahydroisoquinoline **272**.[293] This variation is an effective method for the synthesis of 1-alkyl- or 1-aryl-1,2,3,4-tetrahydroisoquinolines.

Bobbitt and Dutta[294] have developed a new synthesis of the intermediate acetals by a Mannich condensation of the appropriate phenols with formaldehyde and the substituted amino acetals. This procedure, in combination with the cyclization step, constituted a very practical modification of the Pomeranz–Fritsch reaction (Eq. 64).



The cyclizations of aminoacetals to 1,2,3,4-tetrahydroisoquinolines proceed through the intermediacy of 4-hydroxyisoquinolines that can be isolated if the catalytic hydrogenolysis is omitted.[295,296] This fact adds to the importance of Bobbitt's contribution, because syntheses of 4-hydroxyisoquinoline derivatives are difficult to achieve by other methods. For example, 1,2,3,4-tetrahydro-4-hydroxy-7,8-dimethoxy-2-methylisoquinoline (**274**) can be obtained in 90% yield from the tertiary aminoacetal **273** on treatment with 6*N* hydrochloric acid at room temperature overnight.[297]

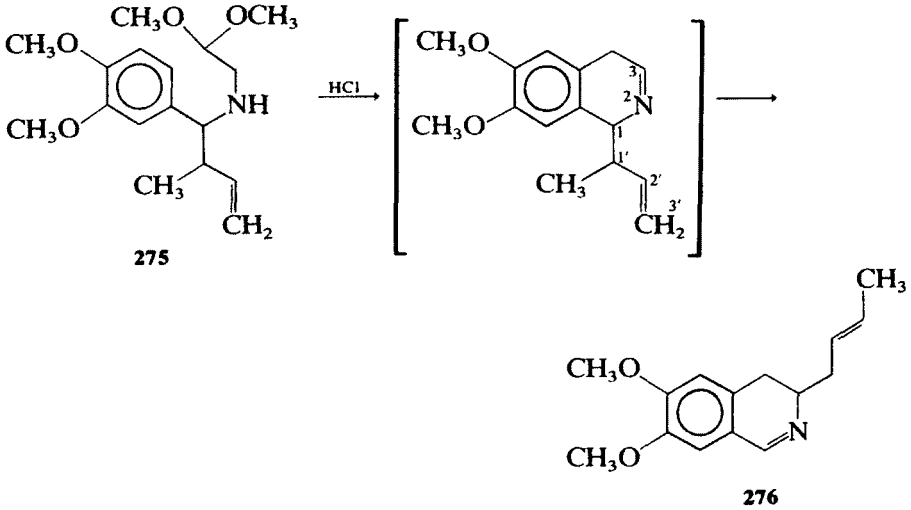


273 274

Because of its simplicity, Bobbitt's modification has been widely applied in the synthesis of isoquinoline alkaloids. Benzylisoquinoline,[298] proaporphine,[299] and protoberberine alkaloids[300] and alkaloids of the cularine[301]

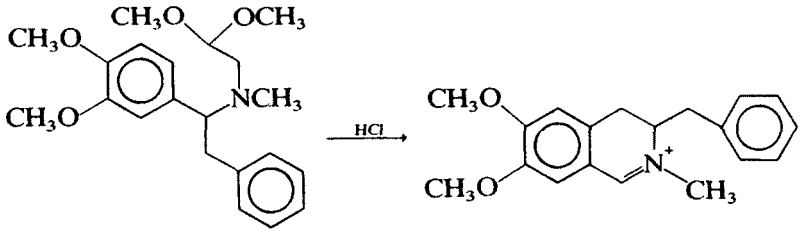
and ochotensine types[302] are some of the isoquinoline alkaloids that have been prepared by this method.

In this cyclization some abnormal reactions occur. A rearrangement has been observed during the attempted formation of 1-allyl- and 1-propynylisoquinolines.[303] Acid treatment of the secondary amine **275** gave 3-allyl-3,4-dihydro-6,7-dimethoxyisoquinoline (**276**) by a concerted supra-



275 **276**

facial [3,3]sigmatropic rearrangement of the intermediate dihydroisoquinoline. A similar rearrangement is observed during the synthesis of 1-benzylisoquinolines (Eq. 65), and an intermolecular reaction mechanism is

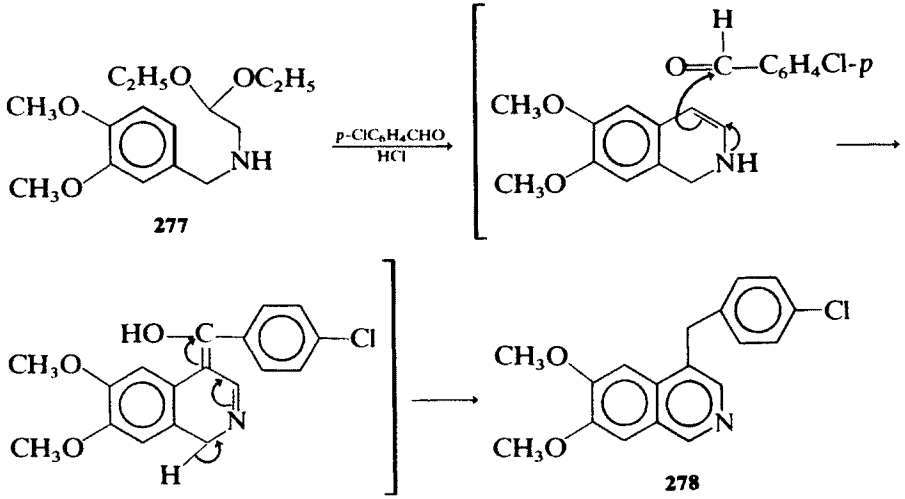


(65)

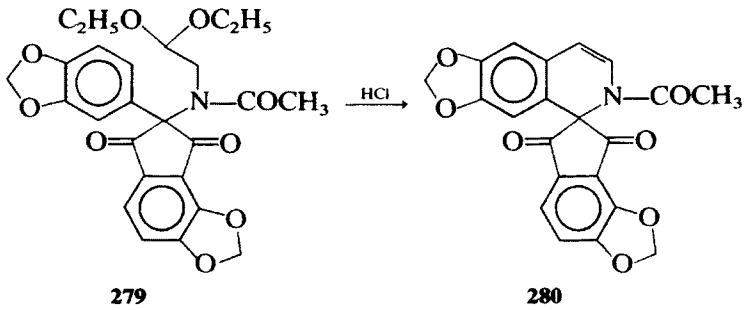
proposed for the rearrangement of 1-benzyl-1,2-dihydroisoquinolines into 3-benzyl-3,4-dihydroisoquinolines.[304]

The reactivity of the intermediate 1,2-dihydroisoquinolines has been utilized in the preparation of 4-substituted tetrahydroisoquinolines. Treatment of the amino acetal **277** with aromatic aldehydes in the presence of hydrochloric acid gave the 4-benzylisoquinolines **278** in high yield.[291,305] Similarly, the reaction of aminoacetal and glyoxylic acid afforded 4-carboxymethylisoquinoline.[297]

Acid treatment of the *N*-acyl derivative **279**[302] or the *N*-tosylaminoacetals **281**[306,307] afforded in good yield the *N*-acyl- or *N*-tosyl-



1,2-dihydroisoquinolines **280** or **282**, respectively, and further treatment of the latter gave the fully aromatic isoquinolines **283** (Scheme 23).[306]

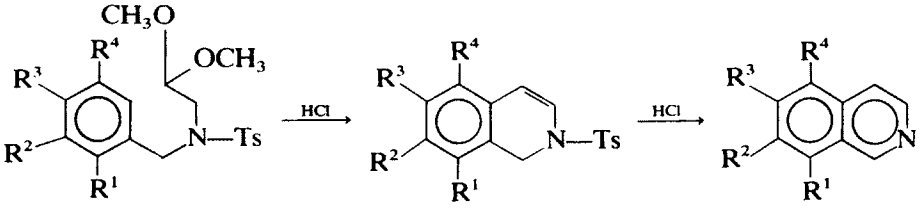


D. Friedel–Crafts Reactions

(a) *Alkylation*

Treatment of benzylamine or substituted benzylamines with 2-bromoethanol and then hydrobromic acid, followed by Friedel–Crafts alkylation in the presence of aluminum chloride in hot decalin, gave isoquinolines (Eq. 66).[308] This simple method for the preparation of tetrahydroisoquinolines has been used only sparingly.

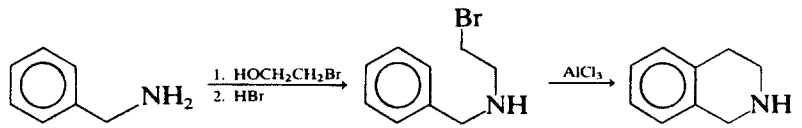
N-β-Hydroxyethylbenzylamines **284** have been converted into 1,2,3,4-tetrahydroisoquinolines by action of acids such as hydrobromic acid,[309] sulfuric acid,[310] and polyphosphoric acid (Scheme 24).[311] Similarly, *N*-β-alkoxyethylbenzylamine **285** has been transformed into cherylline **286**.[312]



281 282 283

R^1	R^2	R^3	R^4	Yield (%)
$OCH_2C_6H_5$	OCH_3	H	H	74
H	OCH_3	OCH_3	H	90
H	OCH_3	H	H	70
OCH_3	OCH_3	H	H	88
OCH_3	H	H	OCH_3	75
H	OCH_3	H	OCH_3	91
H	OCH_2O		H	85
OCH_3	OCH_3	OCH_3	H	87
H	OCH_3	OCH_3	OCH_3	98
OH	OCH_3	H	H	60

Scheme 23



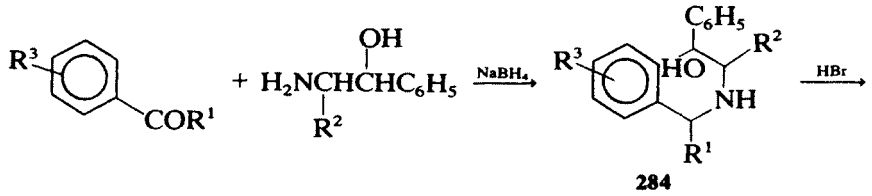
(66)

On the other hand, cherylline has been synthesized by reaction of the β-amino alcohol **287** with ammonia along the biogenetic pathway.[313]

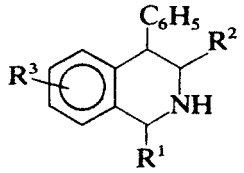
N-(1-Phenylprop-2-ynyl)benzylamines **288** have been cyclized in polyphosphoric acid, giving in good yield the unstable 1,2-dihydro 4-methyl-3-phenylisoquinolines **289**, which underwent atmospheric oxidation to the isocarbostyrils **290**. Similarly, polyphosphoric acid treatment of the 1,2-diphenylamine **291** causes double cyclization, thus affording the isopavine-type compound **292**.[314] This reaction provides an effective route to 4-alkylisoquinolines.

(b) *Reaction with Carbonyl Compounds*

When *N*-benzylaminoacetaldehydes or their derivatives are left in contact with acid, cyclization occurs and 1,2,3,4-tetrahydro-4-hydroxy- or 1,2-dihydroisoquinolines are isolated in yields comparable to those obtained in the Pomeranz–Fritsch reaction or the Bobbitt modification. For example, the isoquinoline **293** was treated with glycidol, and the resulting aminoglycol

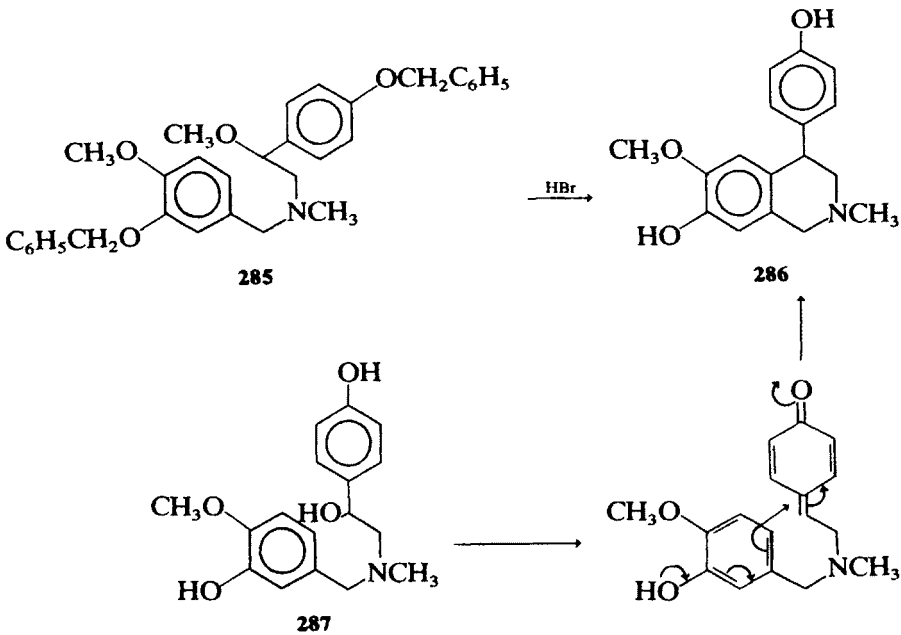


284



R^1	R^2	R^3	Yield (%)
H	CH_3	H	84
H	CH_3	H	53
H	H	H	58
H	CH_3	6-OH	76
H	CH_3	6,7-$(OH)_2$	55
H	CH_3	7,8-$(OH)_2$	57
H	CH_3	6,7-$(OCH_3)_2$	67
H	CH_3	7,8-$(OCH_3)_2$	53
H	CH_3	8-Cl	13
H	CH_3	6-Cl	66
H	CH_3	6-NO_2	9
CH_3	CH_3	H	63
C_2H_5	CH_3	H	35
C_6H_5	CH_3	H	44

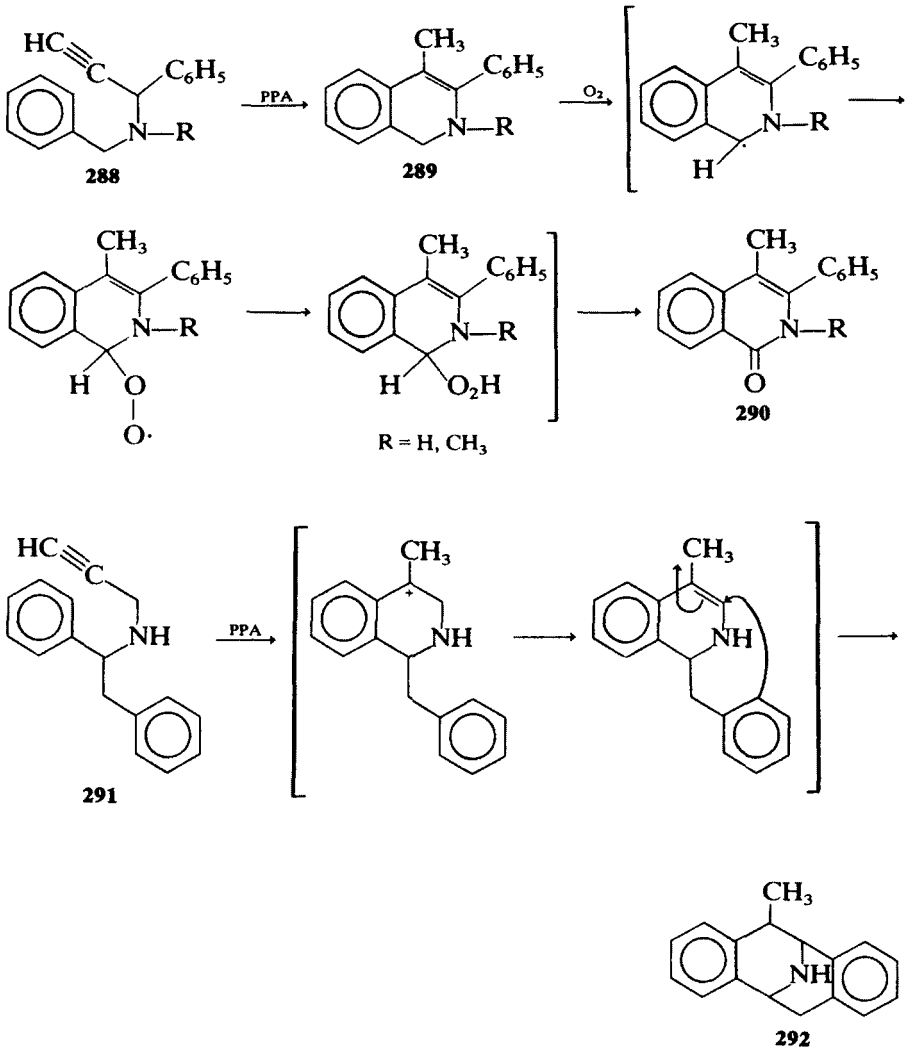
Scheme 24



285

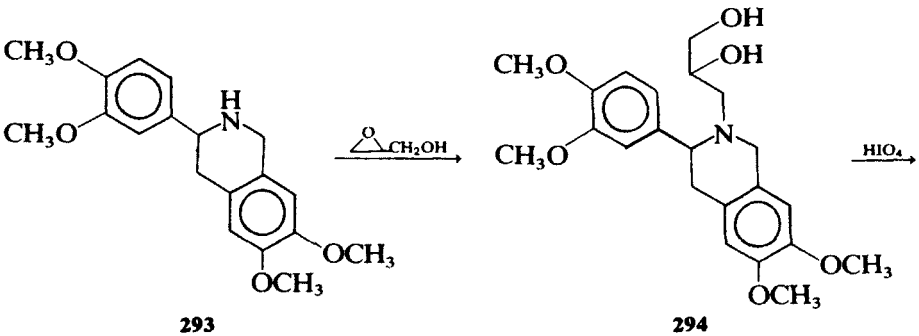
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287

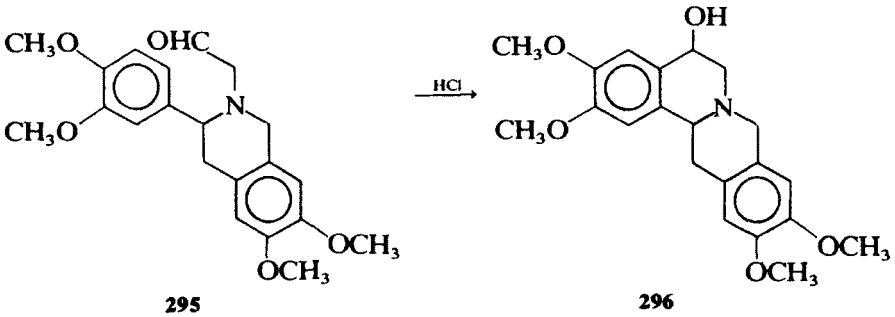


294 was, without isolation, oxidized with periodic acid to provide the aminoaldehyde **295**. On treatment with hydrochloric acid, this compound gave the 5-hydroxyprotoberberine **296** in 70% yield.[315] A similar reaction was also reported by Dutta et al.[316] and Kupchan et al.[317] β-Amino ketones were also cyclized under acidic conditions to afford isoquinoline derivatives,[318] as shown for the formation of the protoberberine **297**.[319]

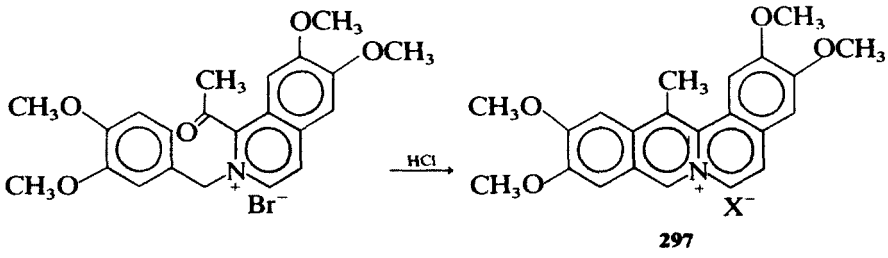
Compounds containing carbonyl equivalent groups undergo the same reaction, as exemplified by the acid-catalyzed cyclization of the aldoxime **298** to the benzoquinolizinium derivative **299**.[320] This reaction has also been used by Bradsher for the synthesis of protoberberine-type compounds.[321] Acetals **300** are converted into the corresponding isoquinolines by treatment with mineral acid (Eq. 67).[322,323]



293 294



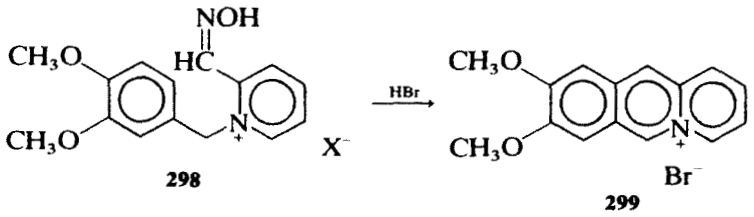
295 296



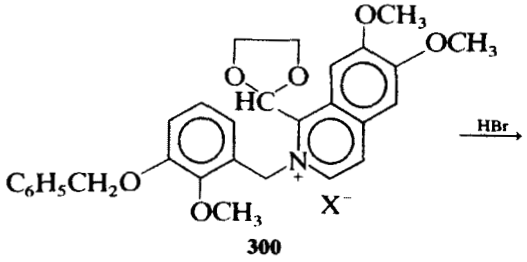
297

(c) *Acylation*

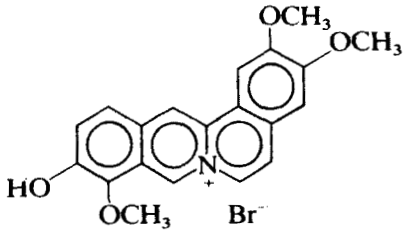
Intramolecular Friedel–Crafts acylation of *N*-benzylglycines or their esters easily gives 2,3-dihydro-4(1H)-isoquinolones.[324,325] For example, the Schiff base obtained from the condensation of veratraldehyde with methylamine was reduced with sodium borohydride. The resulting benzylamine was alkylated with ethyl chloroacetate to yield the *N*-benzylglycine derivative **301**. Friedel–Crafts cyclization in hot 70 to 90% sulfuric acid then furnished the isoquinolone **302**. If required, the 4-keto group of this compound can be removed either by catalytic hydrogenation over 10% palladium–carbon or through desulfurization of the corresponding thioketal. On the other hand, dehydrogenation with palladium–carbon in hot toluene



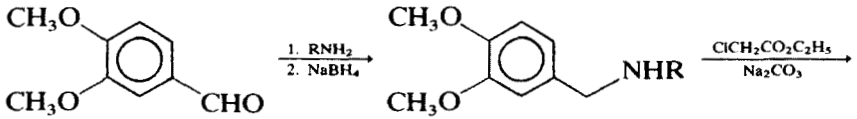
298 299



300



(67)





301 302

affords 4-hydroxyisoquinoline.[326] Polyphosphoric acid[326,327] and phosphoryl chloride[328] also have been used for the cyclization of benzylglycines. This general method for the preparation of 4-oxoisoquinolines is useful because the carbonyl group allows for facile conversion into various other isoquinoline derivatives.[329] The Hoffmann–LaRoche group has prepared many 2,3-dihydro-4(1H)-isoquinolones by this route.[324,325]

Umezawa et al. reported that cyclization of *N*-formyl-*N*-veratrylglycine

with polyphosphoric acid at 74 to 78°C afforded the *N*-formyl-2,3-dihydro-4(1H)-isoquinolone.[330] Furthermore, *N*-benzenesulfonyl-*N*-benzylglycine has been cyclized to the corresponding 4-oxoisoquinoline.[331] This type of Friedel–Crafts acylation is widely used for the synthesis of phenanthroindolizine and phenanthroquinolizidine alkaloids.[5,332]

α-Aminonitriles **303**, mono- or disubstituted at the α-carbon, can be cyclized to 2,3-dihydro-4(1H)-isoquinolones **304** in the presence of concentrated sulfuric acid at 50°C. However, this reaction has not been extended to the preparation of 2,3-dihydro-4(1H)-isoquinolones unsubstituted at C-3.[333] Cyclization of the 3,4,5-trimethoxybenzylamine derivative **305** gave a mixture of the normal product **306** and the rearranged product **308** formed through the spiro intermediate **307**.[334] Benzoquinolizidine also has been synthesized by this method.[335]

E. Cyclization through Benzyne Intermediates

Reaction of *N*-acetyl-*o*-chlorobenzylamines **309** with potassium amide in liquid ammonia gives 1,4-dihydro-3(2H)-isoquinolones **311** through the benzyne intermediate **310**.[336] Similarly, the nitrile **312** or the ester **313** are converted into the corresponding isoquinolines by reaction with sodium amide in liquid ammonia.[337] Ueda et al.[338] synthesized the lycoran skeleton **314** by an application of this type of reaction.

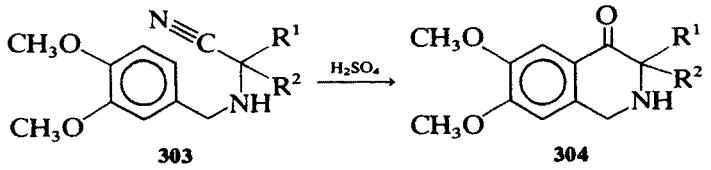
Treatment of chloranil **315** with potassium amide in liquid ammonia led to the formation of the phenanthridine **316**. The reaction probably proceeds through a benzyne intermediate and is used for the synthesis of benzophenanthridines.[339] Similarly, *N*-aryl-*N*-(*o*-chlorobenzyl)amine **317**[340] or *N*-aryl-*o*-bromobenzamide[341] also cyclizes to the corresponding phenanthridines (Eq. 68). This reaction has been applied recently by Stermitz to the synthesis of benzophenanthridine alkaloids.[342]

F. Photochemical Cyclization

(a) *Photocyclization of Enamides*[343]

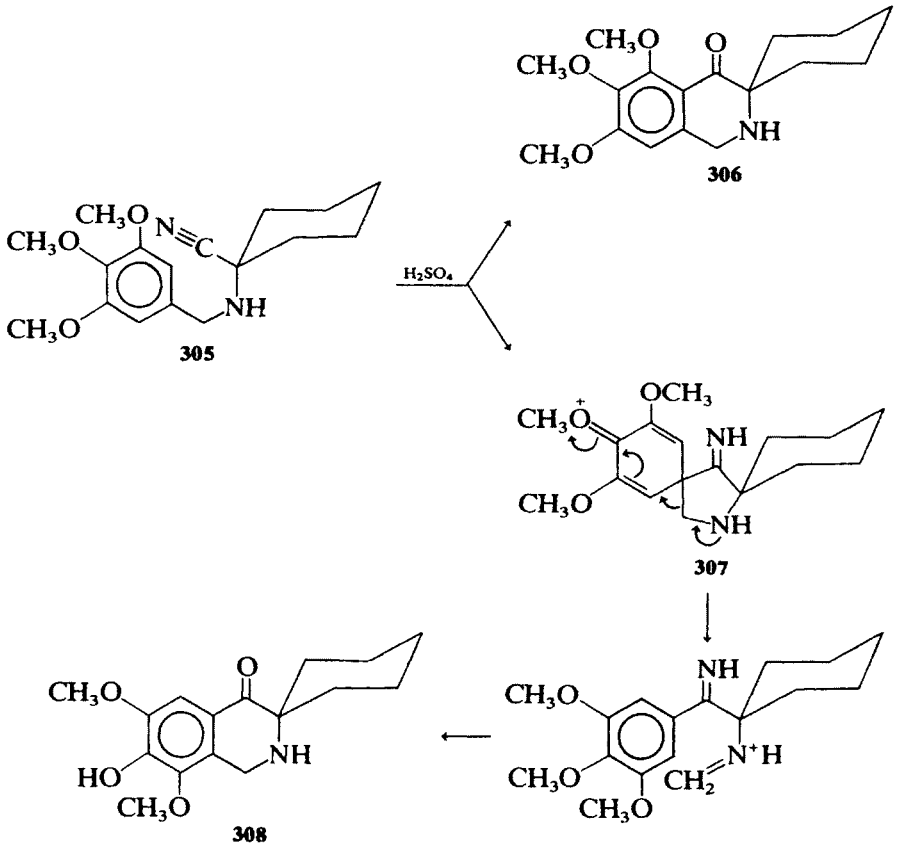
Recently, stereospecific photocyclization has been found to occur with enamides containing an additional double bond in conjugation to the carbonyl group. An electrocyclic mechanism has been suggested for this cyclization (Eq. 69). After excitation of the enamide (**318** ↔ **319**), cyclization occurs in a conrotatory manner to afford the cyclic intermediate **320**, which after a [1, 5]suprafacial thermal hydrogen shift gives, stereospecifically, the trans lactam **321**.

When the *N*-benzoylenamine **322** was irradiated, the *trans*-benzophenanthridone **323** was obtained stereospecifically in 51% yield.

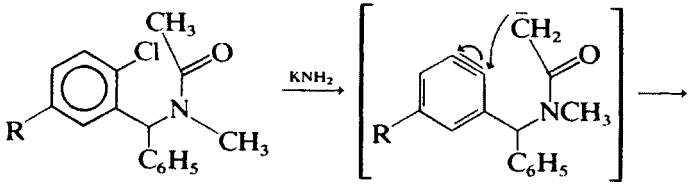


303 304

R^1	R^2	Yield (%)
H	H	30–50
C_6H_5	H	60
CH_3	CH_3	53
—$(CH_2)_5$—		80
C_6H_5	CH_3	83
3,4-$(CH_3O)_2C_6H_3$	H	24



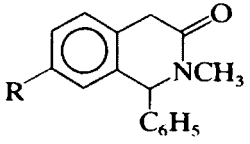
306 305 307 308



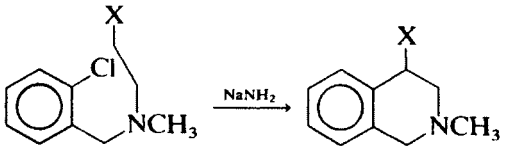
R = H, CF_3

309

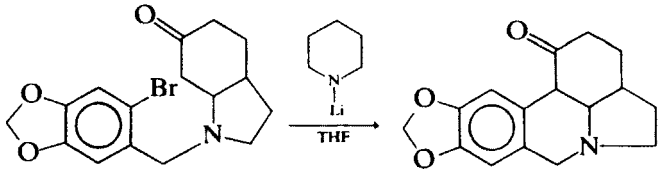
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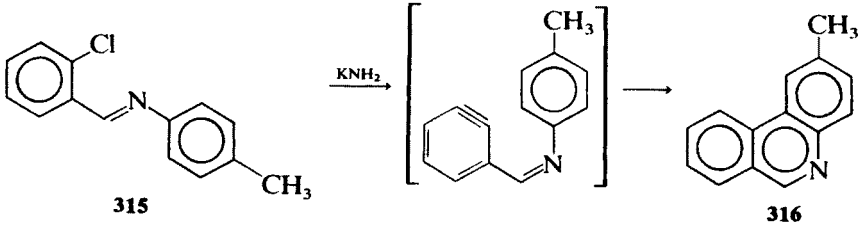
311



312, X = CN
313, X = CO_2CH_3

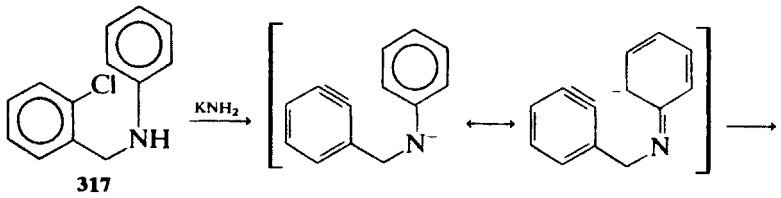


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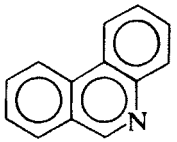


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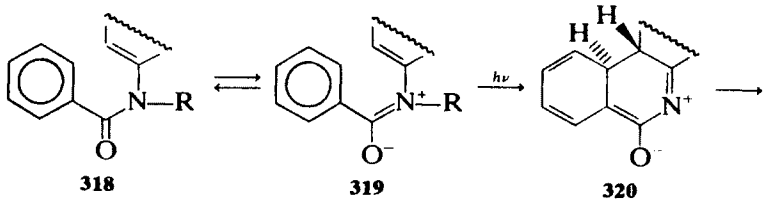
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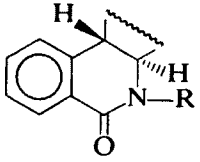
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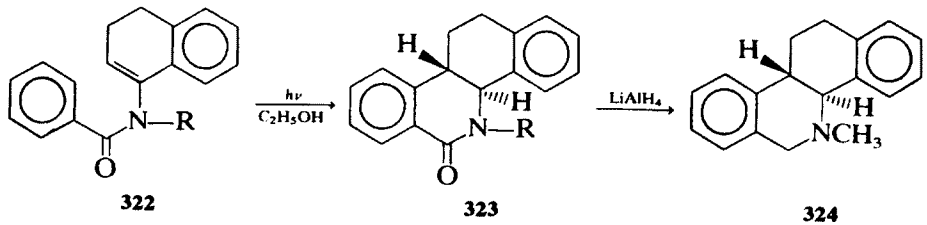
(68)



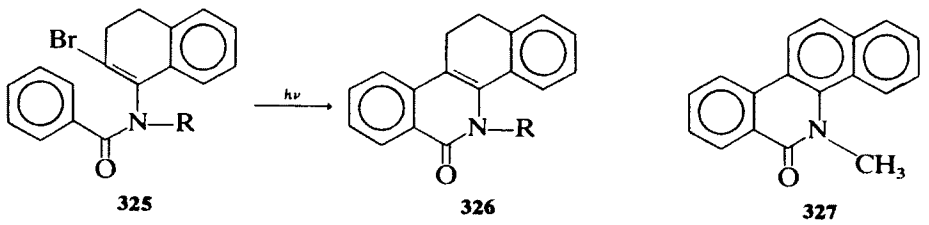
318 319 320



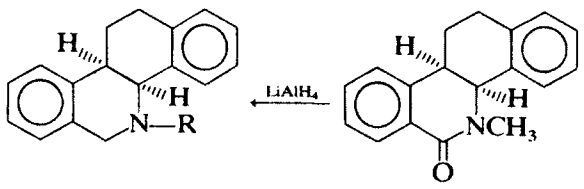
321 (69)



322 323 324



325 326 327



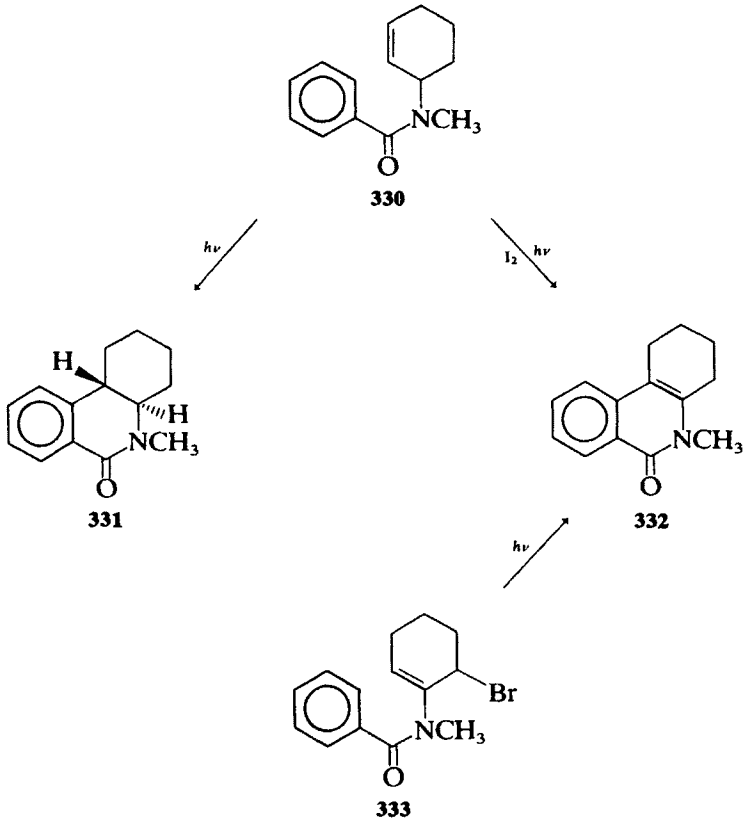
328 329

R = H,CH_3,$CH_2C_6H_5$

Scheme 25

Reduction of this product gave the *trans*-benzophenanthridine **324**. Irradiation of **322** in the presence of iodine provided the dehydrolactam **326** in good yield. The same compound was obtained by photolysis of the bromoenamide **325**. Selenium dehydrogenation of the photoproduct **323** ($R = CH_3$) afforded a mixture of the abnormal cis lactam **328** and the expected aromatized compound **327**. The former was converted into the *cis*-benzophenanthridine **329** ($R = CH_3$), which was also obtained by reduction of derivative **326** (Scheme 25).[344,345]

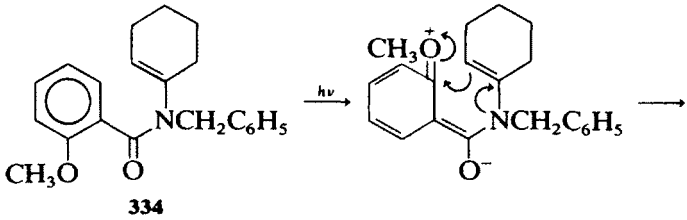
Similarly, irradiation of *N*-benzoylenamine **330** in methanol afforded in 15 to 35% yield the *trans*-phenanthridone **331** in a stereospecific manner, whereas in the presence of iodine an oxidative cyclization took place to give the dehydrolactam **332** in 54% yield.[346] Interestingly, the bromoenamide **333** yielded the same dehydrolactam on photolysis. Benzo[*a*]phenanthridone was also obtained in the same way.[347]



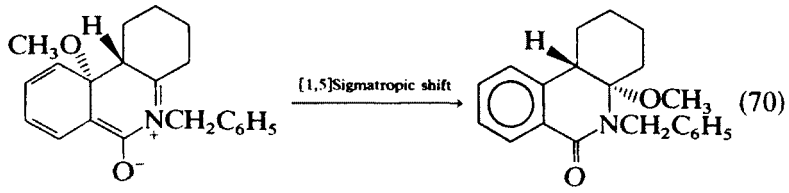
Although this photocyclization of enamides and bromoenamides cannot be used for the preparation of simple isoquinoline derivatives, it can be applied advantageoeusly to the synthesis of more complex isoquinoline

systems. Examples for the synthesis of alkaloids of the benzophenanthridine,[348] protoberberine,[349,350] yohimbane,[351] crinane,[352] and lycorine type[353] have been reported.

A 1,5-migration of the ortho-substituent reportedly occurs during the photocyclization of certain *N*-benzoylenamines of type **334** and *N*-acylanilides, substituted in the benzene ring with groups such as methoxyl, methoxycarbonyl, acetyl, cyano, and aminocarbonyl (Eq. 70).[354]



334

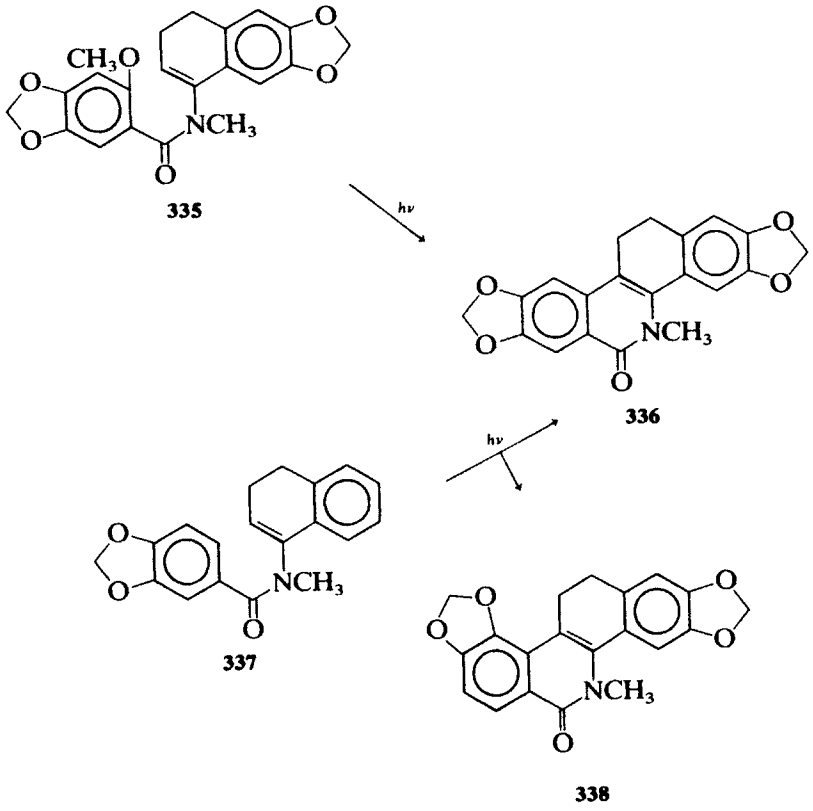


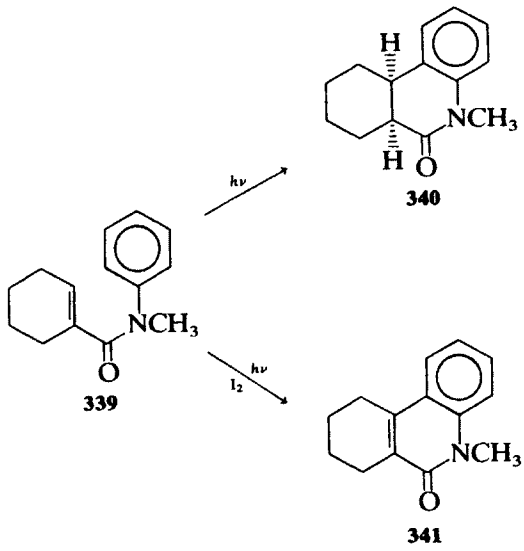
(70)

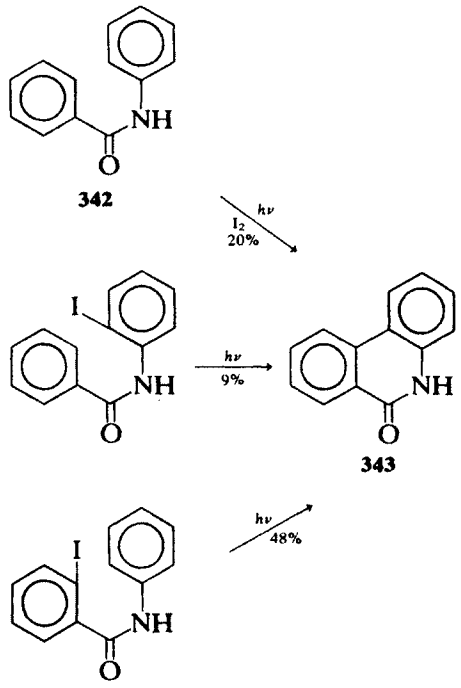
Another interesting phenemenon occurring on these reactions is the elimination of an ortho methoxyl group on an aromatic ring; thus photocyclization of the enamide **335** gave, by elimination of the methoxyl group, only the dehydrolactam **336** in 45% yield. This product was also obtained in 25% yield in addition to the undesired product **338**[348] from the enamide **337**, which did not have an ortho methoxyl group on the aromatic ring; hence this group is essential for higher yields and regioselectivity in the photocyclization. Analogous to the photocyclization of *N*-benzoylenamines, anilides of type **339** afforded the hydrogenated isoquinolines of type **340** or **341**.[355]

In contrast to the nonoxidative photocyclization mentioned earlier, benzanilide **342** underwent cyclization only under oxidative conditions to afford the phenanthridone **343**.[356] This type of photocyclization was accelerated by the addition of iodine or by the introduction of a halogen substituent at the cyclization position (Scheme 26). Photolysis of benzanilides with a methoxyl group in ortho position proceeds with elimination of the substituent to afford phenanthridones.[357]

The cyclization of halogen-substituted benzanilides was used in the synthesis of narciprimine,[358] a degradation product of the mitose poison, narciclasine (or lycoricidinol), and in the synthesis of anhydrolycorine,[359] a degradation product of the Amaryllidaceae alkaloid lycorine. Recently, a benzophenanthrene has been synthesized by this reaction.[360]


CH3O
O
O
O
O
NCH3
O
335
hν
O
O
O
O
NCH3
O
336
hν
O
O
NCH3
O
337
O
O
O
O
NCH3
O
338


H
NCH3
H
O
340
hν
NCH3
O
339
hν
I2
NCH3
O
341



Scheme 26

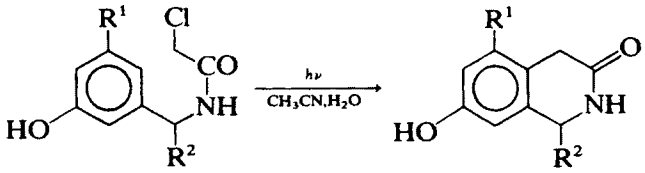
(b) *Other Photocyclizations*

Isoquinoline synthesis by irradiation of Schiff bases[361] and of *N*-benzylchloroacetamides[362] has been reported (Eq. 71). The latter cyclization proceeds in poor yields, and its value for the synthesis of isoquinolines is limited.

G. Pschorr Reaction

Although this reaction has not been used generally for the synthesis of isoquinolines, many phenanthridines have been obtained from *N*-methylbenzanilide-2-diazonium salts by the Pschorr reaction.[363] For example, *N*-methyl-2-aminobenzanilide **345** is diazotized with sodium nitrite in sulfuric acid and then decomposed in the presence of cuprous oxide to give the phenanthridone **346** in 24 to 32% yield.[363] Because of poor yields, large amounts of uncyclized by-products, and severe reaction conditions, this method cannot be considered a general reaction for the synthesis of phenanthridones.

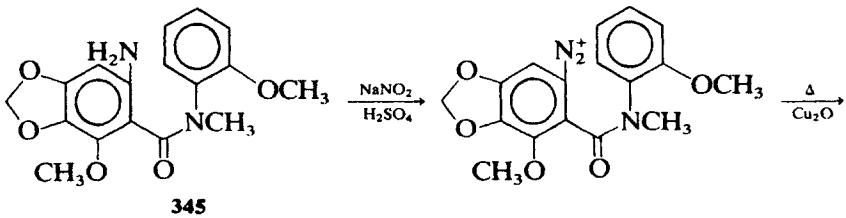
Hey et al.[364] reported some abnormal reactions occurring during the



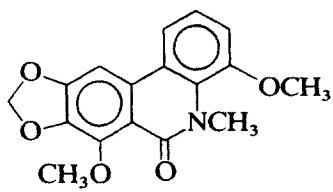
(71)

R^1	R^2	Yield (%)
H	H	55[a]
OH	H	45[b]
H	CH_3	74[a]
H	$CH_2C_6H_5$	69[a]
OH	$CH_2C_6H_5$	64
H	$CH_2C_6H_4(OCH_3\text{-}p)$	49
H	$CH_2C_6H_2[(OCH_3)_3\text{-}3, 4, 5]$	36[a]
OH	$CH_2C_6H_2[(OCH_3)_3\text{-}3, 4, 5]$	59

[a] 4-Hydroxy isomer was isolated as minor product.
[b] Isolated as dimethyl ether.



345



346

Pschorr cyclization; in the absence of metallic catalysts, thermal decomposition of aqueous solutions of the diazonium sulfates obtained from the aminobenzanilides **347** resulted in the formation of the isoindolines **349** and oxazepinones **350** in addition to the expected phenanthridones **348**.

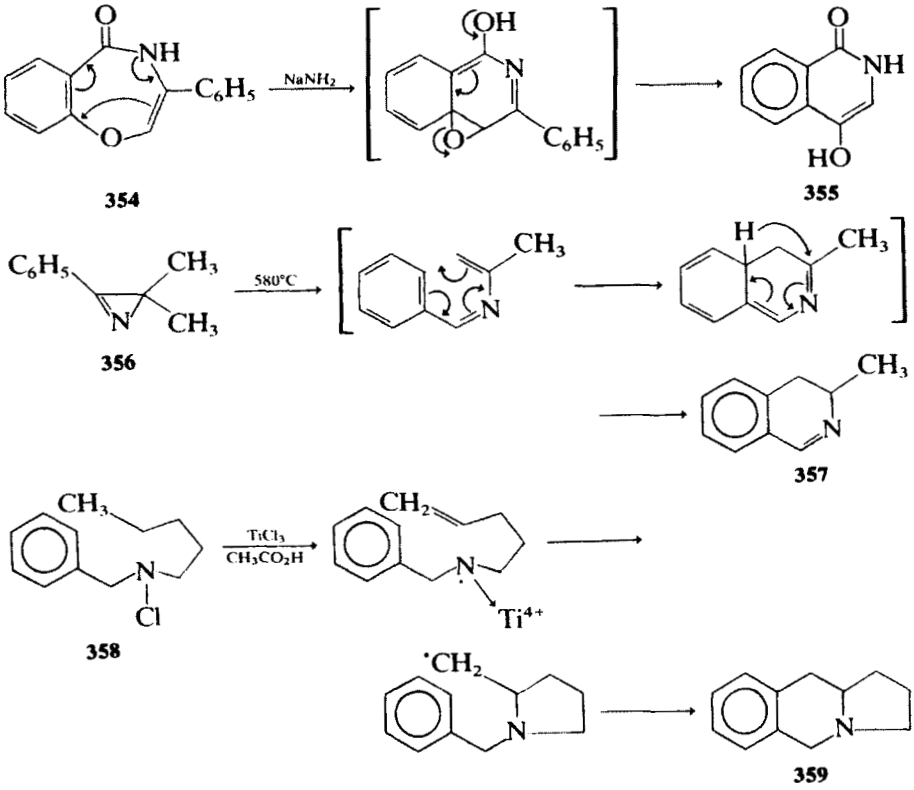
Alternatively, the reaction of *N*-methylbenzanilide-2-diazonium fluoroborate (**351**) with hydrogen iodide proceeded smoothly in oxygen-free methylene chloride at room temperature to give *N*-methylphenanthridone (**352**) and the spirodiene **353** in 35% and 45% yields, respectively, through radical intermediates. The reaction of **351** with sodium iodide in acetone afforded a spirodiene dimer and **352**.[365]

NCH3
O
352
353
H
a
b
HI
N2+
BF4
351

The copper-catalyzed decomposition of the diazotized *N*-(*p*-bromobenzyl)-*N*-tosyl-*o*-phenylenediamine gives phenanthridine derivatives in moderate yields.[366] Recently, the lycorane system has been obtained by this method.[367]

H. Miscellaneous Reactions

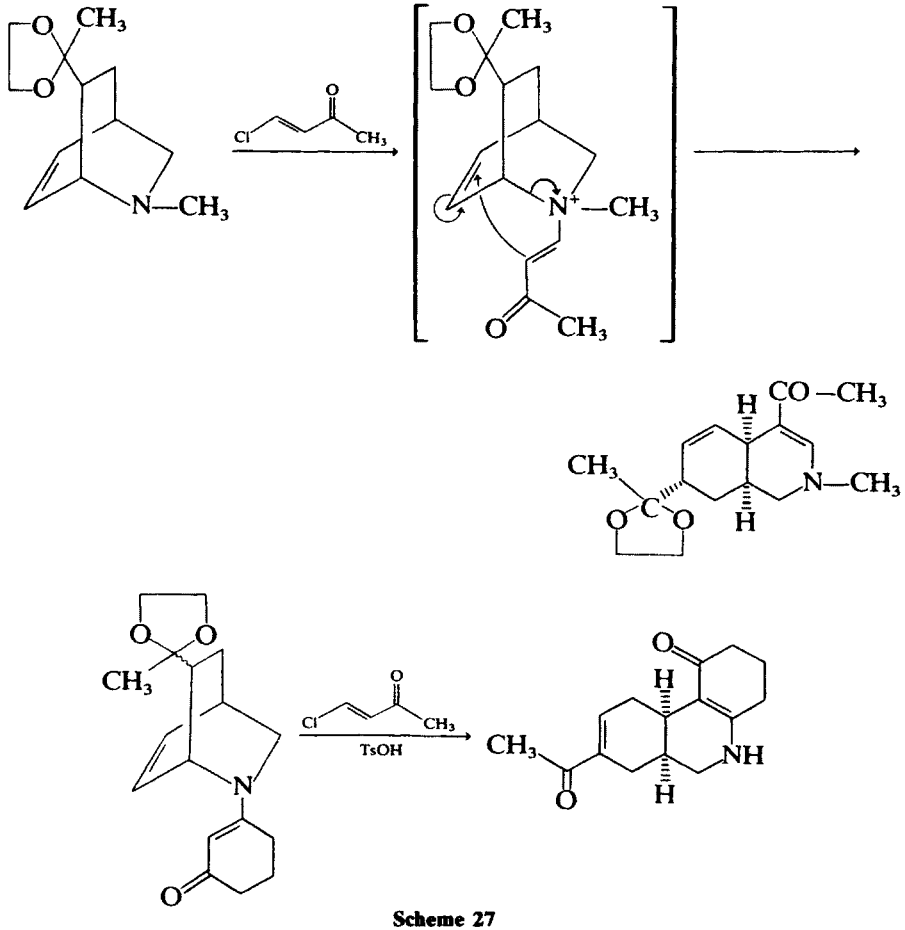
The following reactions lead to isoquinoline derivatives by forming a bond between C-4 and C-4a but do not have any preparative value. Reaction of the 1,4-benzoxazepine **354** with sodium amide resulted in ring contraction to give the isoquinoline derivative **355**.[368] Pyrolysis of **356** gave the 3,4-dihydroisoquinoline **357**,[369] and *N*-benzyl-*N*-amyl-*N*-chloroamine (**358**) was converted into the isoquinoline derivative **359** by a double radical cyclization.[370]



354 **355** **356** **357** **358** **359**

Hydroisoquinoline synthesis through the aza-Claisen rearrangement is reported by Mariano et al.[371] Treatment of isoquinuclidene with 2-chlorovinyl methyl ketone in tetrahydrofuran containing potassium carbonate at room temperature for 15 hr gives in 60% yield 4-

acetylhexahydroisoquinoline stereospecifically through rearrangement of the initially formed *N*-vinylisoquinuclidenium salt. A tricyclic isoquinoline derivative is also obtained by the same reaction (Scheme 27).



Scheme 27

VII. ISOQUINOLINE SYNTHESES BY CYCLOADDITION AND RELATED REACTIONS

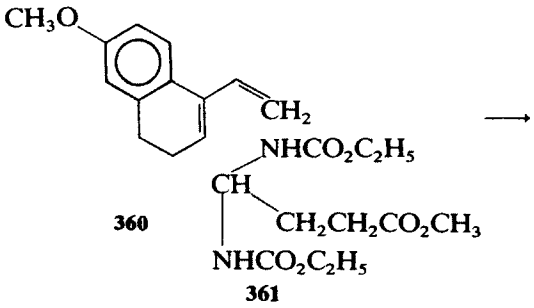
This section will describe isoquinoline syntheses classified as type 6, type 7, and type 8 (Scheme 1). The common feature in these syntheses is the formation of the pyridine ring by the one-step addition of two or four adjacent atoms.

The Ritter–Murphy reaction in which the C_1–N unit is derived from a nitrile may be classified as a type 6 synthesis. Because of the suggested

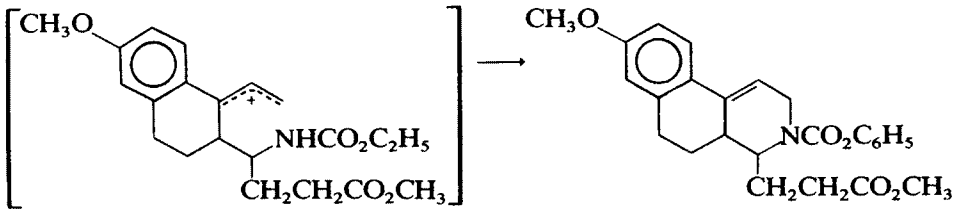
mechanism that postulates the intermediacy of an *N*-acyl derivative (Scheme 10), this reaction has been discussed already [Section II.A(g)].

A. Type 6 Syntheses

Imines are generally unreactive compounds in cycloaddition reactions, but condensation with dienes can be effected either in a pseudo-Diels–Alder-type reaction or by activation of the C=N bond. By applying the first reaction type, Speckamp et al.[372] achieved a synthesis of the isoquinoline ring system in one single step by condensation of a biscarbamate with a suitable diene under the influence of Lewis acid. When ethyl biscarbamate **361** was condensed with diene **360** in the presence of boron trifluoride etherate in benzene at 70°C, the benzoisoquinoline **363** could be obtained in 30 to 40% yield. The observed regiospecificity of the addition agrees well with the formation of the polar intermediate **362** in the transition state.

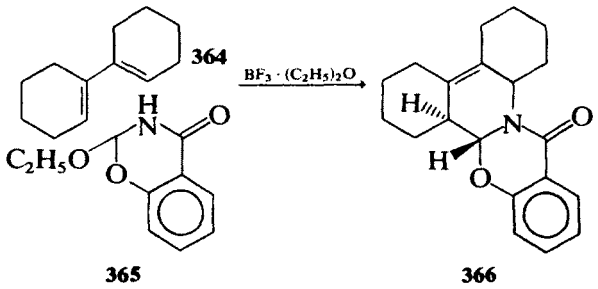


360 **361**



362 **363**

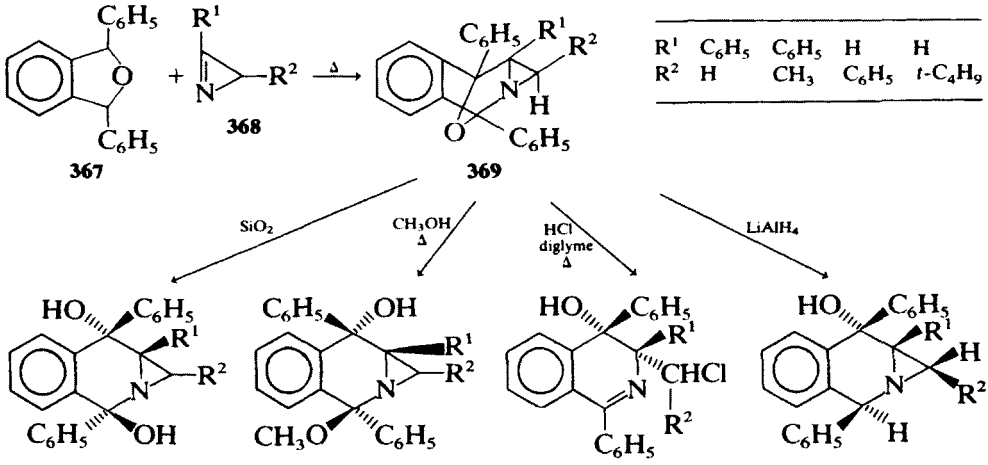
Acylimines are reactive compounds that readily add weak nucleophiles across the C=N bond to give addition products. Ben-Ishai and Warshawsky[373] found that alkoxyamides could be converted into acylimines by elimination of the alcohol. Application of this finding resulted in a one-step synthesis of isoquinoline derivatives. Diels–Alder reaction of 1,1-bicyclohexenyl (**364**) with two equivalents of the ethoxybenzoxazine **365** in the presence of boron trifluoride etherate gave the adduct **366** in 90% yield. But these cycloadditoins are not too valuable from a synthetic point of view.



B. Type 7 Syntheses

Because 1-azirines with their reactive 2π-electron system can participate in thermally allowed ($\pi^4 + \pi^2$) cycloadditions, they are a good choice for the C_3–N building block in type 7 syntheses of isoquinolines. Nair[374] and Hassner and Anderson,[375] independently, have examined the cycloaddition of 1-azirines to 1,3-diphenylisobenzofuran and the rearrangement of the adducts to isoquinoline derivatives.

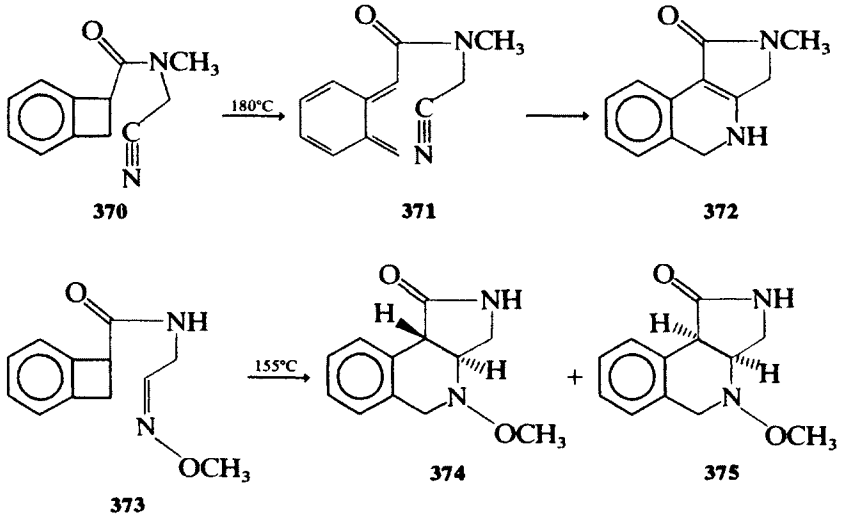
Reaction of 1-azirines **368** and 1,3-diphenylisobenzofuran **367** in refluxing toluene afforded in 82% yield the 1:1 adducts **369** possessing the exo configuration. Chemical reactions of **369** involving initial opening of the oxide bridge in a regiospecific manner and leading to isoquinoline derivatives are shown in Scheme 28.[375] The second interesting example of a type 7



Scheme 28

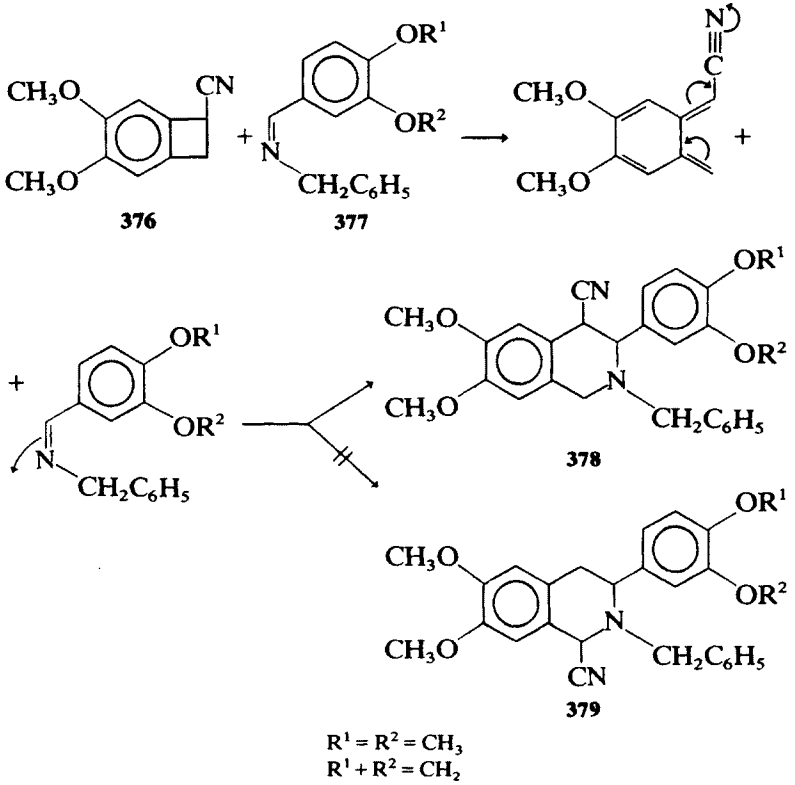
synthesis involves the cycloaddition reaction of a nitrile, imine, or oxime with an *o*-quinodimethane generated *in situ* by thermolysis of a benzocyclobutene derivative.[201,202] This application of cycloaddition reactions to isoquinoline synthesis is divided into intramolecular[376] and intermolecular reactions.[377–381]

Heating the cyanobenzocyclobutene **370** at 180°C gave the 1,2-dihydroisoquinoline **372** in 76% yield through the intermediate *o*-quinodimethane **371**;[376] similarly, the oxime **373** was converted into the tetrahydroisoquinolines **374** and **375**.[376]



An intermolecular cycloaddition reaction of 1-cyanobenzocyclobutene **376** with the Schiff base **377** carried out at 150 to 160°C without solvent gave only the 3,4-disubstituted 1,2,3,4-tetrahydroisoquinoline **378** and not even a trace of the isomer **379**.[377] Although the stereochemistry at C-3 and C-4 has not been proven, the trans configuration is preferred since epimerization at C-4 would give the thermodynamically more stable isomer. Because the 3,4-disubstituted isoquinoline **378** was obtained as a single stereoisomer, it may be concluded that the cycloaddition proceeded in a both regioselective and stereoselective manner.[377] The regioselectivity is controlled by the electron attracting cyano group at the benzocyclobutene ring.

If it were not for the lengthy preparation of the starting benzocyclobutenes, this reaction would constitute a simple synthetic method for the preparation of isoquinolines. The yields are generally good, and the reaction is carried out easily; heating the component mixture without addition of extra reagents is sufficient. Recently, this method was successfully applied to the synthesis of protoberberine-type compounds, where 1-bromobenzocyclobutene was heated with 3,4-dihydro-6,7-dimethoxyisoquinoline

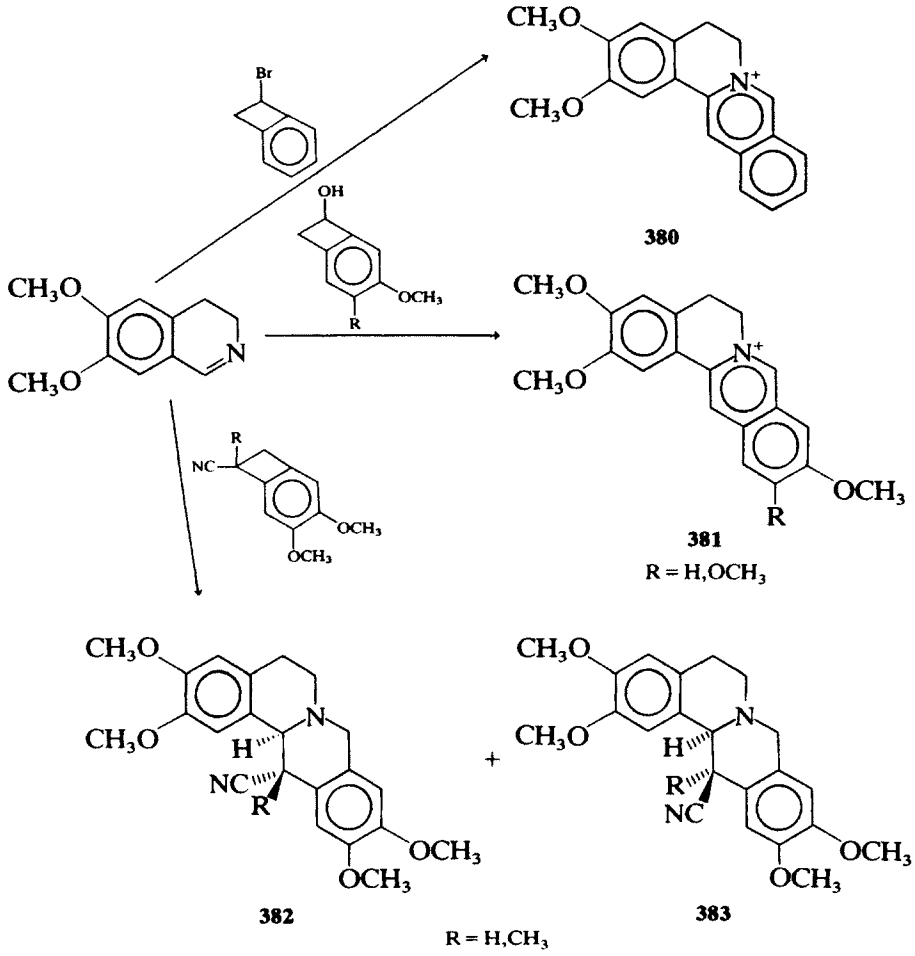


without solvent on a water bath for 20 hr to give the protoberberinium salt **380**.[378] The use of benzocyclobutenol and heating the reaction mixture in benzene at 80°C for 5 hr gave regioselectively the protoberberine **381** in 52% yield.[379] When 1-cyanobenzocyclobutene or 1-cyano-1-methylbenzocyclobutene was heated with the 3,4-dihydroisoquinoline at 150 to 160°C, a mixture of the respective isomeric 13-cyano-7,8,13,13a-tetrahydroberberines **382** and **383** was obtained in good yield.[380] Similarly, an intermolecular cycloaddition of 1-cyanobenzocyclobutene to 3,4-dihydro-β-carboline at 150 to 160°C without solvent gave, regioselectively, the corresponding 14-cyanohexadehydroyohimbane in 85% yield.[381]

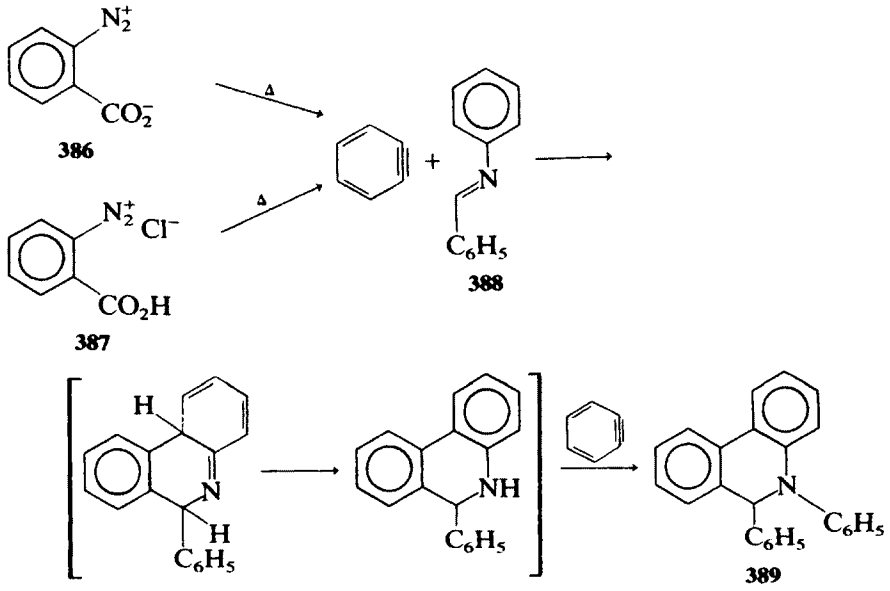
Kaiser et al.[382] developed a new isoquinoline synthesis by cross condensation of two nitriles in the presence of a strong base. Thus lithium dimethylamide in hexamethylphosphoric triamide effected condensation of *o*-tolunitrile **384** with various nonenolizable nitriles to give the 1-amino-3-substituted isoquinolines **385**.

C. Type 8 Synthesis

The only reaction belonging into this category was reported by a Japanese group and consists of an intermolecular cycloaddition of phenylazomethine


Br
OH
OCH3
R
CH3O
CH3O
N
N+
380
NC
381
R = H,OCH3
382
383
R = H,CH3
LiN(CH3)2
384
CH2
CN
C
N−
70%
C6H5
NH2

to benzyne.[383] Heating benzenediazonium-2-carboxylate **386** with *N*-benzylideneaniline **388** under reflux in methylene chloride yielded the 1,2-diphenylisoquinoline derivative **389**. The same compound was obtained by reaction of 2-carboxybenzenediazonium chloride **387** and **388** in boiling 1,2-dichloroethane in the presence of propylene oxide. Only a few examples of this synthesis have been reported; this synthesis is probably restricted to specific cases.



VIII. ISOQUINOLINE SYNTHESES BY FORMATION OF THE NONPYRIDINE RING

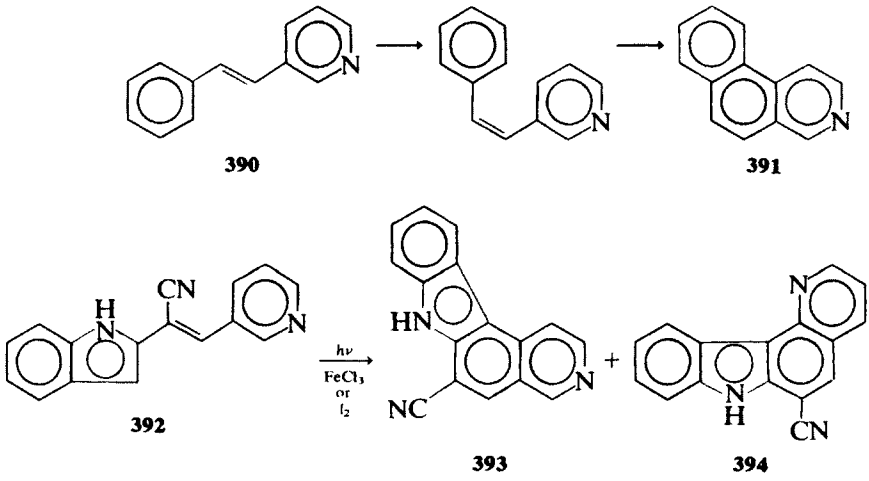
There are many reports on the synthesis of isoquinolines with the use of pyridine or hydropyridine derivatives as starting materials, but these methods have been used mainly for the syntheses of isoquinoline derivatives in which the isoquinoline nucleus is fused to other ring systems such as indoloisoquinolines.

A. Type 9 Syntheses

This type of synthesis is characterized by bond formation between C-4a and C-5. Of the two methods available, one is a photolytic electrocyclic reaction of 3-(2-arylvinyl)pyridines and the other, an aldol condensation of γ-piperidones.

(a) *Photolytic Electrocyclic Reaction*

Photochemical cyclodehydrogenation of the 3-stilbazoles **390** in cyclohexane solution yields the benz[*f*]isoquinolines **391**. Benzo[*h*]quinoline, the other possible cyclization product, was not isolated.[384] However, the quinoline derivative **394** was isolated in addition to the indolo[*f*]isoquinoline **393** in the oxidative photolytic cyclization of **392** in the presence of ferric chloride or iodine.[385] Similarly, electrocyclic reaction of the corresponding 1,2,5,6-tetrahydropyridine derivative has been reported.[386]

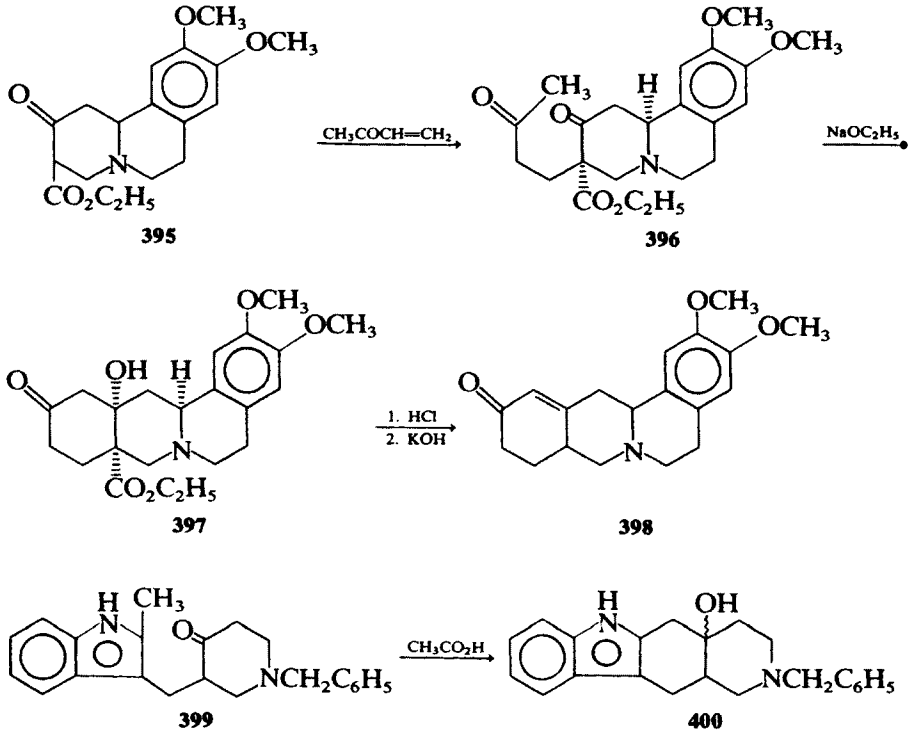


(b) *Aldol Condensation*

Brossi et al.[387] synthesized the isoquinoline derivative **398** by a sequence involving Robinson annelation and aldol condensation. The 3-ethoxycarbonyl-4-piperidone **395** was treated with methyl vinyl ketone to afford the diketo ester **396**. Internal aldol condensation of this compound then gave the isoquinoline derivative **397**. The synthesis of the indoloisoquinoline derivative **400** by aldol condensation of the piperidone **399** has also been reported.[388]

B. Type 10 Syntheses

This method involves bond formation between C-5 and C-6 and is used for the synthesis of indoloisoquinolines. Rupe-type reaction of the 3-arylmethylated 4-ethynyl-4-hydroxypiperidine **401** with formic acid affords in one step the isoquinoline derivative **402**.[388] The related compound **404**

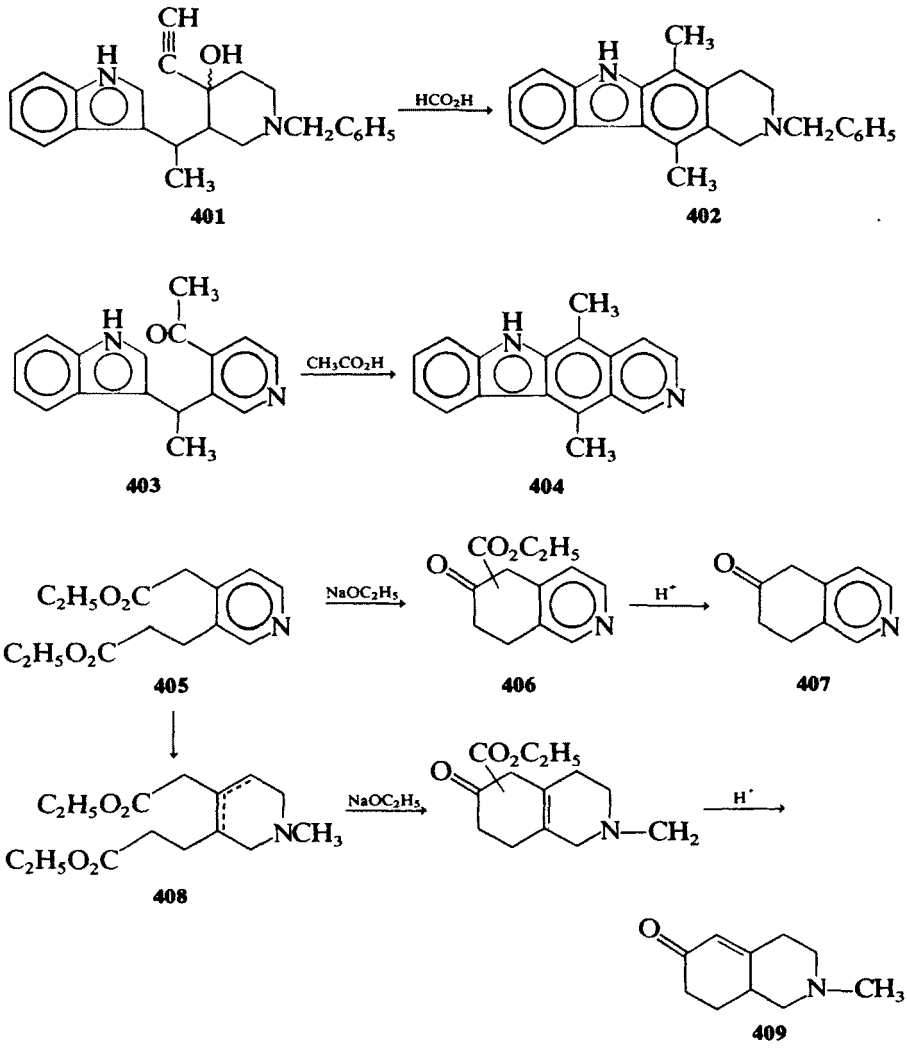


has been synthesized from 4-acetyl-3-arylmethylpyridine **403** in the presence of an acidic catalyst.[389]

C. Type 11 Syntheses

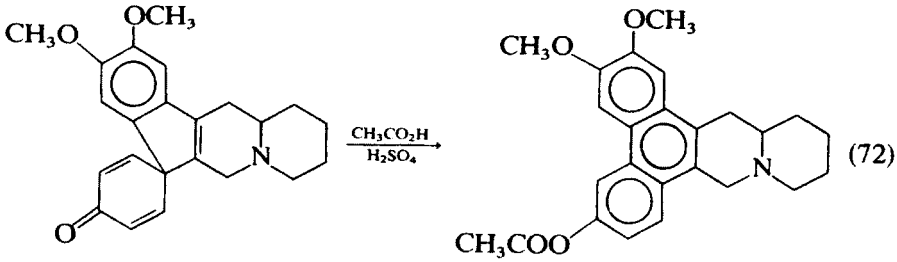
The preparation of isoquinoline derivatives from diesters such as the pyridine derivative **405** by an intramolecular Dieckmann cyclization cannot be classified unambiguously because either the C_5–C_6 or the C_6–C_7 bond can be formed. The choice of placing this method into this category has been made arbitrarily and does not imply any mechanistic preference. Cyclization of the diester **405** under the influence of sodium ethoxide afforded the isoquinolinone **407** through the intermediate **406**; similarly, the tetrahydropyridine derivative **408** gave the octahydroisoquinoline **409**.[390] This type of cyclization has been applied successfully to the synthesis of isoquinolines fused to other ring systems. This reaction, for example, played a crucial role in Szántay's total synthesis of yohimbine.[391,392]

Special cases of C_6–C_7 bond formation occur in the ring enlargement during a dienone–phenol rearrangement (Eq. 72)[393] and in the acid-catalyzed cyclization of the vinyl aldehyde **410**.[394]

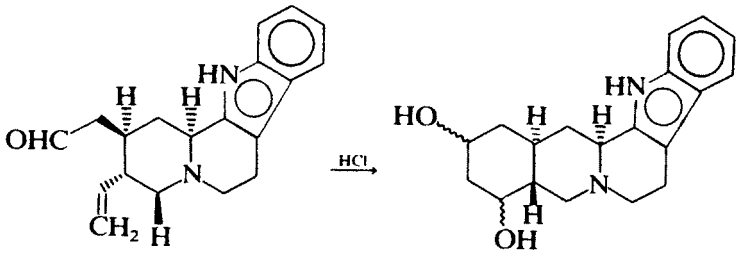


D. Type 12 Syntheses

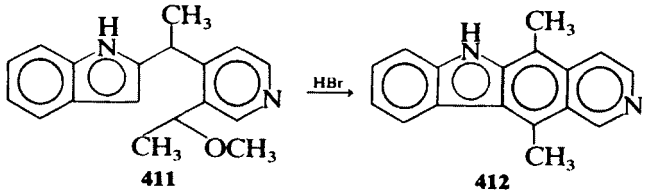
Bond formation between C-7 and C-8 is the characteristic feature of those reactions that, similar to type 10 syntheses (Section VIII.B), have only been used for the preparation of indoloisoquinolines,[395,396] and not for simple isoquinoline derivatives. The alkaloid ellipticine (**412**) is obtained from the 4-indolylmethylpyridine derivative **411** by treatment with hot hydrobromic acid.[397] Besselievre et al. recently synthesized the ellipticine derivative **414** through the intermediate iminium salt **413**.[398]



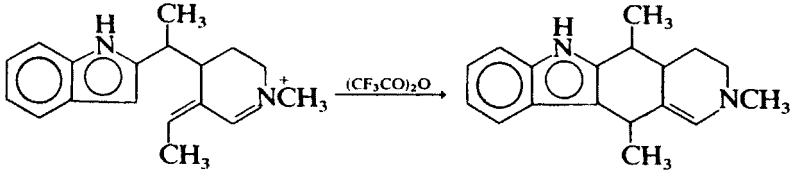
(72)



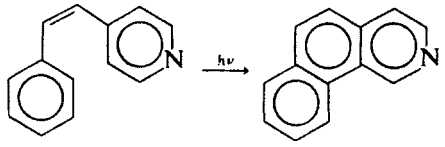
410



411 **412**



413 **414**



(73)

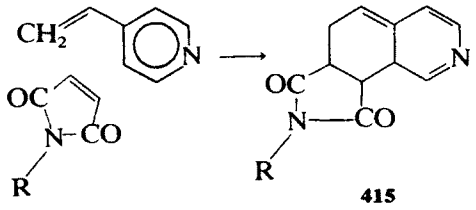
E. Type 13 Syntheses

Oxidative photocyclization of 4-stilbazole[384] and related compounds[399] gives the fully aromatized isoquinoline derivatives by bond formation between C-8 and C-8a (Eq. 73).

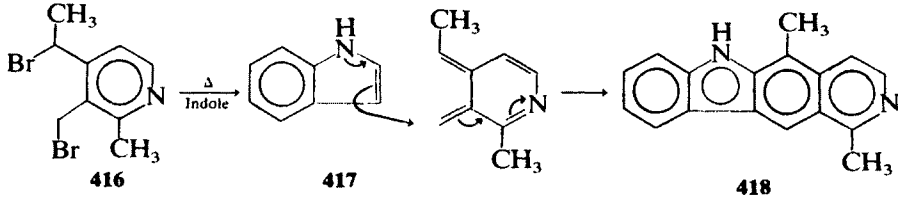
F. Type 14 Syntheses

(a) *Cycloaddition Reactions*

In these reactions the pyridine derivative can act as either a diene or a dienophile. The former is illustrated by the Diels–Alder reaction of 4-vinylpyridine with *N*-alkylmaleinimides to afford the unstable 6,7,8,8a-tetrahydroisoquinolines **415**, which undergo further reaction.[400] Another example is the preparation of indoloisoquinolines from 3,4-dihalomethylpyridines and indole,[401] a reaction in which the dibromide presumably is first converted into the *o*-quinodimethane **417**, which then reacts regioselectively with indole.[402] This method allows for the one-step synthesis of olivacine (**418**) from the dihalide **416**.[401] In the second type of cycloaddition iso-

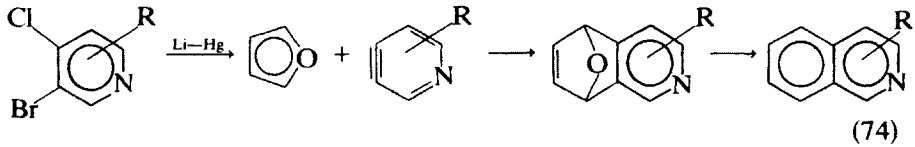


415



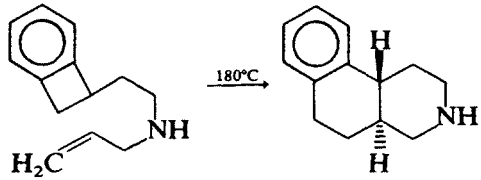
416 **417** **418**

quinoline derivatives are prepared by a Diels–Alder reaction between furan and pyridynes generated from 3,4-dihalopyridines and strong bases such as *n*-butyllithium[403] or lithium amalgam.[404] The products are converted into the fully aromatized isoquinolines by acidic treatment (Eq. 74).[403]

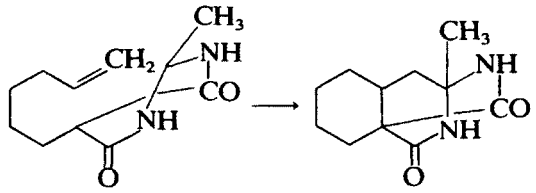


(74)

Other interesting preparations belonging into this section are intramolecular cycloadditions of benzocyclobutene with an allylamine system (Eq. 75)[405] and of olefines with 4,6-dihydroxypyrimidines (Eq. 76).[406]



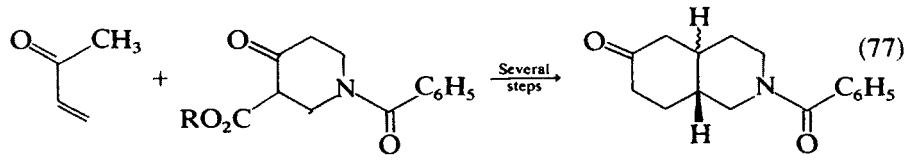
(75)



(76)

(b) *Robinson Annelation*

The Robinson annelation has found widespread use in terpene chemistry for the preparation of octalin derivatives. Recently this cyclization reaction has been applied successfully to the preparation of isoquinoline derivatives with a partially or fully hydrogenated carbocyclic ring. Reaction of 4-piperidone derivatives with methyl vinyl ketone afforded in several steps octahydro-6(2H)-isoquinolones (Eq. 77).[407] Subsequently, this reaction has

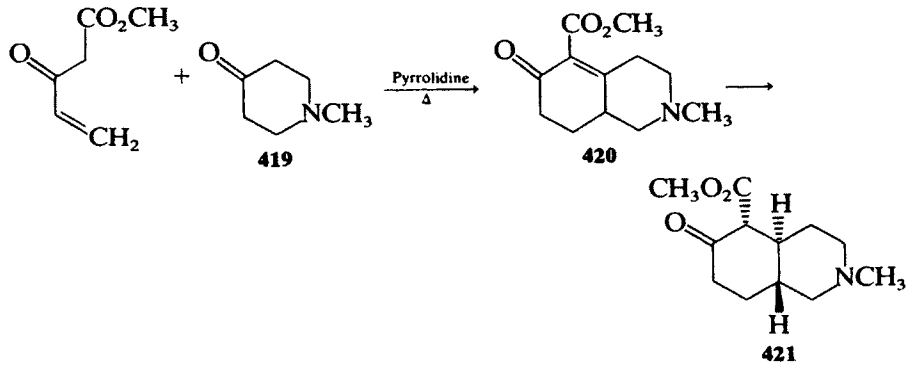


(77)

also been applied to the synthesis of the more complex yohimbane system.[408,409] In Stork's variation[409] the pyrrolidine enamine of *N*-methyl-4-piperidone (**419**) was treated with methyl 3-oxo-4-pentenoate in hot benzene to give in good yield the isoquinolone **420**, which was stereospecifically reduced to the isoquinoline **421**. Similarly, the indoloquinolizidine was converted into dehydroyohimbinone and then yohimbine.[410]

IX. TYPE 15 SYNTHESES

This section deals with isoquinoline syntheses in which rearrangement or isomerization is the key step for the formation of the pyridine part in the

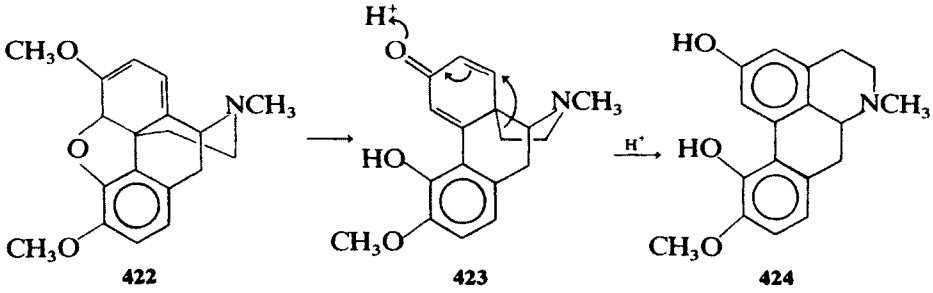


419 420 421

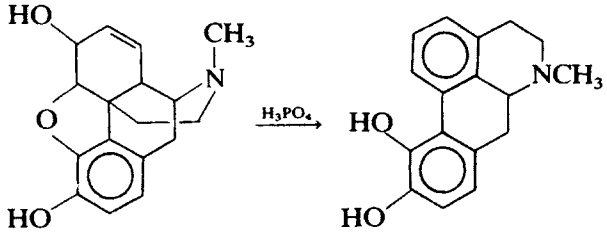
isoquinoline ring system. These reactions are divided into two groups, ring enlargements and ring contractions. Some rearrangements, such as the Beckmann and the Schmidt rearrangements, have been mentioned earlier (Section IV.H).

A. Isoquinoline Syntheses by Ring Enlargement

The classical example of this type is the formation of the apomorphines from morphine-type alkaloids.[411,412] Recently, 2,11-dihydroxy-10-methoxyaporphine (**424**) was obtained by acidic rearrangement of the dienone **423** derived from thebaine.[413] Similarly, morphine (**425**) was converted into apomorphine (**426**) through the dienone-type compound by treatment with phosphoric acid.[414]

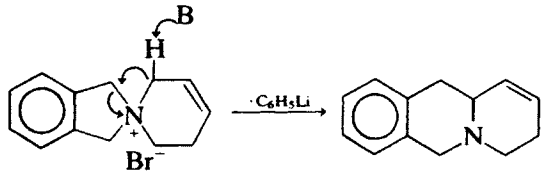


422 423 424



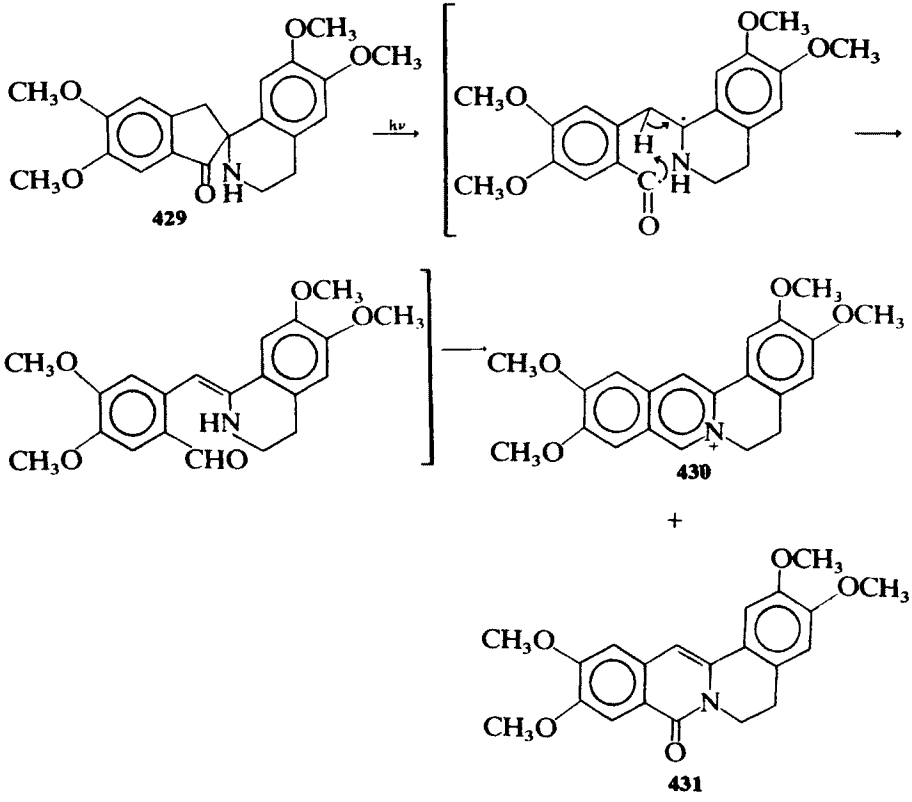
425 426

Ring enlargement by Stevens rearrangement was effected by treating the spiro ammonium salt **427** with phenyllithium to produce the 1,2,3,4-tetrahydroisoquinoline **428**.[415] Ito[416] employed this reaction in his total synthesis of pavinane-type alkaloids.



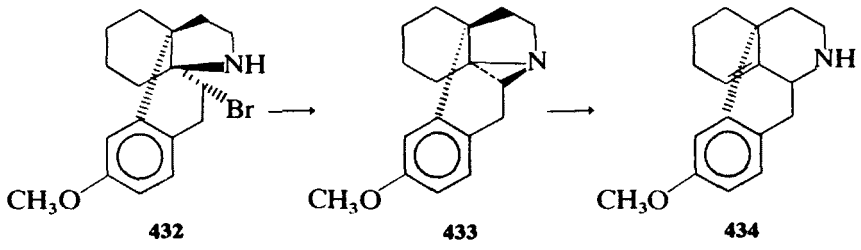
427 **428**

Fully aromatized isoquinolines in addition to isocarbostyrils are obtained from β-amino-α-indanones by photo-induced rearrangement. Photolysis of a solution of the spiro compound **429** in dry tetrahydrofuran with a high-pressure mercury lamp gave a mixture of berberinium salt **430** and lactam **431** in 80% and 10% yields, respectively.[417] The rearrangement presumably proceeds by a Norrish type 1 cleavage and has been applied to the synthesis of the yohimbane ring system.[410,418,419]

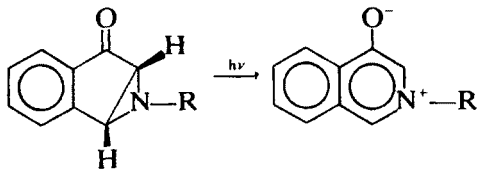


429 **430** **431**

The rearrangement of aziridines has been used in special cases for the preparation of certain isoquinoline derivatives. Base treatment of the perhydroindole **432** having a bromomethyl group at C-7a gave the octahydroisoquinoline **434** through the aziridine intermediate **433**.[420] The indenoaziridines **435** and **437** have been transformed into the corresponding isoquinoline derivatives by ring opening. The 4-hydroxyisoquinoline **436** was obtained from its valence isomer **435** by photochemical ring opening. The thermally forbidden conrotatory ring opening proceeds less readily.[421] However, the similar azidirine **437** has been converted at 135°C into the isoquinoline **438**.[422]

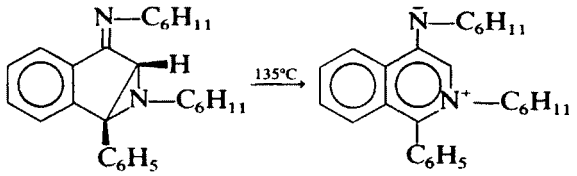


432 **433** **434**



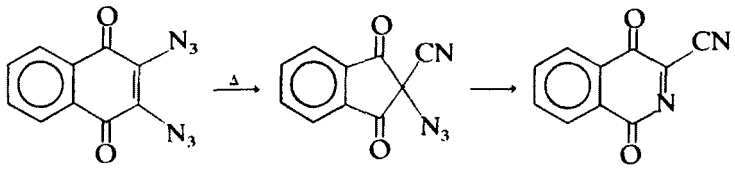
435 **436**

R = CH_3, C_4H_9, C_6H_5, $CH_2C_6H_5$



437 **438**

2,3-Diazidoquinone **439** undergoes a thermal rearrangement to the diketoisoquinolines **441**.[423] This transformation proceeds in two distinct stages. Below 100°C the diazide **439** gives diacyl cyanide and 2-azido-2-cyano-1,3-indandione (**440**). The latter then expands at temperatures above



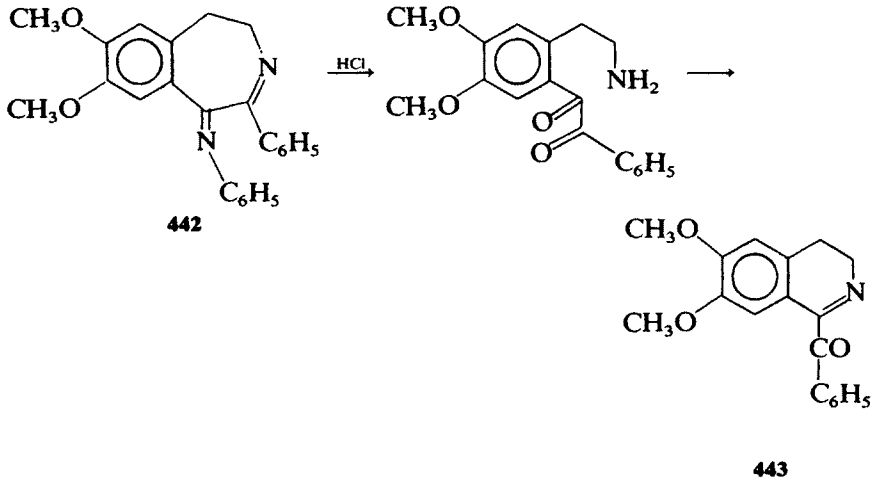
439 **440** **441**

100°C to the isoquinoline derivatives **441**.[423] However, the same authors proposed another mechanism for the formation of an isoquinoline derivative from 1,4-diacetoxy-2,3-diazidonaphthalene by thermal isomerization.[424]

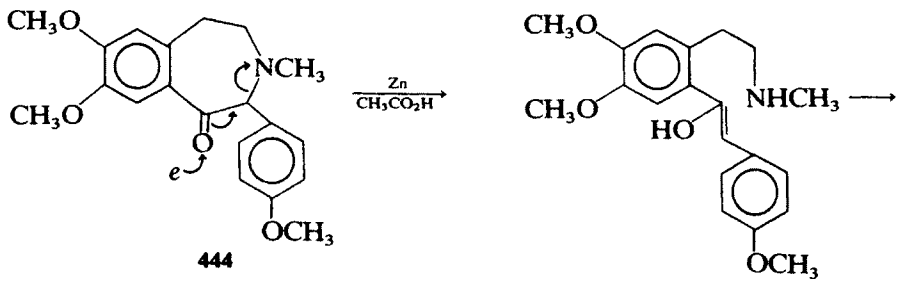
B. Isoquinoline Syntheses by Ring Contraction

Isoquinoline syntheses belonging into this group are ring contractions of benz[*d*]azepines and are related to the chemistry of rheadan alkaloids.[5,6,425]

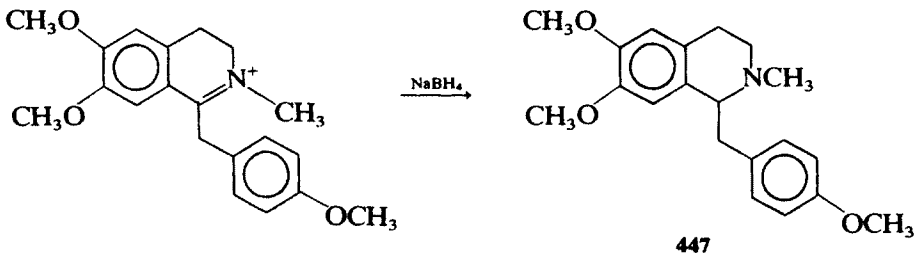
Treatment of the diimine **442** with diluted hydrochloric acid under mild



442 **443**



444 **445**



446 **447**

conditions gave the 1-benzoyl-3,4-dihydroisoquinoline **443**. The reaction presumably proceeds by hydrolysis of both imino functions and subsequent recyclization.[426] Alternatively, reduction of the 1-ketobenzazepine **444** with zinc in hot acetic acid afforded the dihydroisoquinoline **446**, which is not isolated but reduced to the corresponding tetrahydroisoquinoline **447** with sodium borohydride. Compound **446** is assumed to be formed by recyclization of the ring-opened product **445**.[427] Additional examples of isoquinoline formation from benzazepines have been reported in the field of alkaloid chemistry.[428,429]

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CHAPTER III

Biosynthesis of Isoquinolines

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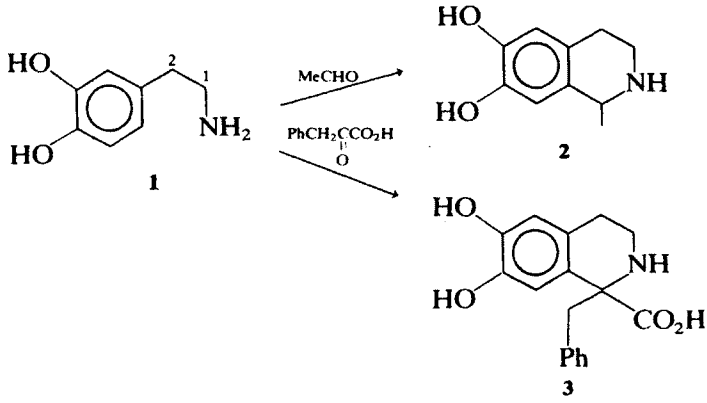
I. HISTORICAL BACKGROUND

The pharmacological effects of plant extracts have been known and utilized for centuries, and the isolation of the active compounds in a pure state has often led the organic chemist into interesting areas of research. Several of the pharmacologically active alkaloids were obtained in a pure state in the early days of organic chemistry, since a crude alkaloid fraction is easily separated from the other plant constituents because of its solubility in aqueous acid, and the major alkaloids can often be purified by crystallization of either the free base or various salts.

With pure compounds available work began on the determination of structure. Traditionally, chemical degradations were carried out, the simple products from these were identified by comparison with compounds prepared by unambiguous syntheses, and the structures of the natural products were deduced by a logic that was often quite brilliant. Soon natural products could be classified according to structure, and it was realized that structural relationships might offer a clue to the biosynthetic pathways in plants. Thus Winterstein and Trier in 1910 suggested[1] that the 1-benzylisoquinoline alkaloids might arise from the condensation of a phenethylamine with a phenylacetaldehyde, and a few years later Robert Robinson presented[2] a detailed proposal for the bioconversion of several types of isoquinoline alkaloid.

These speculations heralded the first biomimetic syntheses, and it was shown that the isoquinolines **2**[3] and **3**[4] were formed when the phenolic amine **1** was condensed with acetaldehyde and phenylpyruvic acid, respectively, under mild conditions of temperature and pH in aqueous solution. The success of these syntheses under so-called physiological conditions was regarded as circumstantial evidence for the biogenetic hypothesis of Winterstein and Trier.[1]

Direct experimental evidence for biosynthetic pathways was first obtained in the late 1950s with the use of the ^{14}C and ^{3}H-labeled compounds that had just become commercially available. Several of the early hypotheses[5] were upheld by these studies, but to avoid confusion, this chapter focuses attention on the experimentally determined pathways, and speculations are



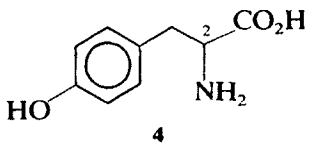
generally ignored. Furthermore, references to preliminary communications of results are not given if a full discussion has subsequently been published.

II. EXPERIMENTAL APPROACH

The rationale for the use of radioactive compounds in biosynthetic studies is that an isotopically labeled molecule is chemically indistinguishable from an unlabeled one. Consequently, if a labeled precursor is introduced into a plant in such small amounts that normal metabolism is undisturbed, it will be treated by the plant in a normal manner and the metabolites will become radioactive.

A. Identification of Primary Precursors

Certain types of molecule are present in all living systems, either in a free state or as an easily recognizable component of the biopolymers. These simple compounds, the amino acids, sugars, bases, fatty acids, and others are usually called *primary metabolites*. The alkaloids, structurally quite complex and found only in a few plant species, are examples of secondary metabolites, and the first step in studying their biosynthesis is to identify the primary building blocks from which they are derived. All the isoquinoline alkaloids studied so far have, in fact, been found to be derived from tyrosine (**4**).



In a typical experiment [2-^{14}C]tyrosine (**4**) would be "fed" as an aqueous solution to a plant, and after a period of normal growth the plant would be harvested and the isoquinoline alkaloid extracted and purified to constant specific radioactivity. The percentage incorporation, defined as:

$$\frac{\text{Total radioactivity of isolated alkaloid}}{\text{Total radioactivity of precursor}} \times \frac{100}{1}$$

is dependent on the plant species, the individual plant, the method of administration, the season, the interval between "feeding" and harvesting, and the position of the precursor in the biosynthetic pathway. A negative result would be inconclusive since there can be no guarantee that the precursor ever reached an active site of alkaloid biosynthesis in the plant. Low incorporation values have often been improved by altering the conditions of the experiment, but the usual range is about 0.1% to about 2%. The actual value is not of great significance, provided that it is sufficiently high for the radioactivity to be measured accurately and for a conclusive chemical degradation to be carried out.

B. Need for Degradation

Once a specifically labeled precursor has been successfully incorporated into alkaloid A, it is possible to undertake a detailed biosynthetic study during which a range of labeled compounds are "fed" to test various hypothetical pathways. Ideally, a repeat feeding of the "standard" precursor should be run in parallel as a check to determine whether plants are actively synthesizing alkaloid A.

Each successful incorporation should then be followed by a degradation of the radioactive alkaloid to test whether the labeling is confined specifically to the expected single atom or set of atoms. This check is necessary because there is always a risk that the radioactive "precursor" might be degraded *in vivo* and the resultant small radioactive fragments incorporated into alkaloid A in a random manner. This risk is always present but is less serious when the precursor molecule carries a skeletal ^{14}C label than when a peripheral functional group (e.g., methoxyl group) carries the radioactivity.

Although it is often cheaper and easier to synthesize a ^{3}H-labeled precursor, there is always a possibility that the radioactivity may be lost by chemical exchange reactions *in vivo* at some stage in the biosynthetic pathway. A skeletal ^{14}C-label is thus ideal, and once a precursor has been positively identified, mixed ^{3}H:^{14}C-labeled precursors may be incorporated; and the change, if any, in the labeling ratio can yield valuable mechanistic information.

Establishing the location of a labeled atom by chemical degradation can be a tedious task, even when the chemistry of the alkaloid has been

described in detail by earlier researchers. Highly enriched ^{13}C-labeled compounds have recently been introduced, and it should theoretically be possible to incorporate a specifically ^{13}C-labeled precursor and to determine the site of labeling in the derived alkaloid by ^{13}C-nmr spectroscopy. Under normal conditions a site of enrichment can be determined by ^{13}C-nmr with certainty if the precursor molecule suffers a dilution of about 10^2 during incorporation into alkaloid A. Unfortunately, a typical dilution during a plant biosynthetic experiment would be about 10^4. It is likely, therefore, that most biosynthetic studies using whole plants will continue to use the sensitive ^3H:^{14}C ratio approach initially, but when incorporation levels are high, or the dilution by endogenous compounds at natural abundance can be minimized, the ^{13}C-approach may be used to avoid chemical degradations.

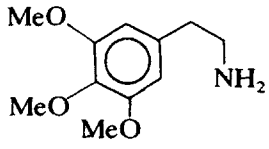
The pathways described in this chapter have been worked out largely by studying the incorporation of labeled precursors as outlined in the preceding paragraphs.

III. 1-ALKYLISOQUINOLINE ALKALOIDS

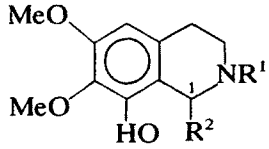
A. Cactus Alkaloids

The isoquinoline alkaloids found in cacti are comparatively simple in structure, but their biosynthesis has been investigated quite thoroughly. This intense interest stems partly from the pharmacological properties of the hallucinogenic Mexican peyote cactus *Lophophora williamsii*, but it is also justified by the useful general conclusions that have emerged and that are applicable to other alkaloid types.

The principal alkaloids of *L. williamsii* are mescaline (**5**) (a simple phenethylamine), and the isoquinolines anhalamine (**6**), anhalonidine (**7**), and pellotine (**8**).



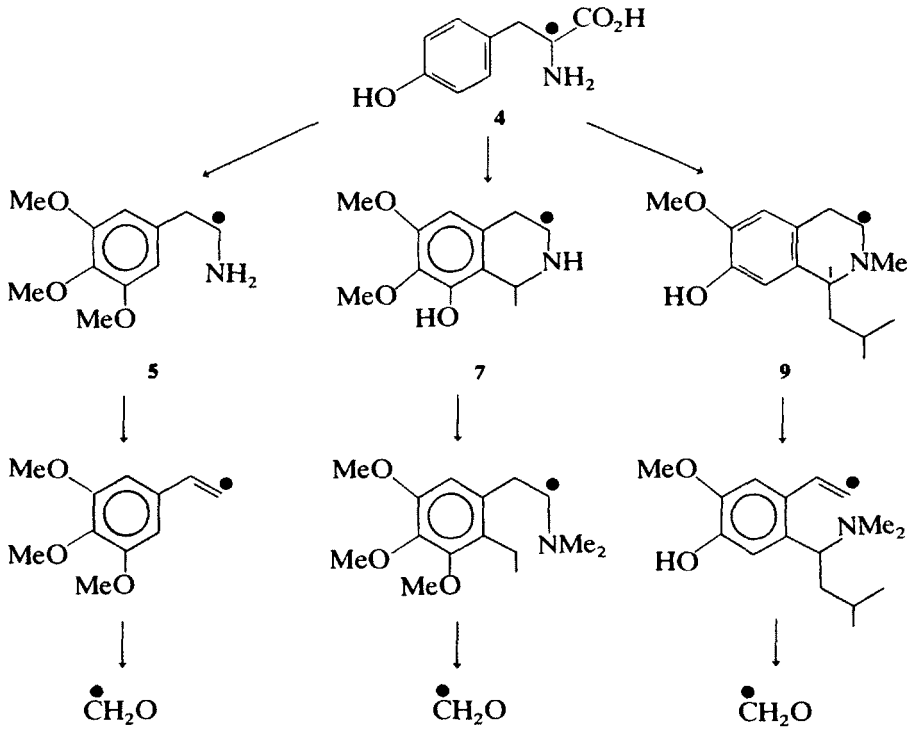
5



6, $R^1 = R^2 = H$
7, $R^1 = H$; $R^2 = Me$
8, $R^1 = R^2 = Me$

(a) *Origin of C_6–C_2 Unit*

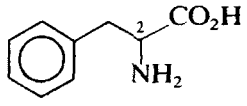
The earliest biosynthetic investigations[6,7] established that [2-^{14}C]tyrosine (**4**) was incorporated into both mescaline (**5**) and anhalonidine (**7**), and the radioactive alkaloids were degraded as shown[7,8] (Scheme 1). In each case



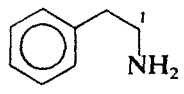
Scheme 1. Degradation of cactus alkaloids.

the formaldehyde dimedone derivative had essentially the same molar specific activity as the original alkaloid, proving that tyrosine (**4**) is a specific precursor of the C_6–C_2(N) units in these alkaloids. It was subsequently shown in a similar way that tyrosine (**4**) is also a specific precursor of lophocerine (**9**) in *L. schottii*[9] and *Pachycereus marginatus*.[10]

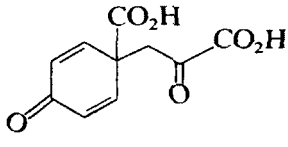
Neither [2-^{14}C]phenylalanine (**10**) nor [1-^{14}C]β-phenethylamine (**11**) were incorporated into the cactus alkaloids. In these plants tyrosine (**4**) is probably formed[11] from the ketone **12** by aromatization to **13** rather than by hydroxylation of phenylalanine (**10**).



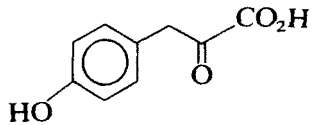
10



11



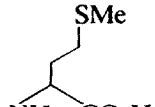
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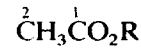
13

(b) *Origin of Remainder of Carbon Skeleton*

It is generally found that [^{14}C-*methyl*]methionine (**14**) is efficiently incorporated into isolated C_1 units of natural products; hence it was not surprising that it was incorporated[12] into anhalamine (**6**). Degradation showed that the *O*-methyl groups were radioactive but a significant proportion of the radioactivity was located at C-1. At this stage it seemed likely that anhalamine (**6**) might be biosynthesized by cyclization of an *N*-methylphenethylamine.

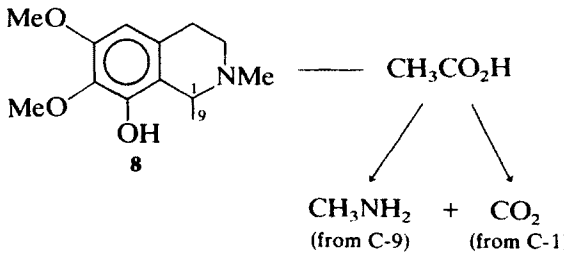


14



15

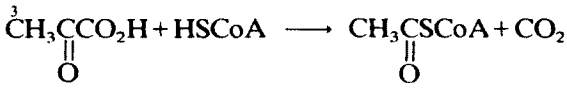
Acetate (**15**) is the normal biosynthetic precursor of a C_2 unit, and [2-^{14}C]acetate was, indeed, incorporated[13] (0.04%) into pellotine (**8**). This time, however, degradation (Scheme 2) revealed that the incorpora-



8

Scheme 2. Kuhn–Roth degradation of Pellotine.

tion was nonspecific, as C-1 and C-9 were labeled approximately equally. From [1-^{14}C]acetate the C-1:C-9 labeling ratio was 2:1. Clearly, acetate was not being incorporated directly, and it seemed possible that the cactus was unable to convert the acetate into a suitably activated form. [3-^{14}C]Pyruvate (**16**), the normal precursor of acetyl coenzyme A (**17**), was

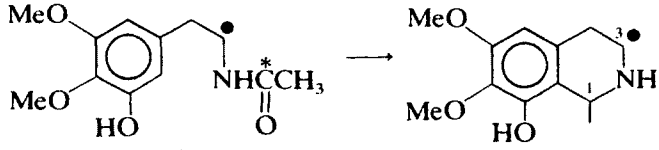


16 **17**

thus fed to *L. williamsii*, and its radioactivity was found to be specifically incorporated[14] into C-1 of anhalonidine (**7**).

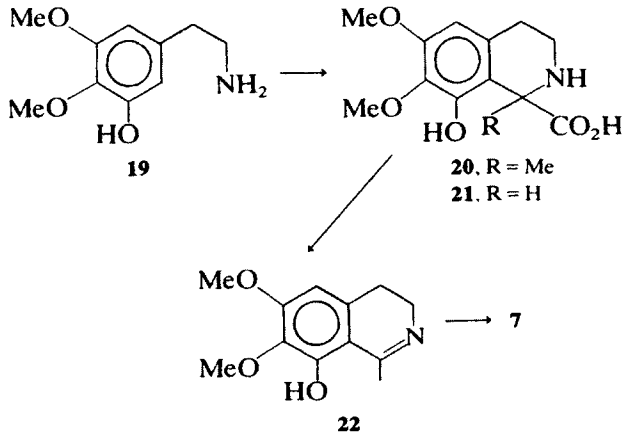
If pyruvate (**16**) was being incorporated by way of acetyl coenzyme A (**17**), an *N*-acetyl intermediate seemed likely. However, although radioactivity from the doubly labeled *N*-acetyl-β-phenethylamine **18** was incorporated

into anhalonidine (**7**), virtually all of it was found[15] to be at C-3, indicating that the precursor **18** was deacetylated prior to incorporation.



18 **7**

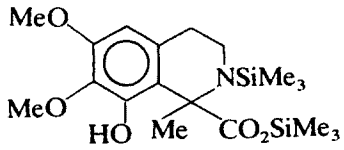
The major clue to the interpretation of all the results described in the foregoing paragraphs came[15] from *in vitro* studies of the reaction of 3-demethylmescaline (**19**) with pyruvic acid (**16**). At pH 4.0 to 4.5 and at room temperature the isoquinoline **20** was formed in near quantitative yield, and the analogous derivative **21** was formed from **19** and glyoxylic acid. In both cases cyclization had occurred ortho to the phenolic hydroxyl group to give the same oxygenation pattern as that found in the phenolic cactus isoquinoline alkaloids. Although peyoruvic acid **20** and peyoxylic acid **21**



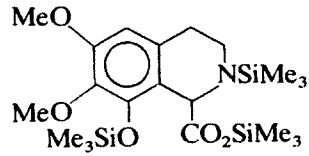
19 **20**, R = Me
21, R = H

22

are not easily decarboxylated *in vitro*, incubation of (±)[^{14}C-*carboxy*] **20** and **21** with peyote slices led to evolution of $^{14}CO_2$. The yield of about 50% in each case suggests that only one enantiomer is being metabolized. The product of the peyoruvic acid (**20**) incubation was identified as dehydroanhalonidine (**22**), indicating that the enzymic decarboxylation may take place by an oxidative mechanism. If this is so, the intact cactus must be capable of achieving a subsequent reduction of **22** since injection of solutions of [1-^{14}C]peyoruvic acid (**20**) and [1,9-^{14}C]peyoxylic acid (**21**) into *L. williamsii* results in good incorporations into anhalonidine (**7**) (6.0%) and anhalamine (**6**) (6.8%), respectively. Finally, the presence of both peyoruvic acid (**20**) and peyoxylic acid (**21**) in peyote was demonstrated by paper chromatography and by gas-liquid chromatography–mass spectrometry of the silyl derivatives **23** and **24**.[15]

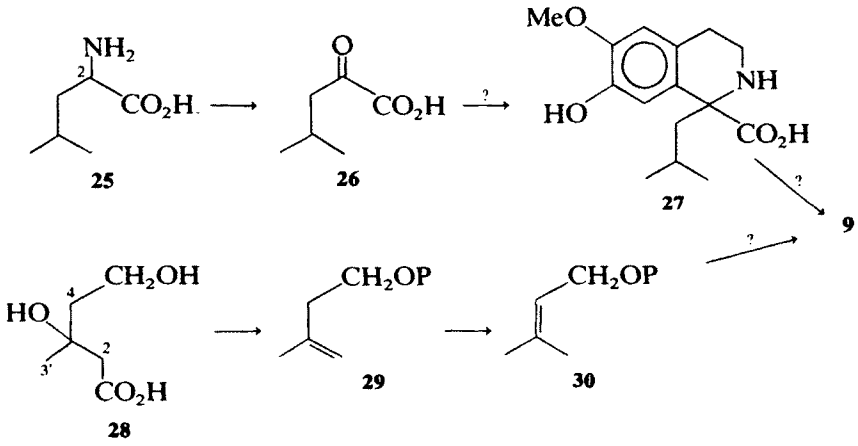


23



24

The exact origin of the isopentyl unit of lophocerine (**9**) has not been determined, but [2-^{14}C]leucine (**25**) gave[9,10] [1-^{14}C]lophocerine (**9**) (0.016%) in *L. schottii*, and this result is consistent with the operation of a pathway analogous to that found for isoquinoline alkaloid biosynthesis in *L. williamsii*. Thus pyridoxal-catalyzed transamination of leucine (**25**) would yield the keto acid **26**, which could condense with a suitable phenethylamine to afford the isoquinoline **27**. It should be emphasized that this scheme is hypothetical and that it does not account for the incorporation[9,10] (0.044%) of [2-^{14}C] and [3',4-^{14}C]mevalonic acid (MVA; **28**) into lophocerine (**9**), which presumably occurs by way of dimethylallyl pyrophosphate (DMAPP; **29**) and *iso*-pentenyl pyrophosphate (IPP; **30**).

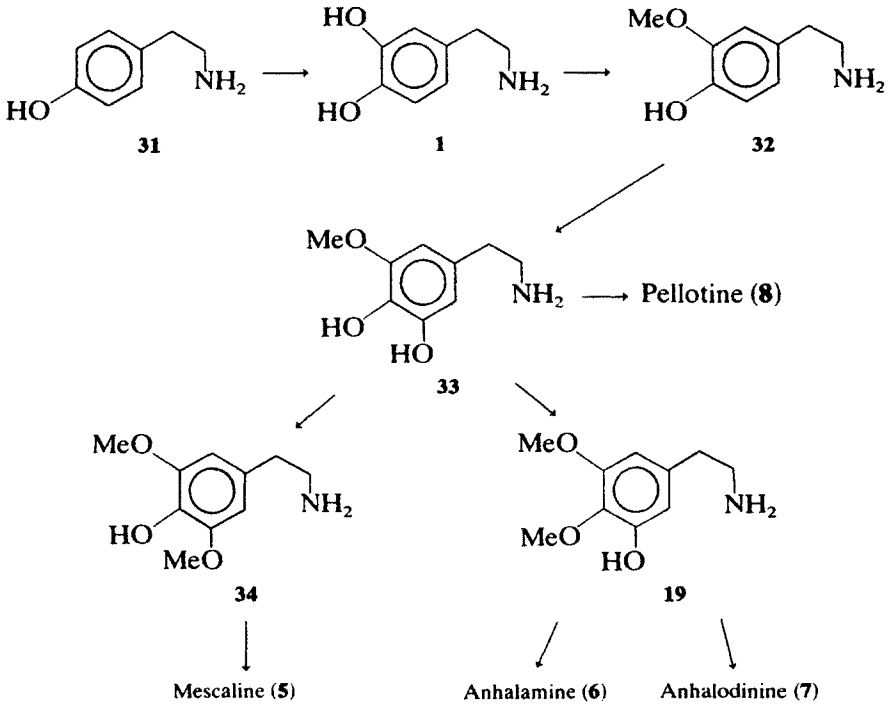


25 26 27 28 29 30

(c) *Phenethylamine Intermediates*

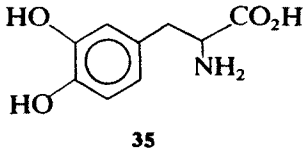
The preceding evidence establishes that the isoquinoline alkaloids of peyote are built up from tyrosine and pyruvic acid (**16**) (or glyoxylic acid) by way of peyoruvic acid (**20**) [or peyoxylic acid (**21**)]. At some stage the tyrosine must suffer decarboxylation, oxygenation, *O*-methylation, and—in the case of pellotine (**8**)—*N*-methylation. The sequence of these events has been studied by (1) feeding labeled compounds[12,13,16-20] to cacti and determining levels of incorporation into mescaline and the isoquinoline alkaloids and (2) feeding [2-^{14}C]tyrosine (**4**) and diluting the resultant plant extract with various radioinactive compounds to identify possible intermediates.[21]

From the results of these experiments it has been deduced that the major pathway proceeds via tyramine (**31**),[12,20] dopamine (**1**),[8,12,20] and 3-*O*-methyl dopamine (**32**)[13,17,20] to give **33**. The catechol (**33**) is a good precursor of mescaline (**5**),[20] anhalamine (**6**),[20] and pellotine (**8**),[13] but the pathway seems to diverge at this point. *O*-Methylation can give either **19** or **34**, and these compounds are metabolized in quite different directions. Thus

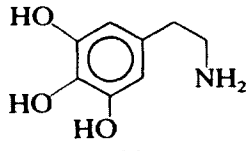


the 3-hydroxy derivative **19** is a poor precursor of mescaline[17,20] but is incorporated well into anhalamine (**6**)[18,20] and anhalonidine (**7**).[18] On the other hand, the isomeric 4-hydroxy derivative **34** is an excellent precursor of mescaline (**5**)[18,20] but not of the cactus isoquinoline alkaloids.[20] The apparent preference for the formation of the 4-hydroxy derivative **34** in *Trichocereus pachanoi* is consistent[19] with the absence of isoquinolines in this plant. Since neither **19** nor **34** is efficiently converted into pellotine (**8**),[13] it seems quite possible that *N*-methylation of the common intermediate **33**[13] is a key step in pellotine biosynthesis.

Although the preceding sequence does seem to be the major pathway for alkaloid biosynthesis in the cacti studied, it has not been rigorously established as the *only* sequence. Thus dopa (**35**)[20] and trihydroxy phenethylamine (**36**)[13,17,18,20] are able to enter the pathway by decarboxylation and methylation, respectively. Furthermore, anhalonidine (**7**) was incorporated[13] into pellotine (**8**), but as the reverse reaction was also observed in



35

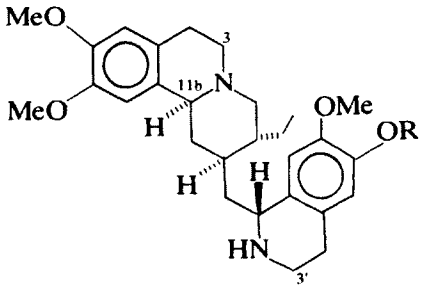


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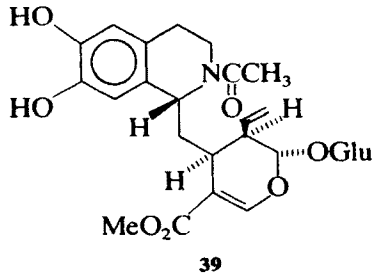
the same plant,[13] there may be a network of closely related intermediates rather than a unique metabolic sequence for cacti alkaloid biosynthesis.

B. Ipecac Alkaloids

Extracts of *Cephaelis ipecacuanha* have been used for hundreds of years to treat amoebic dysentery. The active component is emetine (**37**), which occurs alongside its phenolic analogue, cephaeline (**38**), and the simpler alkaloid, ipecoside (**39**). These three alkaloids are derived from tyrosine (**4**),



37, R = Me
38, R = H

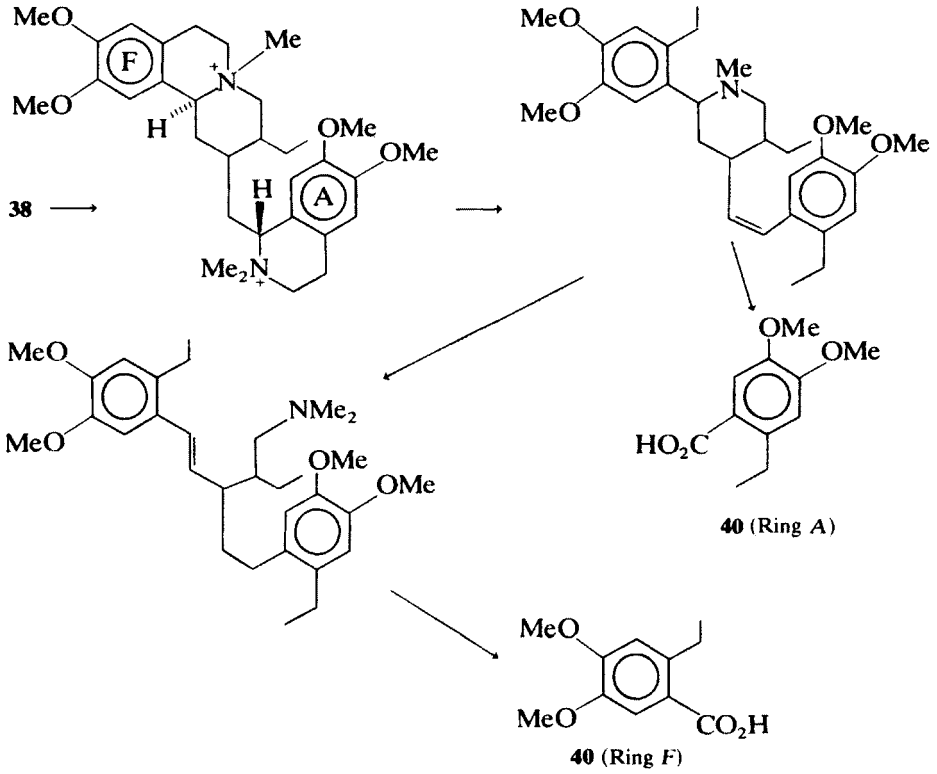


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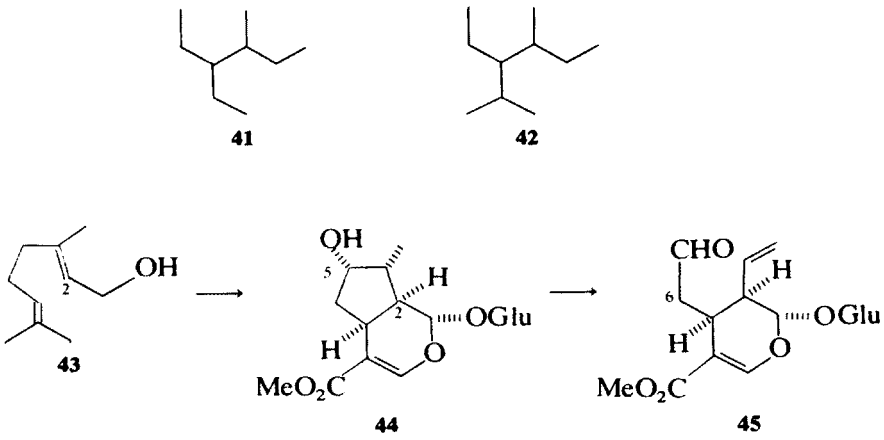
probably by way of dopamine (**1**). Thus [2-^{14}C]tyrosine (**4**) was incorporated[22] into cephaeline (**38**) by *C. ipecacuanha*, and degradation (Scheme 3) gave 6-ethylveratric acid (**40**) with half of the original radioactivity, whether it was derived from ring *A* or from ring *F*. Kuhn–Roth oxidation of each sample of **40** gave radioactive acetic acid, which yielded radioactive methylamine on Schmidt degradation. Consequently, the radioactivity in cephaeline (**38**) is located at C-3 and C-3′.

(a) *Origin of* C_9–C_{10} *Unit*

Much attention has focused on the origin of the remainder of the carbon skeleton—a C_9 unit (**41**) in emetine and cephaeline and a C_{10} unit (**42**) in ipecoside. This type of C_9–C_{10} unit is more typical of the indole alkaloids, whose biosynthesis has been reviewed in an earlier volume,[23] and is now known to originate from the monoterpene geraniol (**43**) through loganin (**44**) and secologanin (**45**). One of the earliest pieces of evidence in any



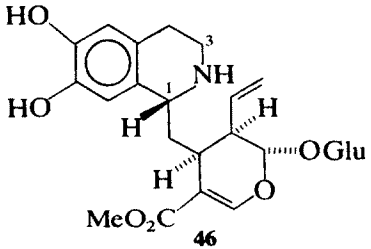
Scheme 3. Degradation of cephaeline.



system that the C_9–C_{10} unit was monoterpenoid was the demonstration[24] of intact incorporation of [2-^{14}C]geraniol (**43**) and of [*O-methyl*-^{3}H,2-^{14}C]loganin (**44**) into ipecoside (**39**). Intact incorporation of [*O-methyl*-^{3}H,6-$^{3}H_2$]secologanin (**45**) was shown later.[25]

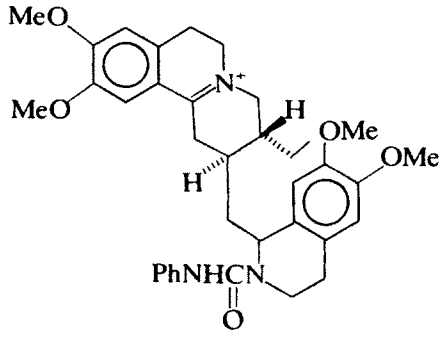
(b) *Relationship Between Ipecoside, Cephaeline, and Emetine*

A surprising result was obtained[25] when [3-^{14}C]desacetylipecoside (**46**) and [3-^{14}C]desacetylisoipecoside (**47**) were fed to *C. ipecacuanha*. The former compound was incorporated well into ipecoside (0.59%), cephaeline (0.34%), and emetine (0.07%), whereas the latter compound failed to serve as precursor for any of the *Ipecac* alkaloids, *although it has the correct configuration at* C-1. The absolute configuration of ipecoside (**39**) was recently established[26] by X-ray analysis of its *O,O*-dimethyl ether, and there is no doubt that the bioconversion of desacetylipecoside (**46**) into cephaeline (**38**) and emetine (**37**) involves a change in configuration at C-1. Further-

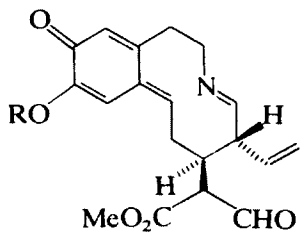


46

47, epimer at C-1



48



49

more, this change occurs without removal of the hydrogen at C-1, since [5-^{3}H]-loganin (**44**) affords radioactive emetine (**37**; ^{3}H at C-11b), which loses 95% of its activity after mercuric acetate oxidation of the *N*-phenylurea derivative to the iminium salt **48**. A similar change in configuration occurs

during the biosynthesis of the indole–monoterpene alkaloids,[23] and a plausible mechanism has been proposed,[27] together with some supported circumstantial evidence from *in vitro* experiments. The analogous mechanism for the conversion of desacetylipecoside (**46**) into emetine (**37**) would involve equilibration of a phenolic benzoquinolizidine intermediate through a quinone methide (e.g., **49**).

IV. 1-PHENYLISOQUINOLINE ALKALOIDS

Alkaloids that have the 1-phenylisoquinoline skeleton are rare, although it should be noted that the *Amaryllis* alkaloids[28] have the same basic C_6–C_2–N–C_1–C_6 structure. The only biosynthetic study[29,30] on this group of alkaloids is concerned with the origin of (−)-cryptostyline-I (**50**) in the orchid *Cryptostylis erythroglossa*. [2-^{14}C]Tyrosine (**4**) was incorporated[29] and the alkaloid was degraded as shown (Scheme 4). Essentially all the radioactivity was found in the dimedone derivative of formaldehyde, thus proving that tyrosine is incorporated specifically into the C_6–C_2 unit of cryptostyline-I (**50**). [1-^{14}C]Tyramine (**31**), [2-^{14}C]dopa (**35**), and [1-^{14}C]dopamine (**1**) were also specifically incorporated in the same way but with lower efficiency.[29] However, [2-^{14}C]-dopamine (**1**) was also incorporated[30] into cryptostyline-I (**50**), and degradation by way of the acid **51** to the ketone **52** revealed that only 35% of the radioactivity was present at C-4; thus dopamine (**1**) must provide *both* the C_6–C_1 and the C_6–C_2 units.

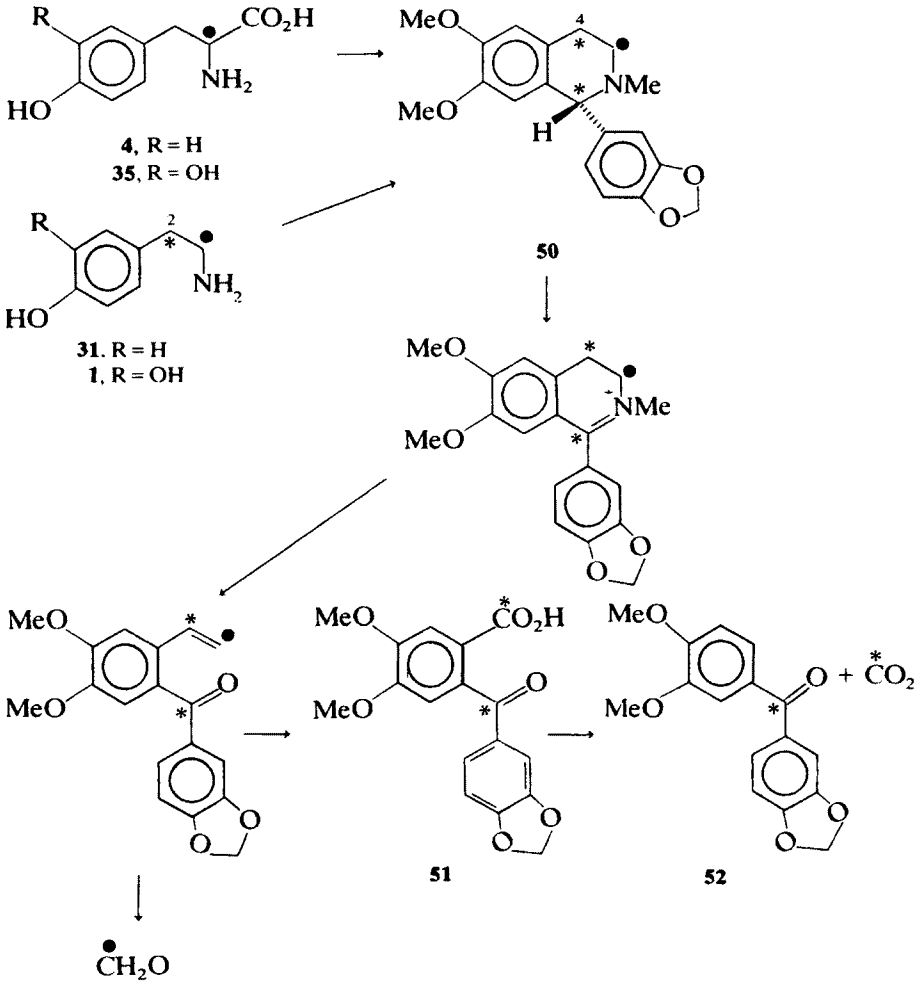
[1,2-$^3H_2$]-3-Hydroxy-4-methoxy-β-phenethylamine (**32**)[29] and [1-^{14}C]-3,4-dimethoxy-β-phenethylamine[30] afforded radioactive cryptostyline-I, but experiments with doubly labeled samples of these compounds will be required to check for *intact* incorporation (without prior demethylation).

V. 1-BENZYLISOQUINOLINE ALKALOIDS

A. Norlaudanosoline

Norlaudanosoline (**53**) played a central role in early speculations[5] about the origin of many complex alkaloids, including the morphine, protoberberine, aporphine, and bisbenzylisoquinoline types. These speculations have largely been verified experimentally. In fact, the very first experimental evidence[31] that the morphine alkaloids are actually modified 1-benzylisoquinolines was achieved by administering ^{14}C-labeled norlaudanosoline (**53**) to the opium poppy. In the same plant [1-^{14}C]norlaudanosoline was also specifically incorporated[32] into papaverine [Section V.B(d)].

These were exciting results, and they stimulated further study of the

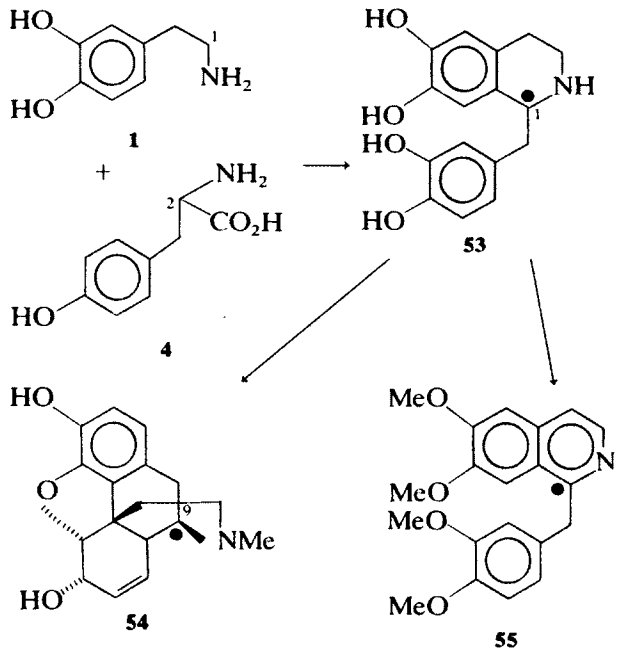


Scheme 4. Degradation of cryptostyline-I.

pathway *beyond* norlaudanosoline in several plants. For some years the precise origin of the simple benzylisoquinolines was not investigated, but this part of the puzzle has since also been clarified.

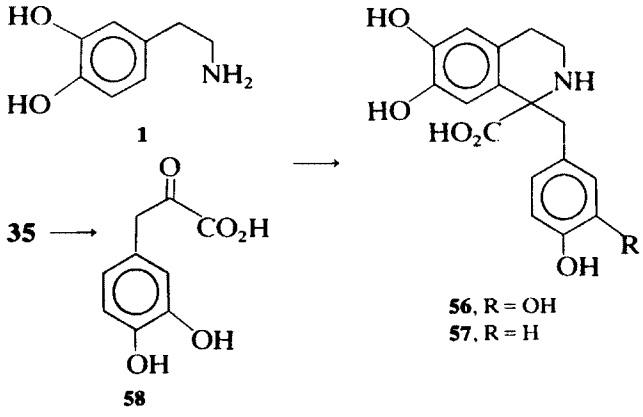
(a) *Biosynthesis of Norlaudanosoline*

Results obtained by incorporating simple precursors into morphine (**54**) and papaverine (**55**) also provide indirect evidence of the biosynthesis of their precursor norlaudanosoline (**53**). When [2-^{14}C]tyrosine (**4**) was incorporated into morphine (**54**)[33] and papaverine (**55**),[34] subsequent degradation revealed that both C_6–C_2 units were labeled approximately equally.



[1-^{14}C]Dopamine (**1**) was incorporated into morphine (**54**),[35] but all the radioactivity was located in that C_6–C_2 unit that is built into the isoquinoline ring. [2-^{14}C]Dopa (**35**) was also incorporated only into the isoquinoline ring residue of morphine (**54**).[36]

The preceding results suggested that norlaudanosoline (**53**) is built up from dopamine (**1**) and tyrosine (**4**) as illustrated. The discovery that the biosynthesis of the simple isoquinoline alkaloids [Section III.A(b)] proceeds through the 1-carboxyisoquinolines peyoruvic acid (**20**) and peyoxylic acid (**21**) subsequently led to a profitable study of the analogous 1-carboxy-1-benzylisoquinoline derivatives. Thus it was found that [3-^{14}C,4-^{3}H]-1-carboxynorlaudanosoline (**56**) was decarboxylated by latex from the seed



capsules of *Papaver somniferum* to give norlaudanosoline (**53**)[37] (2.2% incorporation) with the same $^{3}H:^{14}C$ ratio. The same precursor **56** was incorporated into morphine (**54**) (0.07%)[36] in the intact plant, where the triphenolic analogue **57** was much less effective (0.02%). Thus it seems that the 1-benzylisoquinoline system is built up in nature by condensation of dopamine (**1**) with 3,4-dihydroxyphenylpyruvic acid (**58**) to give the 1-carboxyisoquinoline **56**. The pyruvic acid (**58**) should be formed from dopa (**35**), and in agreement with this, [1-^{14}C]dopa (**35**) was specifically incorporated[37] into 1-carboxynorlaudanosoline (**56**) by seedlings of *P. somniferum*. However, the failure to incorporate [2-^{14}C]dopa (**35**) into C-9 of morphine (**54**)[36] and several other alkaloids in mature plants seems inconsistent with this result. Possibly the administered dopa is able to reach only the appropriate site for enzymic decarboxylation, and *not* that for enzymic transamination due to compartmentalization of the enzymes.

B. *O*-Methyl and *N*-Methyl Derivatives of Norlaudanosoline

A variety of mono-, di-, tri, tetra-, and pentamethyl derivatives of norlaudanosoline are known, and the methylation pattern plays an important part in deciding the further metabolism of these compounds.

(a) *Norprotosinomenine*

This dimethyl ether (**60**) serves as a specific precursor of the aporphine alkaloids in *Dicentra eximia* and of the *Erythrina* alkaloids [Section VII.B(c)(ii)]. In neither case is any isomeric dimethyl ether incorporated.

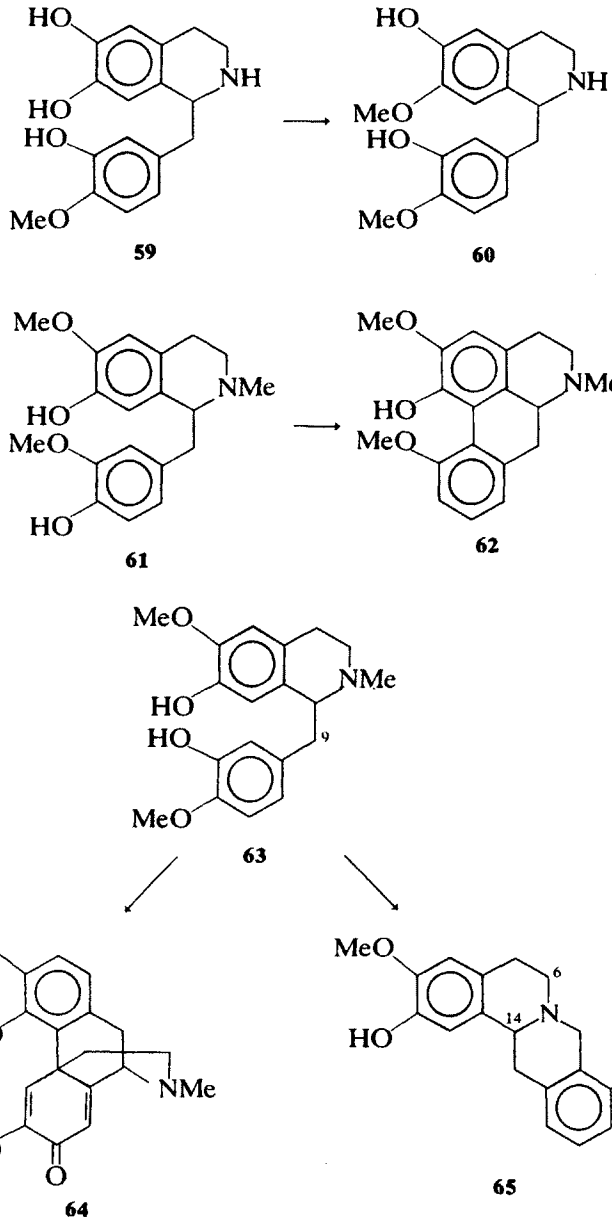
Norlaudanosoline (**53**) and its four monomethyl ethers were also tested as precursors of the aporphine alkaloids of *D. eximia*. The results[38] [Section VII.B(c)(i)] implied that norprotosinomenine (**60**) is biosynthesised from norlaudanosoline (**53**) uniquely through the 4-*O*-methyl derivative (**59**).

(b) *Orientaline*

Orientaline (**61**) has the methylation pattern uniquely required for conversion to isothebaine (**62**) in *Papaver orientale* [Section VII.B(b)]. The biosynthetic pathway to orientaline (**61**) has not been studied in detail.

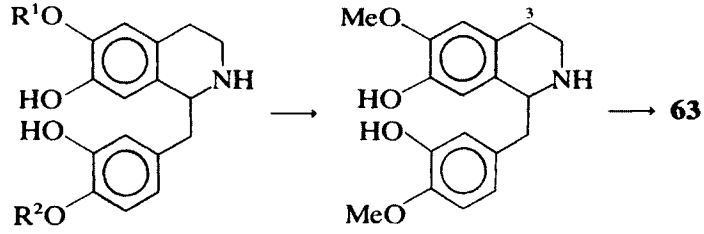
(c) *Reticuline*

Reticuline (**63**) is the key precursor of several alkaloid types. Oxidative phenol coupling generates salutaridine (**64**), the parent compound of the



morphinan alkaloids, whereas a different oxidative cyclization leads to scoulerine (**65**) and hence to the protopine, narcotine, and chelidonine skeletal types (see later sections).

The biosynthesis of reticuline (**63**) has been studied[39] in *Litsea glutinosa*, where it was found that the monomethyl ethers **59** and **66** were incorporated to similar extents (0.12 and 0.18%). Norreticuline (**67**) served[39] as an



59, $R^1 = H$; $R^2 = Me$
66, $R^1 = Me$; $R^2 = H$

67

even better precursor (0.45%) indicating that *O*-methylation precedes *N*-methylation, at least in this plant. Although both C_6–C_2 units in reticuline are derived from tyrosine (**4**), [2-^{14}C]dopa (**35**) is incorporated[39] only into C-3 of the isoquinoline ring.

(d) *Papaverine*

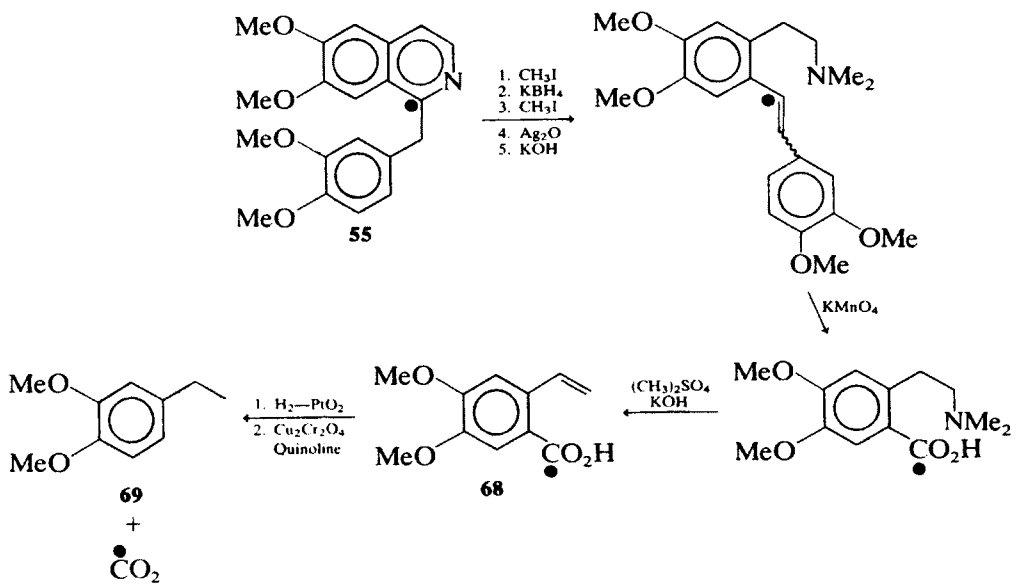
It was mentioned earlier that [1-^{14}C]-norlaudanosoline (**53**) is incorporated into papaverine (**55**). The specificity of the incorporation was established[32] by degrading the radioactive papaverine (**55**) as shown in Scheme 5. Essentially all the radioactivity was found in the CO_2 derived from the degradation product **68**, whereas 3-ethylveratrole (**69**) was radioinactive.

Attention was recently turned to the sequence and mechanism of the various methylation and dehydrogenation reactions needed to transform norlaudanosoline (**53**) into the aromatic isoquinoline papaverine (**55**). The remarkably high incorporation[40] (18%) of norlaudanosine (**70**) indicates that *O*-methylation normally proceeds to completion before aromatization. The aromatization enzyme almost certainly is highly specific for the enantiomer with configuration 1-*S*, since (−)-norreticuline (**67**) is incorporated into papaverine much more effectively that is the (+)-enantiomer[40,41] (Scheme 6).

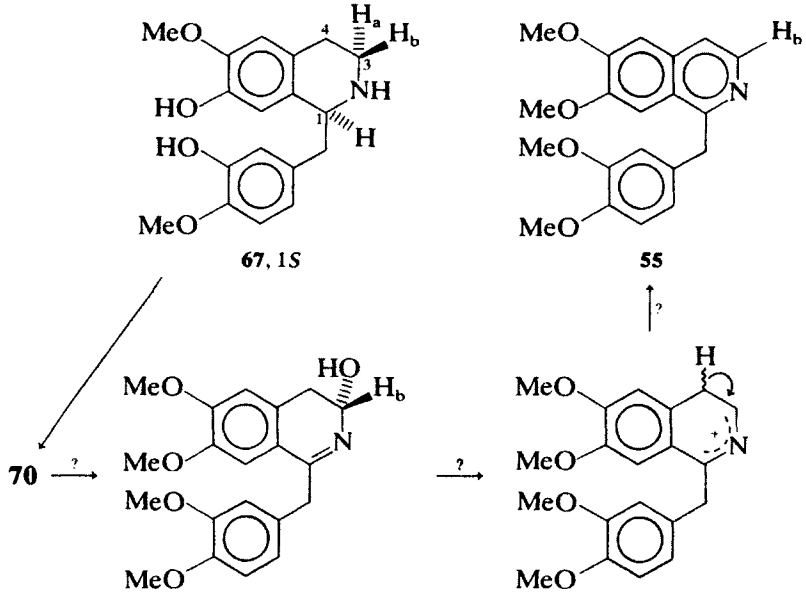
The monomethyl ethers **59** and **66** are incorporated equally well into norlaudanosine (**70**),[40] as they are into reticuline [Section V.B(c)], but the trimethyl ether **71** is a much better precursor of papaverine than the isomer **72**.[41] The sequence from norlaudanosoline to papaverine can thus be summarized as:

$$\mathbf{53} \rightarrow \mathbf{59} \text{ or } \mathbf{66} \rightarrow \mathbf{67} \rightarrow \mathbf{71} \rightarrow \mathbf{70} \rightarrow \mathbf{55}$$

(i) Stereospecificity in Aromatization Step. The aromatization step leading to papaverine necessarily involves removal of four hydrogen atoms from C-1, N-2, C-3, and C-4. The stereochemistry of the processes at C-3 and C-4 has been investigated[42] by using stereospecifically labeled samples of norreticuline (**67**), and the results have important implications for the mechanism of the dehydrogenation.



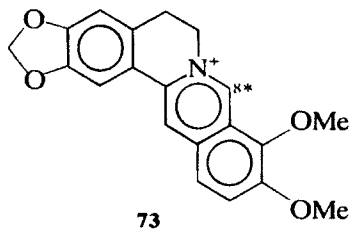
Scheme 5. Degradation of papaverine.


MeO
HO
HO
MeO
H_a
H_b
NH
H
67, 1S
55
70
?
HO
N
MeO
MeO
MeO

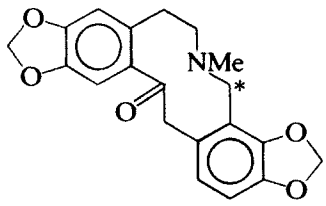
VI. ALKALOIDS POSSESSING A "BERBERINE BRIDGE"

A. Origin of "Berberine Bridge"

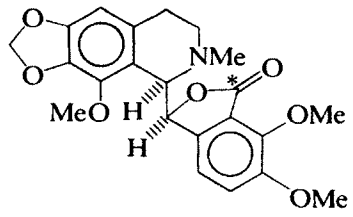
The four alkaloids berberine (**73**), narcotine (**75**), protopine (**74**), and chelidonine (**76**) appear at first sight to be structurally diverse. However, they all possess, in addition to a C_6–C_2–N unit and a C_6–C_2 unit, an extra skeletal carbon atom, marked with an asterisk. This carbon is provided by the C_1 pool as was shown[44] by the specific incorporation of formate and methionine. But the major breakthrough came with the demonstration that reticuline (**63**)[45] and laudanosoline (**77**)[46] are incorporated intact into berberine (**73**), with their *N*-methyl groups transformed specifically into the "berberine bridge" atom C-8. Subsequent studies on the biosynthesis of protopine (**74**),[45,47] narcotine (**75**),[48] and chelidonine (**76**)[47] revealed that in each case reticuline is a good precursor and that C* arises from the *N*-methyl group.



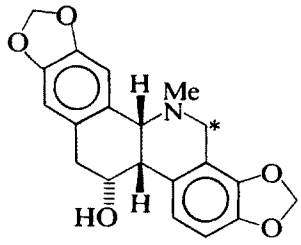
73



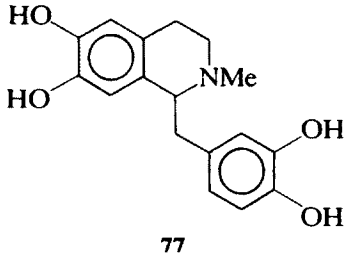
74



75



76



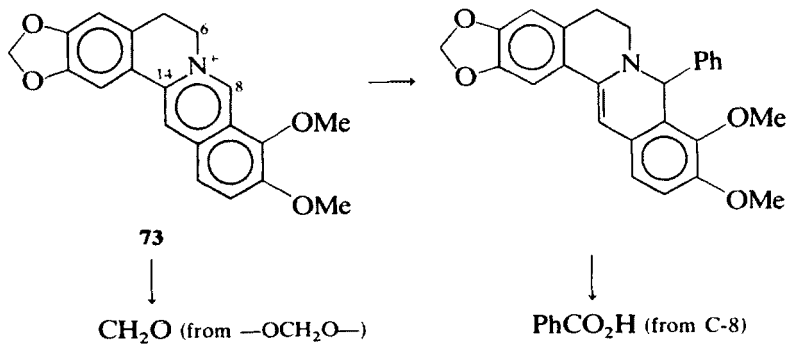
77

These results provide clear evidence for a common pathway to the four alkaloid types at least as far as reticuline, and it seemed likely that oxidative cyclization to the tetrahydroprotoberberine scoulerine (**65**) might occur before the pathway diverges. This was proved by the intact incorporation of scoulerine (**65**) into protopine (**74**),[47] narcotine (**75**),[48] and chelidonine (**76**).[47]

The experimental evidence is now considered in detail for each skeletal type, together with additional information concerning the later stages of each pathway.

B. Berberine

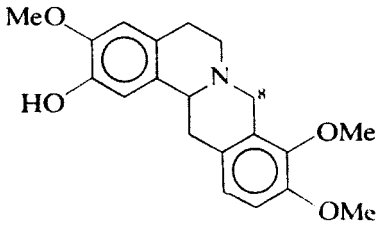
The biosynthesis of berberine (**73**) has been studied in *Hydrastis canadensis*, *Berberis japonica*, and *Papaver somniferum*. Radioactivity from [2-^{14}C]tyrosine (**4**) was incorporated[49] approximately equally into C-6 and C-14, whereas that from [1-^{14}C]dopamine (**1**) was incorporated[49] only into C-6. [*N-Methyl*-^{14}C,3-^{14}C]laudanosoline (**77**) was incorporated into berberine (**73**), and degradation (Scheme 7) showed that no change in the



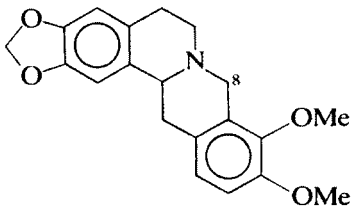
Scheme 7. Degradation of berberine.

labeling ratio had occurred.[46] Both possible mono-*O*-methyl precursors of reticuline were efficiently incorporated[45] into berberine. Intact incorporation of [*N-methyl*-^{14}C,6-*O-methyl*-^{14}C]reticuline (**63**) was demonstrated by degradation, and this experiment[45] proved that the methylenedioxy group of berberine (**73**) is formed by a formal oxidative cyclization of an *o*-methoxyphenol.

It seems highly likely that scoulerine (**65**) is a precursor of berberine (**73**); although the necessary experiments have not been carried out, [8-^{14}C]isocorypalmine (**78**) and [8-^{14}C]canadine (**79**) were successfully incorporated[47] into berberine (**73**) in *P. somniferum*. Furthermore, [8-^{3}H,8-^{14}C]-canadine (**79**) lost half of its tritium during its bioconversion to berberine



78



79

(**73**), pointing to a stereospecific enzymic process for the aromatization step.[50]

C. Stylopine

The biosynthesis of stylopine (**80**) in *Chelidonium majus* has been examined in considerable detail[46] with the use of multiply labeled precursors. The labeling patterns in the biosynthetically labeled stylopine were determined by the degradation outlined in Scheme 8.

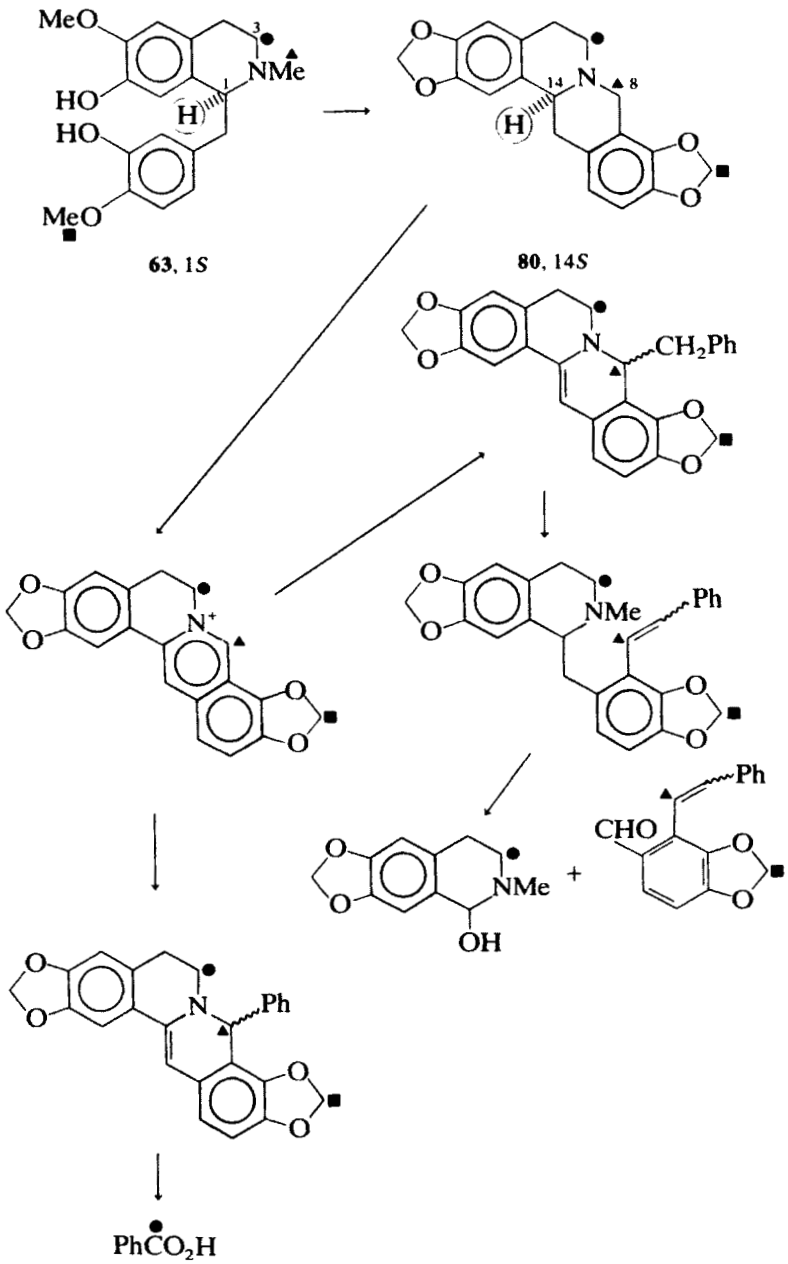
The stylopine in *C. majus* is a partial racemate with a predominance of the (−)-(14*S*) form. The biosynthetic studies showed that (+)-(1*S*) reticuline (**63**) (whose configuration corresponds to that of the major stylopine enantiomer) is much more effectively incorporated than its enantiomer. Similarly, (−)-(14*S*) scoulerine (**65**) was found to be incorporated into stylopine much better than its enantiomer,[46] and (−)-[6-^{14}C,14-^{3}H]scoulerine (**65**) was incorporated without significant change in the labeling ratio.

Earlier it was shown[45] that (+)-reticuline (**63**) is converted 15 times more efficiently than (−)-reticuline into berberine (**73**). Berberine and stylopine, therefore, both originate from isoquinolines of the same absolute configuration.

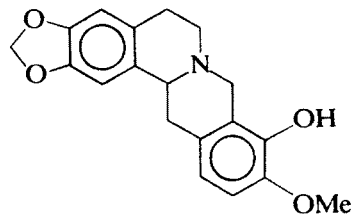
(+)-[3-^{14}C, *N-Methyl*-^{3}H]reticuline (**63**) was incorporated into stylopine without change of the ^{3}H:^{14}C ratio,[46] thus proving that, as in the biosynthesis of berberine,[45,47] the "berberine bridge" arises directly from the *N*-methyl group of reticuline. Also, degradation of the stylopine derived from (+)-[1-^{3}H,3-^{14}C,*N-methyl*-^{14}C,4′-*O-methyl*-^{14}C]reticuline (**63**) demonstrated[46] that the methylenedioxy group in ring *D* of stylopine arises (as in ring *A* of berberine) by oxidation of an *o*-methoxyphenol. In fact, this methylene dioxy group is probably formed before that in ring *A* since nandinine (**81**) was not incorporated into stylopine.

D. Hydroxylated Alkaloids, Berberastine and Ophiocarpine

Incorporation of [1-^{14}C]dopamine (**1**) into canadine (**79**) and berberastine (**83**) in *Hydrastis canadensis* has been observed.[51] For the biosynthesis of



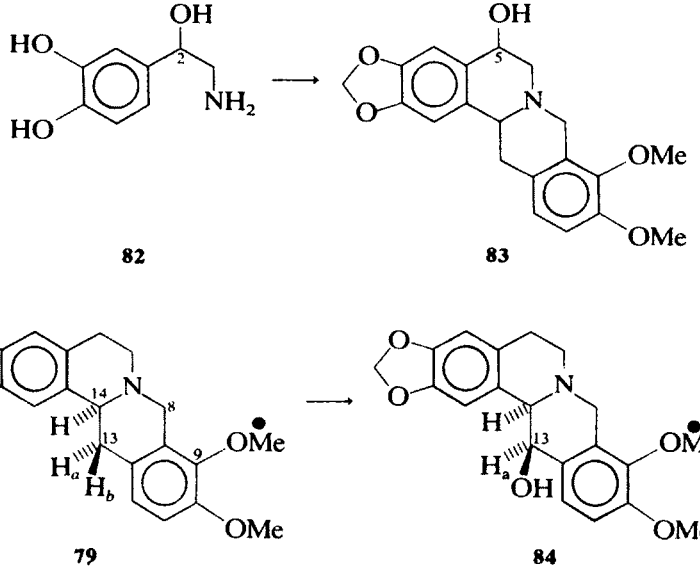
Scheme 8. Degradation of stylopine.



81

the latter compound, hydroxylation at C-5 appears to be an early step since [2-^{14}C]noradrenaline (**82**) is also specifically incorporated.

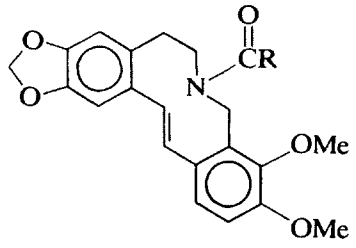
In contrast, the C_{13}-hydroxy group of ophiocarpine (**84**) is introduced at a late stage in its biosynthesis in *Corydalis ophiocarpa*, since [9-*O*-*methyl*-^{14}C,8,14-$^{3}H_2$]canadine (**79**) was incorporated[52] efficiently and without alteration of the $^{3}H:^{14}C$ ratio. The hydroxylation step was shown to proceed with retention of configuration when it was found that (13*S*,14*S*)-[9-*O*-*methyl*-^{14}C,13-^{3}H]canadine (**79**) was incorporated with *retention* of tritium, whereas the epimeric (13*R*,14*S*) compound was incorporated with *loss* of tritium. Labeled (13*S*,14*S*)-canadine (**79**) was prepared[52] from the *seco*-canadine derivative **85** by acid-catalyzed cyclization in the presence of



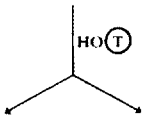
82 **83**

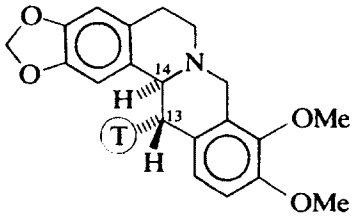
79 **84**

tritiated water. The addition to the double bond proceeds in a clear-cut "anti" manner,[52] and so the (13*R*,14*S*) compound was prepared in an analogous way from the [13-^{3}H] derivative of **85** by using normal water.

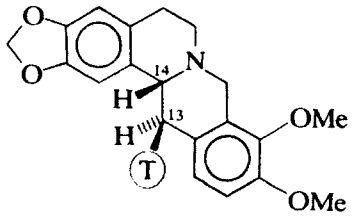


85





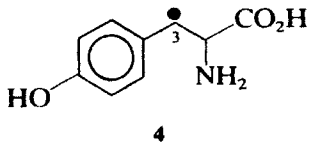
79, 13*S*; 14*S*



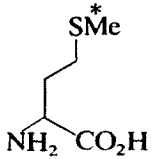
79, 13*R*; 14*R*

E. C_{13}-Methyl Derivative Corydaline

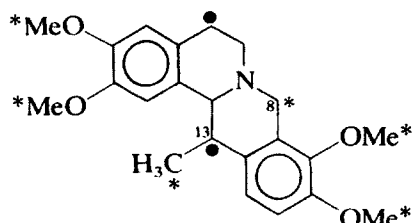
Recent studies[53] of the biosynthesis of corydaline (**86**) in *Corydalis solida* have shown that the 13-methyl group is provided by methionine (**14**) whereas the remainder of the tetrahydroprotoberberine skeleton appears to be built in the usual manner. Thus [3-^{14}C]tyrosine (**4**) was incorporated, and Kuhn–Roth degradation showed[53] that half of the radioactivity of the corydaline was located at C-13. Degradation of the corydaline (**86**) from [*methyl*-^{14}C] methionine (**14**) showed[53] that approximately $\frac{1}{6}$ of the radioactivity was located at C-8, C_{13}–CH_3, and in each of the four *O*-methyl



4



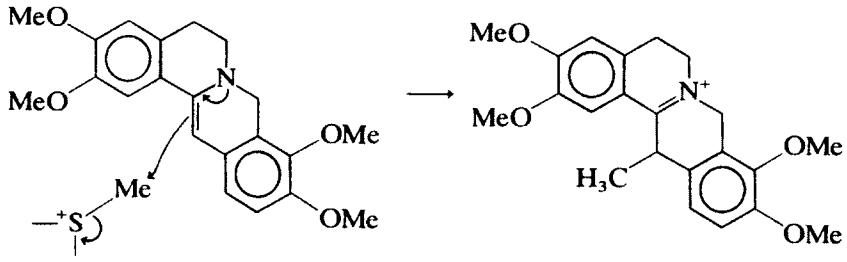
14



86

groups. The incorporation of [*N-methyl*-^{14}C] reticuline (**63**) has also been reported.[54]

Although no tetrahydroprotoberberines have been tested as precursors of corydaline, it seems plausible that the methylation step may take place on a $\Delta^{13,14}$-derivative (e.g., **87**) as shown. Reduction of the iminium salt **88** would then provide corydaline.

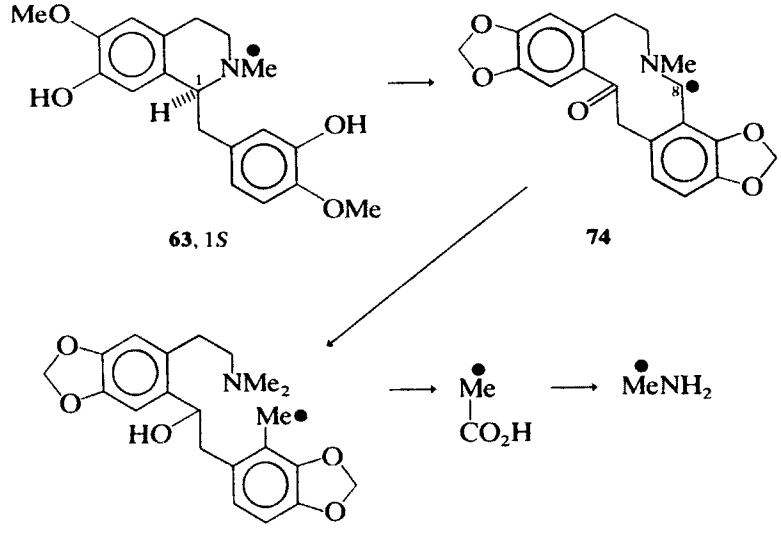


87 **88**

F. Alkaloids Derived from Tetrahydroprotoberberines

(a) *By Cleavage of N–C_{14} Bond; Protopine and Allocryptopine*

The labeled compounds that have been successfully incorporated into protopine (**74**) in various plants include [2-^{14}C]tyrosine (**4**),[38] [*aryl*-^{3}H]norlaudanosoline (**53**),[30] [*aryl*-^{3}H]4-*O*-methylnorlaudanosoline (**59**),[38]

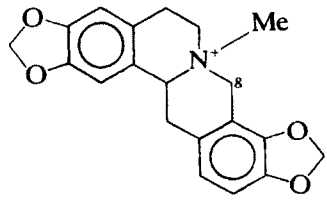


63, 1*S* **74**

Scheme 9. Degradation of protopine.

[*aryl*-^{3}H]norreticuline (**67**),[38] and reticuline (**63**).[38,45,47] The radioactive protopine (**74**) derived from [*N-methyl*-^{14}C]-reticuline (**63**) was degraded as shown in Scheme 9, thus revealing that C-8 was specifically labeled.

The later stages of the pathway have been examined by using optically active precursors, and (+)-(1*S*)-reticuline (**63**) (Scheme 9) was found to be a far more effective precursor than (−)-(1*R*)-reticuline in *D. spectablis*,[45] *Argemone hispida*,[45] *A. mexicana*,[45] and *Chelidonium majus*.[47] Similarly, (−)-(14*S*)-scoulerine (**65**) is incorporated[47] much better than is its enantiomer, and [8-^{3}H, *N-methyl*-^{14}C]stylopine methochloride (**89**) yielded protopine without significant change in the ^{3}H:^{14}C ratio.[47] Singly labeled stylopine methochloride (**89**) was also incorporated[55] into protopine (**74**) in *Corydalis incisa*. Taken together, these results define the pathway for protopine biosynthesis as (+)-reticuline (**63**) → (−)-scoulerine (**65**) → (−)-stylopine (**80**) → methochloride **89** → protopine (**74**). The final transformation must be oxidative, but its exact nature has not been determined. The alkaloid allocryptopine (**90**) is a close relative of protopine (**74**), and both compounds probably share a common biosynthetic pathway at least as far as scoulerine (**65**) and analogous ones thereafter. Thus in *C. majus* [8-^{14}C]isocorypalmine (**78**) serves[55] as a good precursor of allocryptopine (**90**).

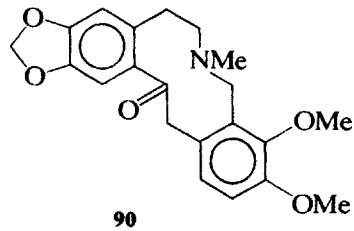


89

(−)-Scoulerine (**65**) ⟶ (−)-Stylopine (**80**) ⟶ (**89**) ⟶ Protopine (**74**)

↘

Isocorypalmine (**78**)

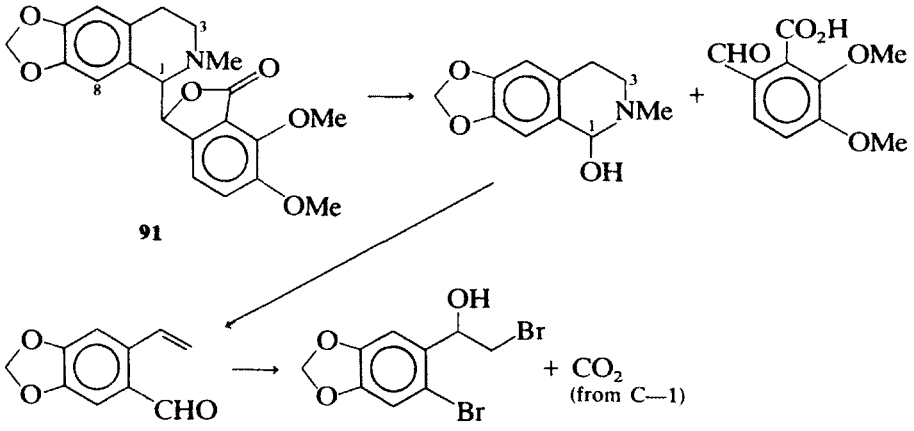


90
Allocryptopine

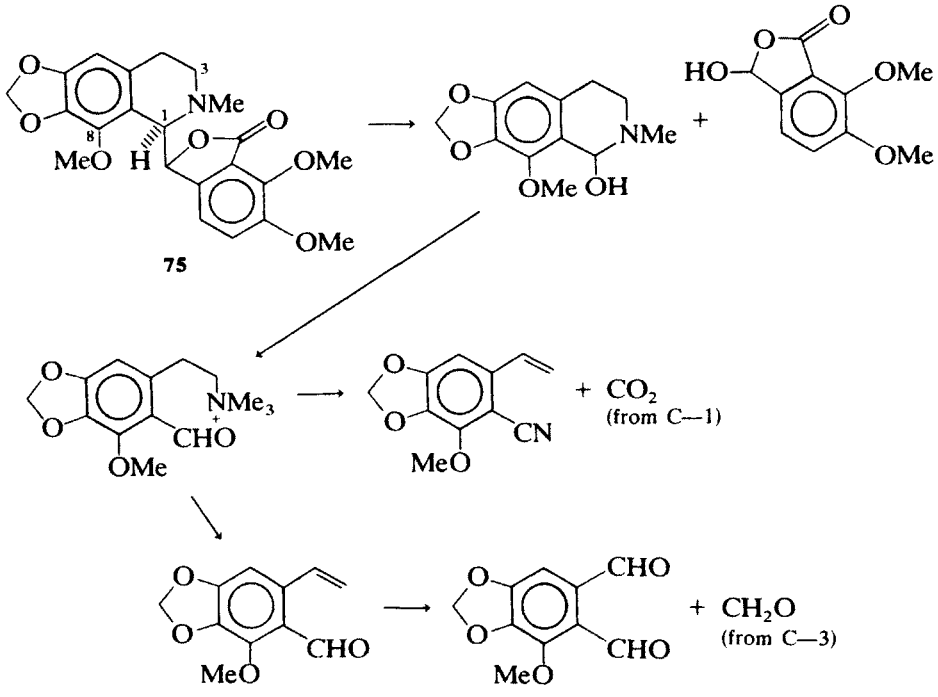
(b) *By Cleavage of N–C$_8$ Bond*

(i) NARCOTINE AND HYDRASTINE. The phthalide isoquinoline alkaloids narcotine (**75**) and hydrastine (**91**) differ only in degree of oxygenation at C-8.

Early biosynthetic studies revealed that the carbon skeletons of both alkaloids are built up from two molecules of tyrosine and a C_1 unit. Thus hydrastine (**91**) derived[49] from [2-^{14}C]tyrosine (**4**) in *H. canadensis* was degraded (Scheme 10) to reveal approximately equal labeling at C-1 and C-3, whereas a somewhat different degradation[48] of narcotine (**75**) (Scheme 11) showed that it is built up from tyrosine in an analogous way in *Papaver*

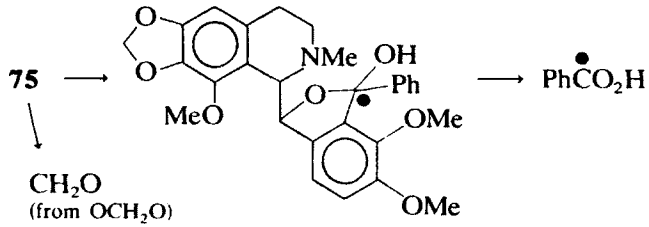


Scheme 10. Degradation of hydrastine.



Scheme 11. Degradations of narcotine.

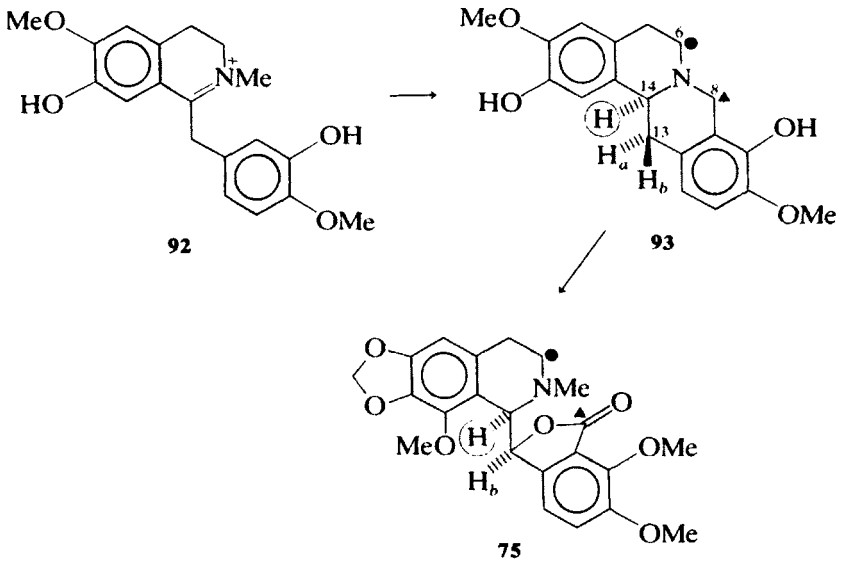
somniferum. The incorporation of the C_1 precursors [^{14}C]formate and [*S-methyl*-^{14}C] methionine was also studied, and degradation[44,48] of the labeled alkaloids showed that in each case the radioactivity was distributed approximately equally between the carbon atoms of the *O*-methyl, *N*-methyl, carbonyl, and methylenedioxy groups.



The investigation of narcotine biosynthesis now proceeded with an examination of possible 1-benzylisoquinoline precursors. Norlaudanosoline (**53**), laudanosoline (**77**), and reticuline (**63**) were all incorporated,[48] and experiments with doubly labeled laudanosoline revealed that its *N*-methyl group is incorporated intact into the lactone carbonyl carbon of narcotine (**75**). Hence *N*-methylation can precede *O*-methylation (as in protopine biosynthesis). The narcotine derived from [1-^{3}H,3-^{14}C,*N-methyl*-^{14}C,4-*O-methyl*-^{14}C]reticuline was degraded, and the ratio of the three ^{14}C labels was found to be the same as in the precursor, thus proving that neither *N*- nor *O*-demethylation occurs prior to incorporation of reticuline. On the other hand, the ^{3}H:^{14}C ratio of the derived narcotine was less than half that of the original reticuline. Furthermore, although (+)-(1*S*)-reticuline (**63**) has the same configuration at C-1 as narcotine (**75**), it was incorporated only slightly better than (−)-reticuline. These findings[48] could be rationalized if 1,2-dehydroreticuline (**92**) were being formed reversibly from both enantiomers of reticuline, thus causing loss of ^{3}H from C-1 and allowing conversion of (−)-reticuline into (+)-reticuline for subsequent incorporation into narcotine.

These studies[48] with laudanosoline (**77**) and reticuline (**63**) thus showed that the lactone carbonyl carbon of narcotine (**75**) arises from the *N*-methyl group of a 1-benzylisoquinoline, as does C-8 of berberine (**73**), protopine (**74**), and related alkaloids. The relationship between these alkaloid types was further demonstrated when scoulerine (**65**) was shown to be a highly effective precursor of narcotine. (−)-(14*S*)-[6-^{14}*C*, 14-^{3}*H*]Scoulerine (**65**) was incorporated[48] specifically, far more effectively than the (+)-enantiomer, and without significant loss of tritium.

No intermediates have been identified for the transformation of scoulerine (**65**) into narcotine (**75**). However, [3-^{14}C,9-^{3}H]reticuline (**63**) yielded narcotine with 50% retention of ^{3}H, thus indicating that the oxidation at C-13 of scoulerine (corresponding to C-9 of reticuline) is a stereospecific enzymic reaction.[50] This was confirmed by the synthesis and testing of stereospecifically tritiated samples of scoulerine.[56] Thus (13*S*)-[13-^{3}H$_1$,8-^{14}C]scoulerine (**93**) was incorporated into narcotine in *P. somniferum* with predominant *loss*



of tritium whereas the narcotine from the 13*R*-enantiomer showed predominant *retention*.[56] Clearly, the (13-*pro*-*S*) hydrogen (H_a) is removed in a stereospecific process en route to narcotine, and direct hydroxylation at C-13 with retention of configuration is a likely explanation of the result. Ophiocarpine (**84**) is biosynthesized in the same manner and might well be an intermediate.

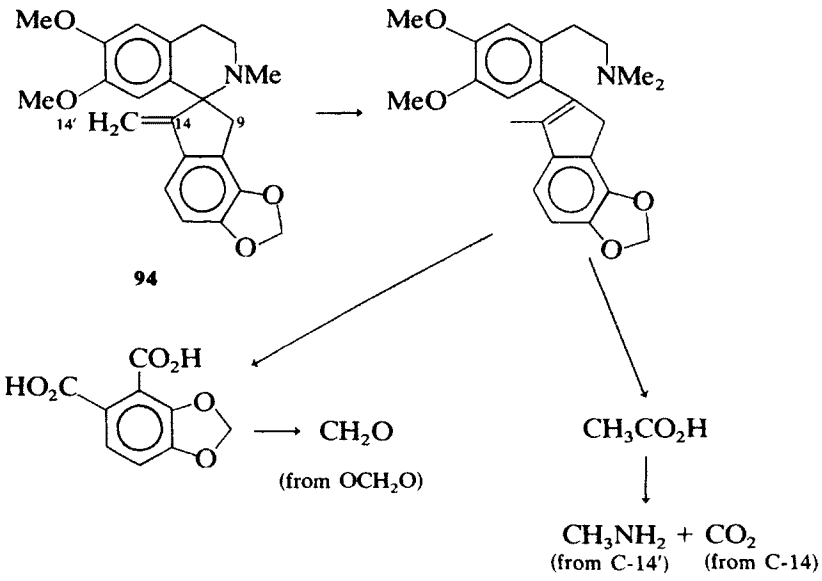
The oxidation at C-8 of scoulerine must take place at a late stage in the biosynthesis, but this has not been investigated.

(ii) OCHOTENSIMINE. So far only a preliminary study of the biosynthesis of ochotensimine (**94**) has been reported,[53] but the results are consistent with intermediacy of a 13-methyltetrahydroprotoberberine precursor. [*Methyl*-^{14}C]methionine (**14**) and [3-^{14}C]tyrosine (**4**) were fed to *Corydalis ochotensis*, and in both cases radioactive ochotensimine (**94**) was isolated. Degradation by the route illustrated in Scheme 12 revealed[53] that half of the tyrosine activity was located at C-14 and that both C-14′ and C-9 are derived, like the methylenedioxy bridge, from methionine.

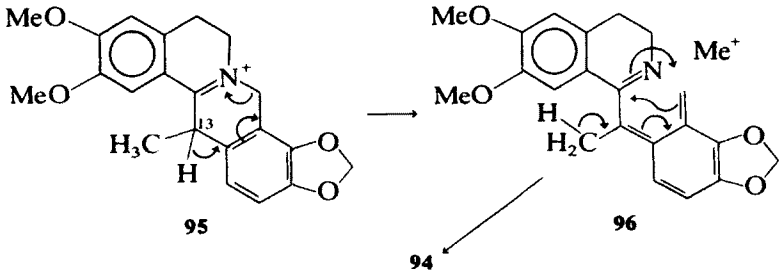
A possible pathway to ochotensimine (**94**) from the 13-methyl canadine derivative (**95**) is depicted in Scheme 13. Here oxidation of the tetrahydroprotoberberine provides the driving force for fragmentation of the N–C_8 bond, leading to the intermediate (**96**). *N*-methylation might then initiate cyclization to ochotensimine (**94**) as shown. Clearly, variations on this theme are possible, and one of these has been elegantly achieved[57] *in vitro*.

(c) *By Cleavage of N–C_6 Bond; Chelidonine and Sanguinarine*

[2-^{14}C]Tyrosine (**4**) was incorporated[58] by *Chelidonium majus* into chelidonine (**76**) and sanguinarine (**97**). Degradation[58] (Scheme 14) of the



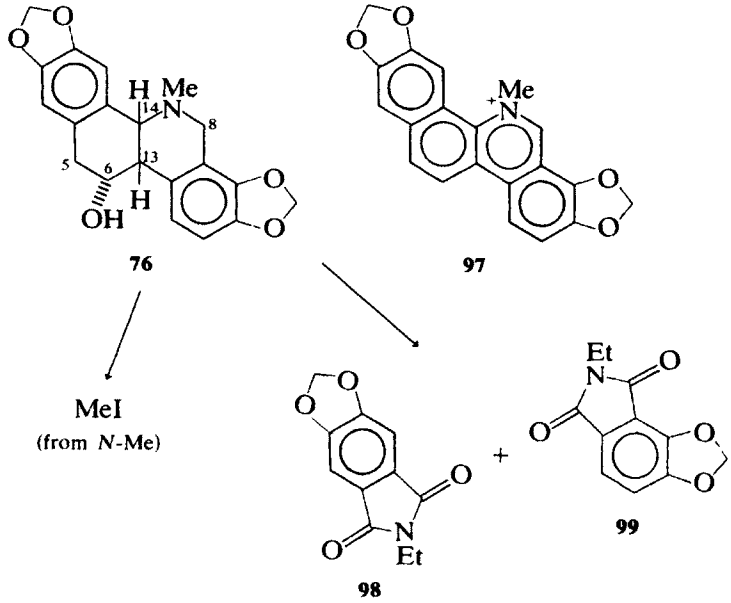
Scheme 12. Degradation of ochotensimine.



Scheme 13. A possible pathway for the biosynthesis of ochotensimine.

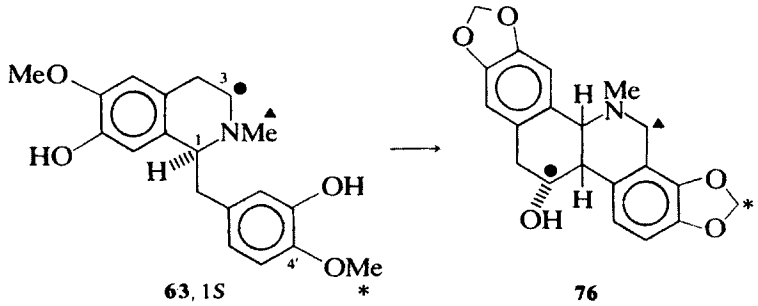
radioactive chelidonine (**76**) gave methyl iodide and two isomeric phthalic acids that were converted into the *N*-ethyl imides (**98**) and (**99**) for purification and counting. Together, these products accounted for only 39% of the radioactivity; thus 61% must be located at C-6 in chelidonine. The 39% is all present in the imide **98**, showing that either C-5 or C-14 of chelidonine was labeled. No further distinction was made since it was sufficiently clear that chelidonine (**76**) is biosynthesized from two C_6–C_2 units. [1-^{14}C]Dopamine (**1**) was incorporated[59] into only one of these units, with the resultant chelidonine (**76**) labeled solely at C-6.

Experiments with multiply labeled reticuline (**63**) now showed[47] that the (+)-(*S*)-enantiomer of this 1-benzylisoquinoline is incorporated intact, whereas the (−)-enantiomer was used to a negligible extent. Thus (+)-(S)-[1-^{3}H,3-^{14}*C*,*N-methyl*-^{14}C,4′-*O-methyl*-^{14}C]-reticuline (**63**) gave chelidonine



76 97 98 99

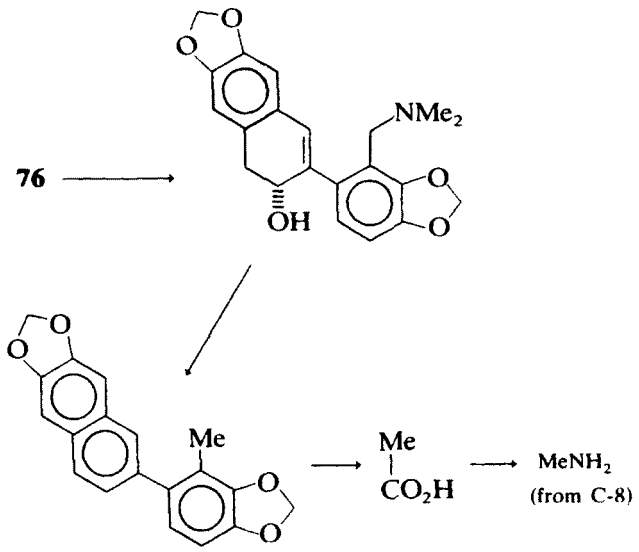
Scheme 14. Degradation of chelidonine.



63, 1S * 76

(**76**) with complete loss of ^{3}H. The distribution of ^{14}C was then determined by extending the degradations already mentioned (Scheme 14). Acid treatment of the imide (**98**) effected cleavage of the methylenedioxy bridge, and the liberated formaldehyde was counted as the dimedone derivative, demonstrating[47] once again the biosynthesis of the methylenedioxy group directly from an *o*-methoxyphenol. Furthermore, C-8 of chelidonine arises directly from the *N*-methyl group of reticuline, and this important result was rigorously proved[47] by a second degradation of chelidonine (Scheme 15). The methylamine eventually obtained carried precisely the amount of radioactivity expected.

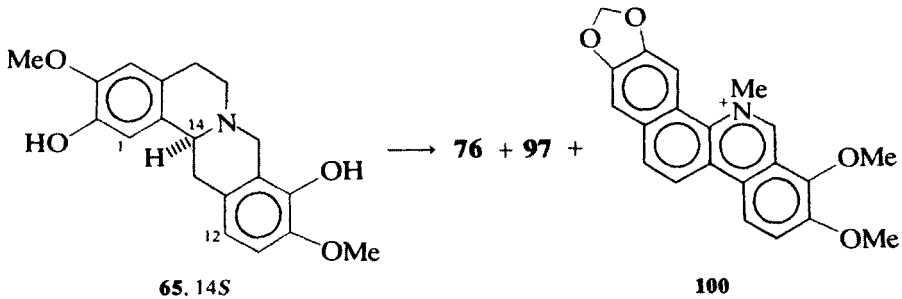
The foregoing experiments prove that (+)-reticuline is a key precursor of chelidonine. This proof that C-8 of chelidonine originated from the



Scheme 15. Degradation of chelidonine.

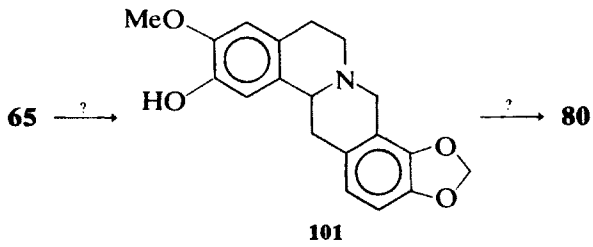
N-methyl group of reticuline—as does the "berberine bridge" of berberine (**73**), protopine (**74**), and narcotine (**75**)—now strongly implicated a tetrahydroprotoberberine intermediate. Accordingly, labeled samples of scoulerine (**65**) and stylopine (**80**) were prepared and fed to *C. majus*.

(−)-(*S*)-[1,12-^{3}H]Scoulerine (**65**)[47] was incorporated into chelidonine (**76**), sanguinarine (**97**), and chelerythrine (**100**). Degradation of the derived

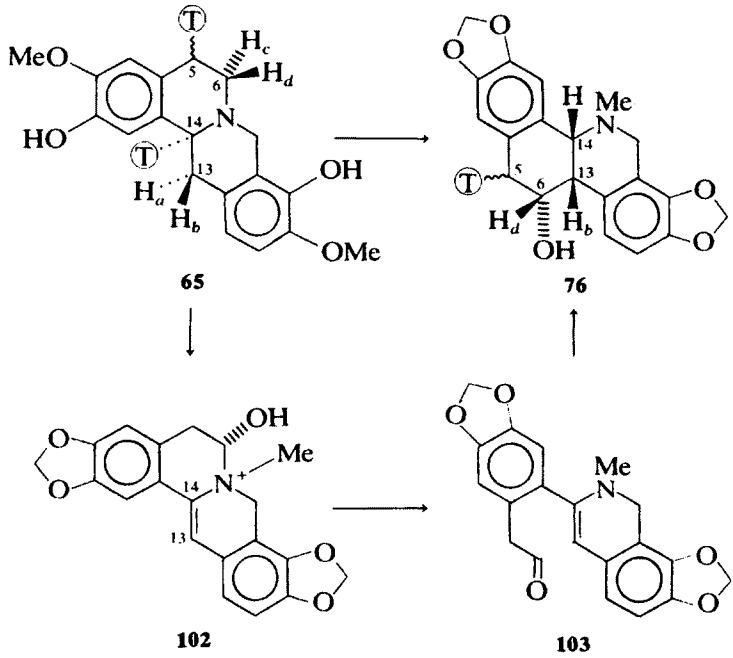


65, 14*S* **100**

chelidonine gave imides (**98**) and (**99**) with equal specific radioactivities as expected. (−)-(S)-[8-^{3}H]Stylopine[47] and [6-^{14}C]stylopine (**80**)[60] were also independently fed to *C. majus*, and in each case the resultant chelidonine was degraded to give radioinactive imides (**98**) and (**99**) as expected for the intact incorporation of these radioactive precursors. Nandinine (**81**) was not incorporated[47] into chelidonine, and it is assumed[47] that the isomer **101** is an intermediate for the conversion of scoulerine into stylopine. The biosynthesis of corynoline (13-methylchelidonine) in *Corydalis incisa* clearly follows a similar pathway.[61]



(i) MECHANISM OF STYLOPINE–CHELIDONINE BIOCONVERSION. The transformation of stylopine into chelidonine requires (not necessarily in the order given) the following changes: (1) *N*-methylation, (2) cleavage of the N–C_3 bond, and (3) formation of a new bond between C-3 and C-13. A likely intermediate for the final cyclization step is the aldehyde–enamine **103**, and this could be derived from stylopine by hydroxylation at C-6, *N*-methylation, and dehydrogenation as shown in Scheme 16. It is unlikely that



Scheme 16. Suggested pathway for biosynthesis of chelidonine from stylopine.

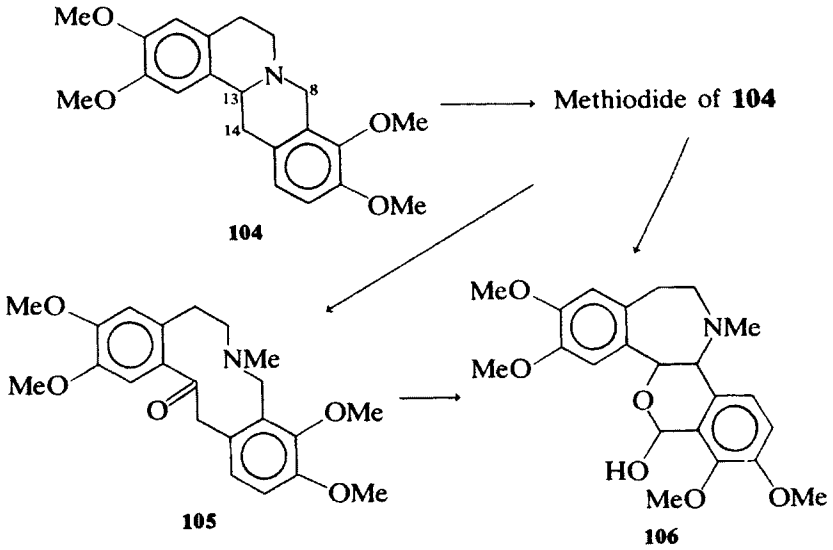
N-methyl stylopine (**89**) is involved since it was incorporated into chelidonine less well than was scoulerine.

None of the hypothetical intermediates in Scheme 16 has been identified, but evidence concerning the nature of the oxidation reactions at C-6, C-14, and C-13 (stylopine–chelidonine numbering) is available from tracer experiments using tritium-labeled precursors. For example, the chelidonine

derived from the multiply labeled [1-^{3}H]-reticuline (**63**) mentioned earlier was devoid of ^{3}H, as was the alkaloid biosynthesized from (−)-(*S*)-[6-^{14}C,14-^{3}H]-stylopine (**80**). Therefore, although chelidonine (**76**) has a hydrogen at C-14, it is not the same atom as was originally at C-14 in stylopine (**80**), and this is exactly the result expected if there is a $\Delta^{13,14}$ intermediate such as **102** or **103**. Furthermore, the mechanism outlined in Scheme 16 requires no change at C-5, as was confirmed by the high tritium retention (123%)[62] observed when [5-^{3}H,6-^{14}C]-scoulerine (**65**) was incorporated into chelidonine.

(ii) Stereospecificity of Oxidations at C-6 and C-13. (6*R*)- and (6*S*)-[6-^{3}H]Scoulerine were prepared and fed to *C. majus* in admixture with [6-^{14}C]scoulerine. The (6*R*)-enantiomer was incorporated into chelidonine without alteration of the ^{3}H:^{14}C ratio, whereas the (6*S*)-enantiomer yielded [^{14}C]chelidonine devoid of tritium. These results[63] clearly show that the (6-*pro*-*S*)-hydrogen (H_c) is removed stereospecifically during the enzymatic conversion of scoulerine into chelidonine.

A similar comparison was made of the incorporations of (13*R*)- and (13*S*)-[13-$^3H_1$]scoulerine into chelidonine.[56] The tritium label from the (13*R*)-enantiomer was retained, whereas that from the (13*S*)-enantiomer was lost.[56] Thus the reaction at C-13 involves the stereospecific removal of the *pro*-*S*-hydrogen atom H_a. The stereochemical result is the same as that found for narcotine biosynthesis[56] and might in both cases be a reflection of enzymic hydroxylation with retention of configuration. On the other hand, the result here is also consistent with the formation of a $\Delta^{13,14}$ bond by cis dehydrogenation.



(d) *By Cleavage of C_{13}–C_{14} Bond; Alpigenine*

Alkaloids of the rhoeadine type were recently shown to be derived from tetrahydroprotoberberines by the excellent incorporation[64] of [8-^{14}C]tetrahydropalmatine(**104**) into alpigenine (**106**) in *Papaver bracteatum*. [*N-Methyl*-^{14}C,8-^{14}C]tetrahydropalmatine methiodide was also incorporated, and degradation revealed that the hemiacetal carbon and the *N*-methyl group of alpigenine (**106**) were radioactive, as the ratio was close to that expected for intact incorporation.

An extension of this study has recently revealed[65] that [8-^{14}C]muramine (**105**) is an excellent precursor of alpigenine. Clearly, then, the C_{13}–N bond cleaves before the C_{13}–C_{14} bond does.

VII. ROLE OF PHENOL OXIDATION IN ISOQUINOLINE ALKALOID BIOSYNTHESIS

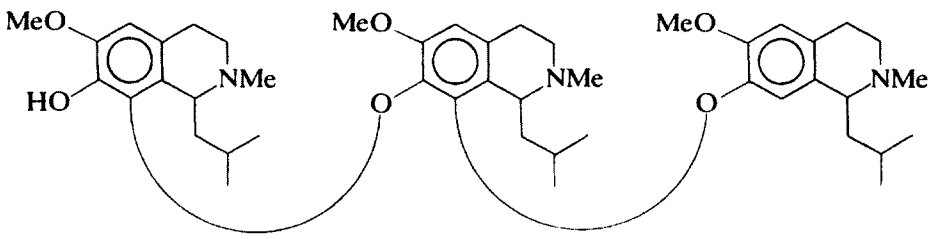
The principles of oxidative phenol coupling, first outlined in detail by Barton and Cohen,[66] have been immensely valuable for both rationalizing and predicting biosynthetic pathways and in influencing the design of the synthesis of complex natural products.

Barton and Cohen pointed out that one-electron oxidation of a phenolate ion generates a phenoxyl radical, which carries appreciable spin density at the ortho and para carbon atoms as well as at the oxygen atom. Two such species can, therefore, react together by a radical-pairing mechanism to generate new O–O, O–C, or C–C bonds, but new bonds to carbon atoms should only be formed at the ortho and para positions. This mechanism for oxidative phenol coupling has not been *proven* for any biosynthetic process, but all the evidence that follows is entirely consistent with such a view. In particular, oxidative coupling between two aromatic rings takes place only when a free phenolic group is located at the appropriate position in both precursor rings.

A. Alkaloids Derived by Carbon–Oxygen Coupling

(a) *Pilocereine*

The cactus alkaloid pilocereine (**107**) appears to be an oxidative trimer of lopocerine (**9**), and [*N-methyl*-^{14}C]-lophocerine (**9**) was incorporated[67] into pilocereine in *L. schottii*. This experiment with a singly labeled species does not prove intact incorporation of lophocerine (**9**), although this seems likely on the basis of the lower incorporation of radioactivity from [*methyl*-^{14}C]methionine (**14**).



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(b) *Epistephanine*

Many bisbenzylisoquinoline alkaloids are known, but there is little experimental evidence concerning their biosynthesis.

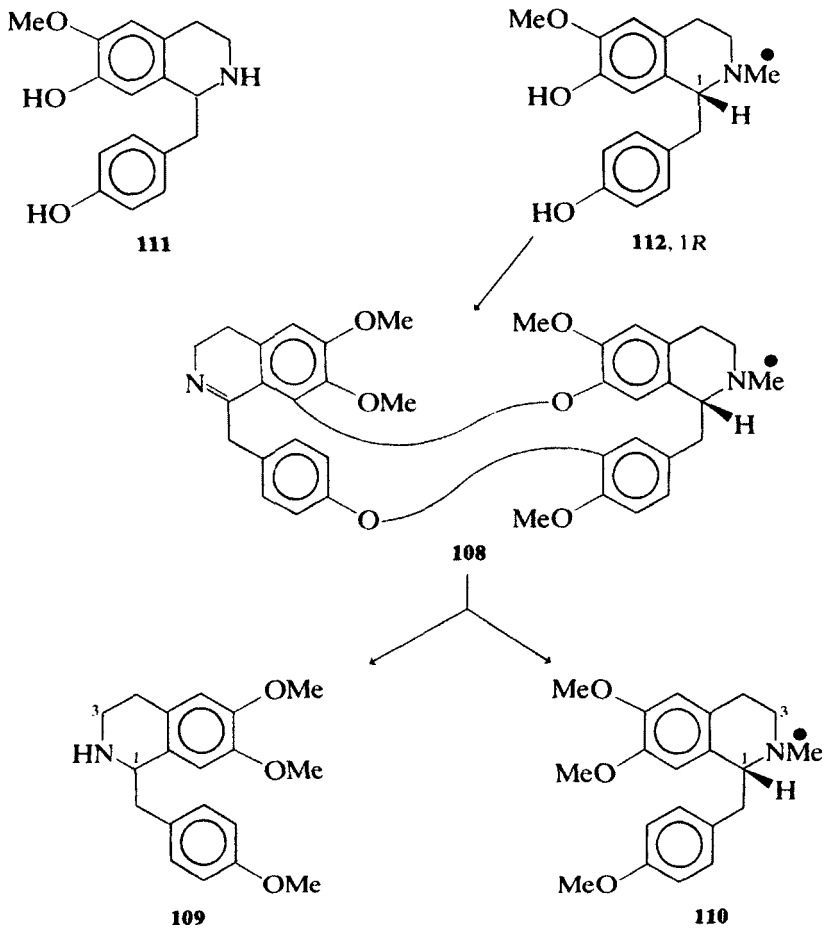
[2-^{14}C]Tyrosine (**4**) was incorporated[68] into epistephanine (**108**) in *Stephania japonica*, and the alkaloid was reductively cleaved to give (after methylation) the monomeric benzylisoquinolines **109** and **110** of equal specific radioactivity. These were not degraded further, but a large number of precedents suggest that both compounds have equal ^{14}C-labeling at C-1 and C-3.

[*Aryl*-^{3}H]Coclaurine (**111**) and [*N-methyl*-^{14}C]methyl coclaurine (**112**) were also incorporated into epistephanine (**108**), but degradation as described in the preceding paragraph showed in both cases that only the tetrahydroisoquinoline unit was labeled. Furthermore (−)-(*R*)-*N*-methylcoclaurine (**112**) having the same configuration as epistephanine was incorporated 20 times more effectively than its enantiomer. The exact origin of the dihydroisoquinoline unit remains unknown at present.

B. Alkaloids Formed by Intramolecular Carbon–Carbon Coupling

(a) *General Considerations*

For a 1-benzylisoquinoline to be capable of intramolecular oxidative phenol coupling, at least one free phenolic hydroxyl group must be present in each aromatic ring. Since all the isoquinolines of proven biosynthetic significance carry oxygen at C-6 and C-7, the simplest possible cases for consideration are the compounds coclaurine (**111**) and isococlaurine (**117**). Suitable oxidation of coclaurine (**111**) would generate the diradical (**113**). Intramolecular coupling might then lead to either **114** or **115**; all other modes of coupling (e.g., ortho–ortho) lead to highly strained intermediates that violate Bredt's rule. Kinetic and thermodynamic arguments both suggest that **114** should be formed in preference to **115**; in fact, no evidence for the intermediacy of double dienone **115** has been obtained either *in vivo* or

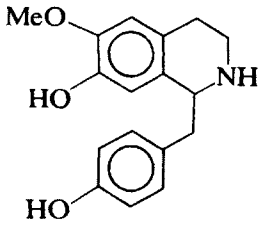


in vitro. The preferred intermediate, however, should aromatize easily to give **116** with the *proaporphine* skeleton.

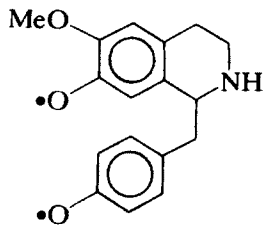
The diradical **118** from isococlaurine (**117**) has only one possible mode of intramolecular coupling available, and even that leads to the high-energy double dienone **119** with a four-membered ring. No evidence exists for this pathway, and isococlaurine should not serve as a direct precursor for any alkaloid derived by intramolecular oxidative phenol coupling.

The introduction of an extra hydroxyl group into ring *A* (of coclaurine or isococlaurine) does not permit any new opportunities for intramolecular carbon–carbon coupling. The presence of a new *o*-hydroxyl group in ring *C*, however, extends the range considerably, as shown by a consideration of the diphenolic alkaloids norprotosinomenine (**60**) and norreticuline (**67**).

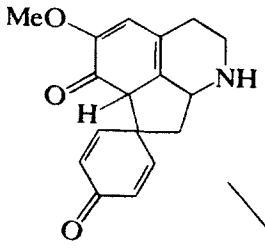
Oxidation of norprotosinomenine (**60**) can lead, after enolization of the intermediates, to the dienones **120** and **121**. Such compounds, now called



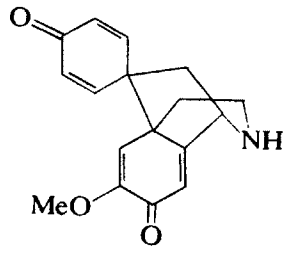
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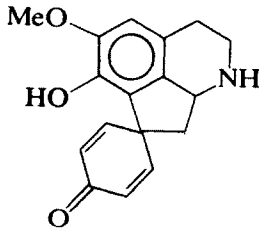
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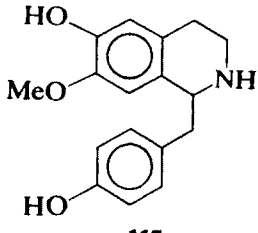
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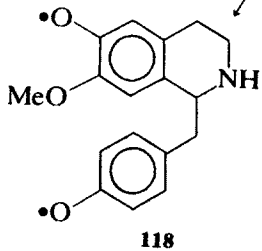
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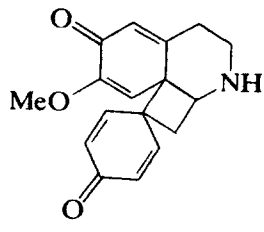
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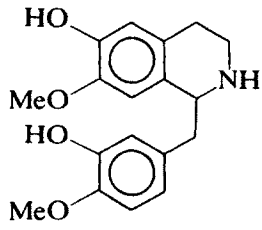
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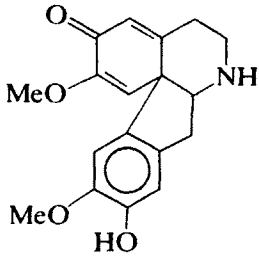
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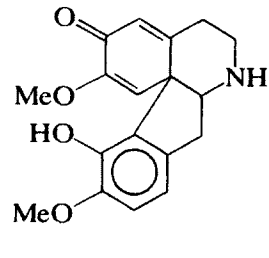
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60



120



121

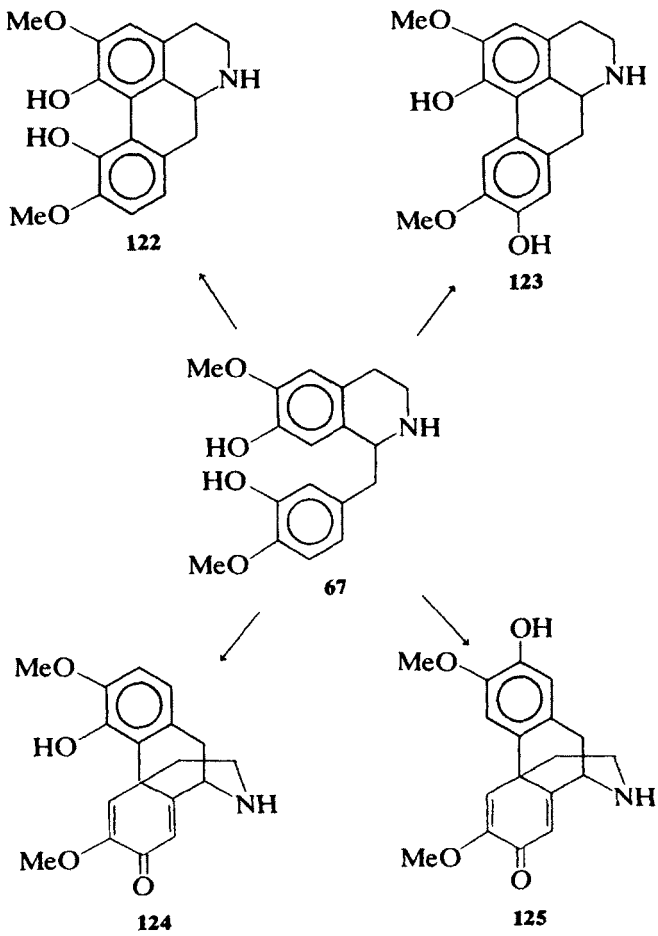
proerythrinadienones, are key biosynthetic precursors of the *Erythrina* alkaloids and of certain aporphines [see Section VII.B(c)(i)].

Norreticuline (**67**) has the most versatile phenolic substitution pattern for intramolecular oxidative coupling. Following the stages described earlier, oxidation of norreticuline (**67**) can give either the aporphine derivatives **122** and **123** or the morphinandienones **124** and **125**.

Further oxygenation of ring *C* does not increase the possibilities for intramolecular coupling, and so the oxidation products referred to previously encompass the full range of skeletal possibilities from the primary oxidation reaction. However, each dienone system is susceptible to rearrangement reactions that lead eventually to a new range of carbon skeletons. Thus oxidative phenol coupling is the key first step in generating a wide range of complex alkaloids from the comparatively simple 1-benzylisoquinoline system. In the detailed discussion that follows, the alkaloids have been classified according to the primary oxidative coupling product.

(b) *Proaporphines*

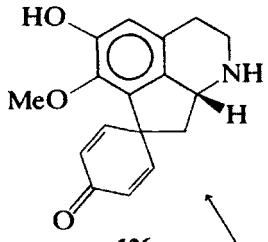
Although crotonosine (**126**) has the same oxygenation pattern as isococlaurine (**117**), the latter compound failed to serve[69] as a precursor of the dienone in *Croton linearis*. This result was fully anticipated [see Section VII.B(a)] since the theory of oxidative phenol coupling requires the new carbon–carbon bond to be formed only ortho or para to a phenolic hydroxyl group. The actual precursor of crotonosine should, therefore, be coclaurine



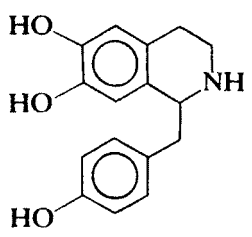
(**111**) or norcoclaurine (**127**), and it has been found[69] that both of these compounds were incorporated well. (+)-(1-*R*)-coclaurine (**111**) has the same absolute configuration as does crotonosine (**126**), and it was incorporated far better than was the (−)-enantiomer, thus indicating that no change in configuration occurs in the plant, and the enzyme shows as expected a high substrate specificity for a single enantiomer of the isoquinoline.

[6-*O*-*Methyl*-^{14}C,*aryl*-^{3}H]Coclaurine (**111**) was also incorporated into crotonosine, but only about 30% of the radioactivity of the *O*-methyl group was retained[69] relative to the skeletal reference. Clearly, the *O*-methyl group is not transferred intramolecularly from position 6 to position 7, but rather demethylation is followed by remethylation. It is not clear whether demethylation occurs before or after oxidative phenol coupling.

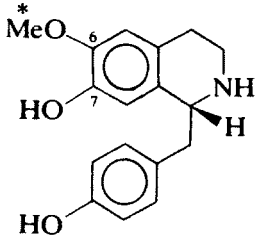
N-methylcoclaurine (**112**) served[70] as a precursor of mecambrine (**128**) in both *Papaver dubium* and *Meconopsis cambrica*. Feeding experiments with multiply labeled *N*-methylcoclaurine revealed[70] that the *N*-methyl group is



126

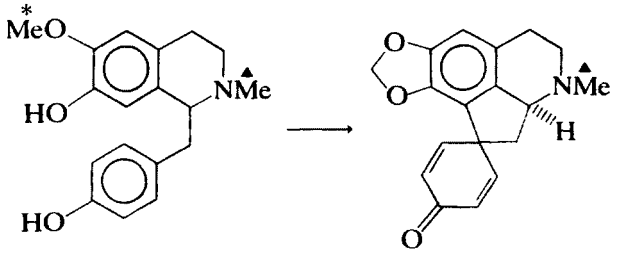


127



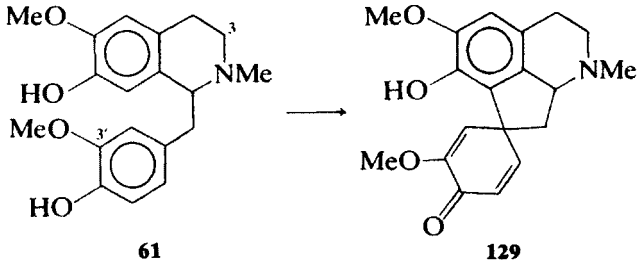
111, 1*R*

retained, but as in the biosynthesis of crotonosine (**126**), the *O*-methyl group is lost. Once again, it is not known whether demethylation occurs at the 1-benzylisoquinoline or at the proaporphine stage.



112 128

The proaporphine alkaloid (−)-orientalinone (**129**) was identified[71] as a minor alkaloid of *Papaver orientale* only after a careful search was conducted. This search was undertaken because an earlier study of the biosynthesis of isothebaine had pointed strongly to the intermediacy of the previously unknown dienone **129** [see Section VII.B(b)(i)].

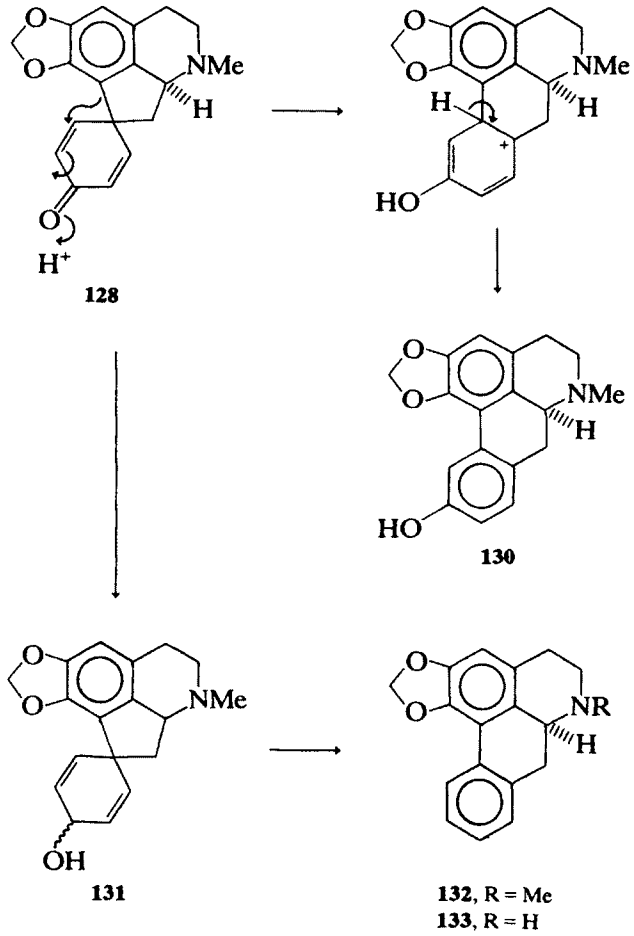


61 129

The biosynthesis of orientalinone (**129**) involves oxidative coupling of the corresponding diphenolic isoquinoline, as shown[71] by the intact incorporation of [3′-*O*-*methyl*-^{14}C,3-^{14}C]orientaline (**61**).

(i) Alkaloids Biosynthesized by Way of Proaporphines

(1) *Mecambroline, Roemerine, and Anonaine.* Cyclohexadienone systems undergo various rearrangement reactions *in vitro*,[72] and some of these are also of importance *in vivo*. Thus mecambrine (**128**) was efficiently incorporated[70] by *Meconopsis cambrica* into the aporphine alkaloid mecambroline (**130**). This transformation involves a dienone–phenol rearrangement in which the aryl group migrates rather than the alkyl group (Scheme 17).

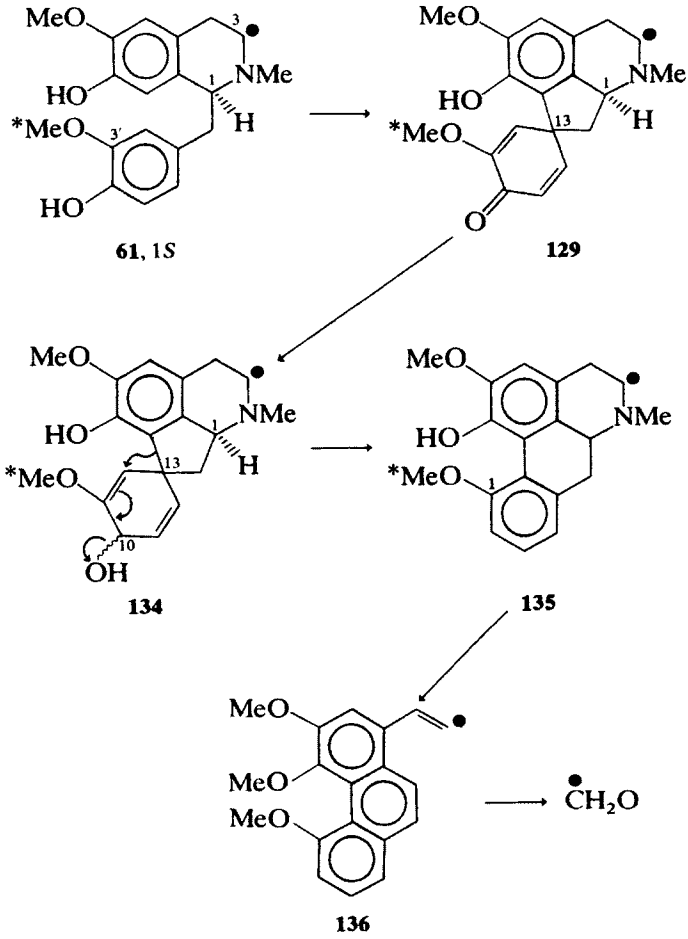


Scheme 17. Biosynthesis of roemerine from mecambrine.

Mecambrine (**128**) was also incorporated well[70] into roemerine (**132**) in *Papaver dubium*. In this case an overall reduction has taken place, and the

transformation is easily rationalized through a rearrangement of the dienol **131**. An analogous pathway to the *N*-nor alkaloid anonaine (**133**) in *Anona reticulata* is fully supported by the incorporations[70] of [*aryl*-^{3}H]coclaurine (**111**) and norcoclaurine (**127**).

(2) *Isothebaine.* A dienol–benzene rearrangement of orientalinol (**134**) is fully documented as a key step in the biosynthesis of isothebaine (**135**) (Scheme 18). [3-^{14}C]Orientaline (**61**) was incorporated[75] by *P. orientale* into



Scheme 18. Biosynthesis and degradation of isothebaine.

isothebaine (**135**), and all the radioactivity was shown to be at C-3 by degradation via the phenanthrene **136**. Furthermore, [3′-*O*-*methyl*-^{14}C,3-^{14}C]orientaline (**61**) gave isothebaine with the same labeling ratio, thus showing[75] that the 1-*O*-methyl group of isothebaine is derived directly from that in orientaline. These results supported a biosynthetic pathway via the

dienone **129** whose configuration at C-1 was suggested by the fact[75] that (+)-(*S*)-orientaline was a much better precursor of isothebaine than was (−)-(*R*)-orientaline. Subsequently, [*N-methyl*-^{3}H]orientalinone (**129**) was prepared and efficiently incorporated[71] into isothebaine, and (−)-orientalinone (**129**) was identified[71] as a minor alkaloid of *P. orientale.*

At this point it should be emphasized that unlike the trioxygenated proaporphines mentioned earlier, the tetraoxygenated proaporphines (e.g., **129**) have two chiral centers, one at C-1 and the other at C-13. The synthetic orientalinone (**129**) used in the feeding experiments was a single diastereoisomer, but the relative configuration at C-1 and C-13 is unknown. Reduction of this diastereoisomer gave a mixture of dienols **134** differing in configuration at C-10, and one of these compounds was incorporated[76] into isothebaine six times better than was its isomer. At present the configurations at C-10 of the dienols are also unknown.

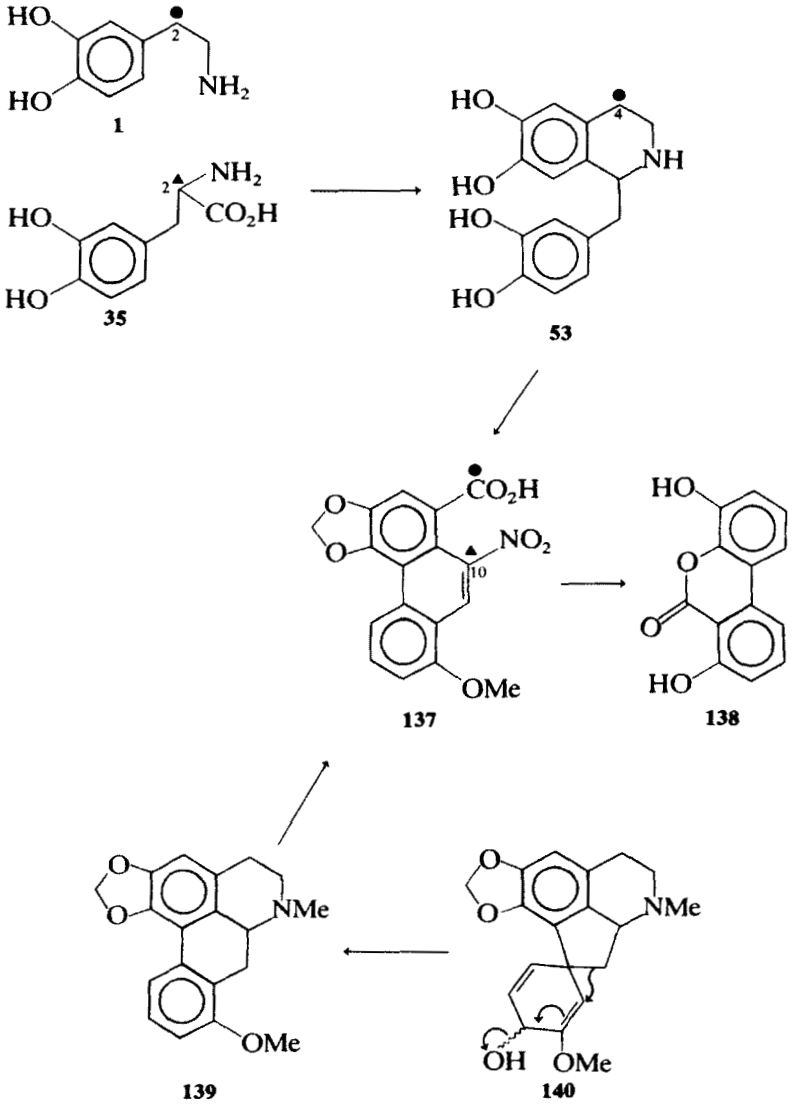
(3) *Aristolochic Acid.* Preliminary tracer experiments on the biosynthesis of aristolochic acid (**137**) have shown that this unusual nitrophenanthrene is built up from dopamine (**1**) and dopa (**35**) through norlaudanosoline (**53**) as shown in Scheme 19. Thus [2-^{14}C]dopamine (**1**)[73] and [4-^{14}C]norlaudanosoline (**53**)[74] both gave [*carboxyl*-^{14}C]aristolochic acid (**137**) when administered to *Aristolochia sipho*, whereas the radioactivity from [2-^{14}C]dopa (**35**)[73] was shown by degradation to **138** to be located specifically at C-10. It was further shown[73] that [3-^{14}C,^{15}N]tyrosine (**4**) was incorporated with 70% retention of ^{15}N.

These results strongly suggest that aristolochic acid is a degradation product of an aporphine such as stephanine (**139**), and the unusual oxygenation pattern calls for the intermediacy of a proaporphine (e.g., **140**). No experimental support for this pathway has yet been published.

(c) *Alkaloids Related to Proerythrinadienones*

No alkaloids have yet been reported with the proerythrinadienone skeleton, but there is sound circumstantial evidence that such dienones are important intermediates in alkaloid biosynthesis. The failure to isolate the proerythrinadienones probably stems from the ease with which molecular rearrangement can take place.

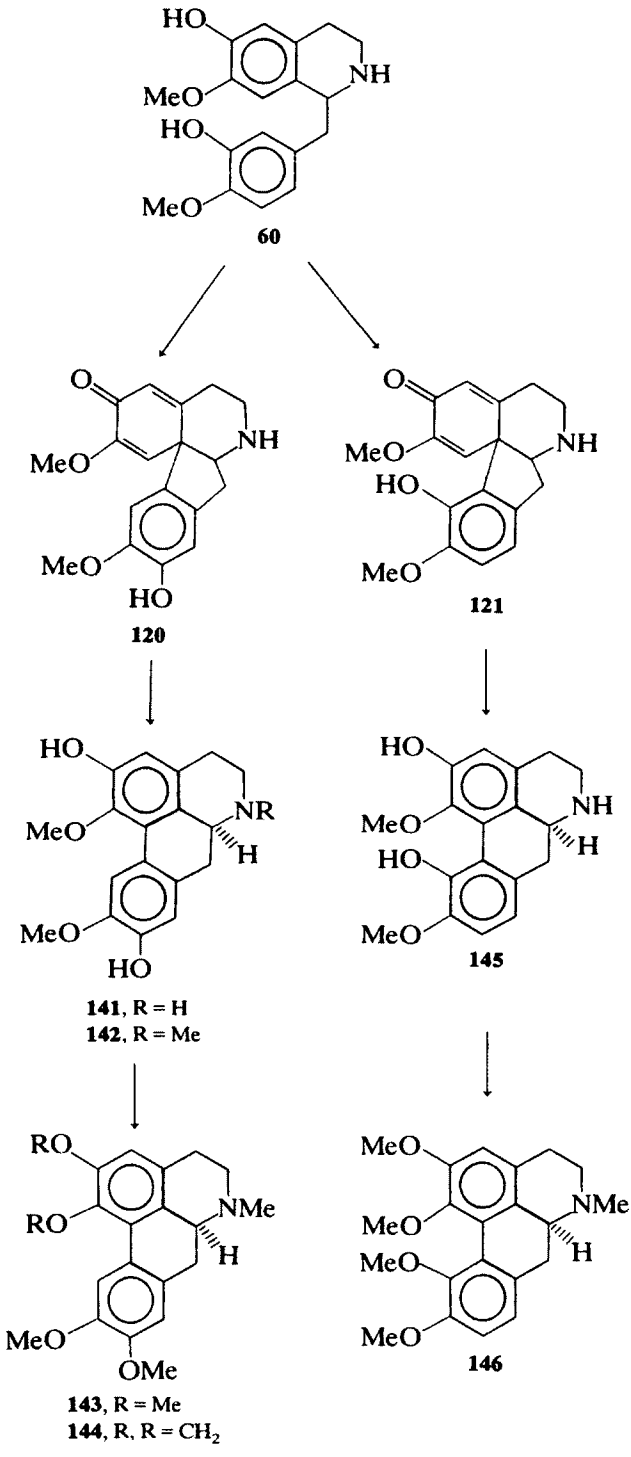
(i) Aporphines. The dienone **120** might undergo dienone-phenol rearrangement (with aryl migration as found for the biosynthesis of mecambroline and isothebaine) to give the aporphine **141**. Experimental evidence for this pathway in *Dicentra eximia* comes from the good incorporations[38] of both [1-^{14}C]norprotosinomenine (**60**) and of [*aryl*-^{3}H]boldine (**142**), the *N*-methyl derivative of **141**, into glaucine (**143**) and dicentrine (**144**). Similarly, the good incorporations[38] of both [1-^{14}C]norprotosinomenine



Scheme 19. Biosynthesis and degradation of aristolochic acid.

(**60**) into corydine (**146**) is best explained by dienone–phenol rearrangement of dienone **121** to the aporphine **145**.

The discovery of this intriguing pathway (Scheme 20) to the aporphine alkaloids of *D. eximia* came as a considerable surprise. At the outset a direct biosynthetic pathway from reticuline (**63**) seemed likely, especially as reticuline is present in *D. eximia* and is the precursor in that plant[38] and in *D. spectabilis*[45] of protopine (**74**). A second possibility—namely, that the *Dicentra* aporphines might arise from rearrangement of the proaporphine



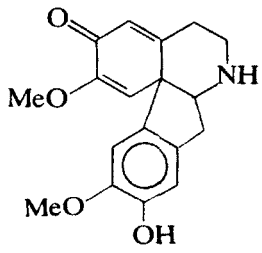
Scheme 20. Biosynthesis of aporphine alkaloids in *D. eximia*.

orientalinone (**129**)—was also considered. However, when these ideas were tested experimentally, no incorporation of reticuline (**63**), or orientaline (**61**) or their *N*-nor derivatives **67** and **147** was observed despite good incorporations of [2-^{14}C]tyrosine (**4**), [2-^{14}C]dopa (**35**), and [*aryl*-^{3}H]norlaudanosoline (**53**). Therefore, the four isomeric monomethyl ethers of norlaudanosoline (**53**) were studied, and only [*aryl*-^{3}H]4′-*O*-methylnorlaudanosoline (**59**) was incorporated. This result finally pointed the way toward the key intermediate norprotosinomenine (**60**). The combined results of these thorough researches clearly define the two pathways (Scheme 20):

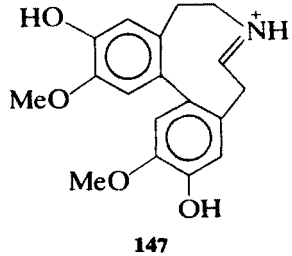
53 ⟶ **59** ⟶ **60** → **120** ⟶ **141** ⟶ **143** and **144**

60 → **121** ⟶ **145** ⟶ **146**

(ii) Erythrina Alkaloids. In the previous section it was suggested that the dienone **120** rearranges in *D. eximia* by way of a dienone–phenol rearrangement to generate the aporphine skeleton. An alternative pathway for aromatization is available in the fragmentation reaction of **120** to **147**, and this appears to be the dominant fate of dienone **120** in *Erythrina* species.



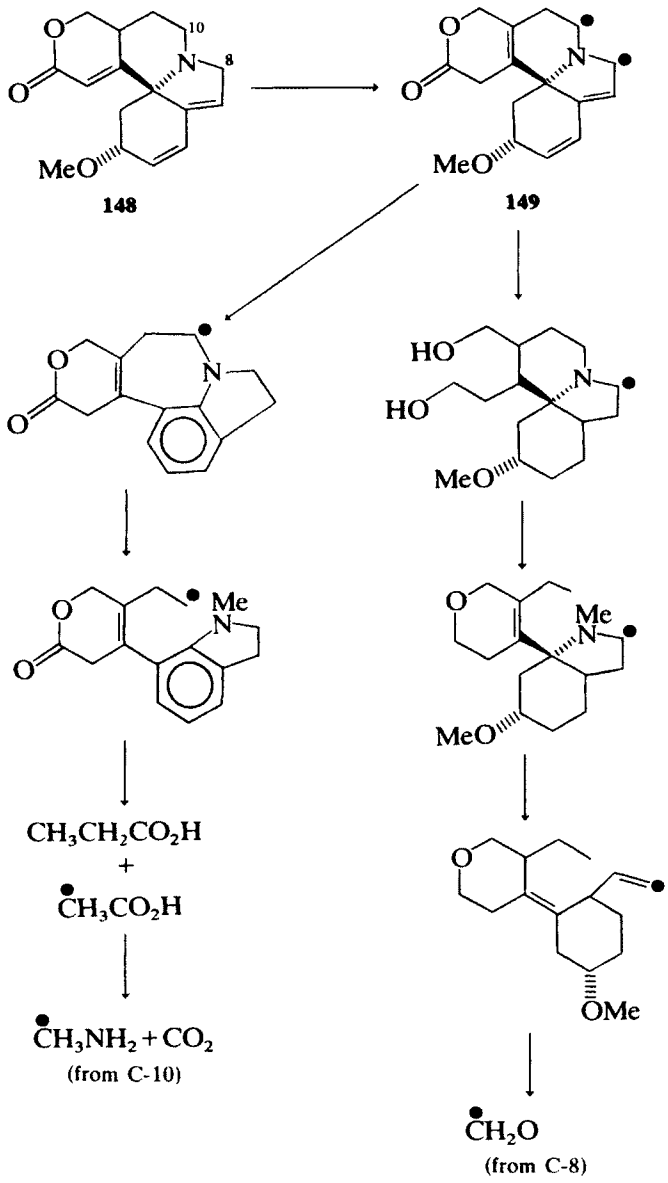
120



147

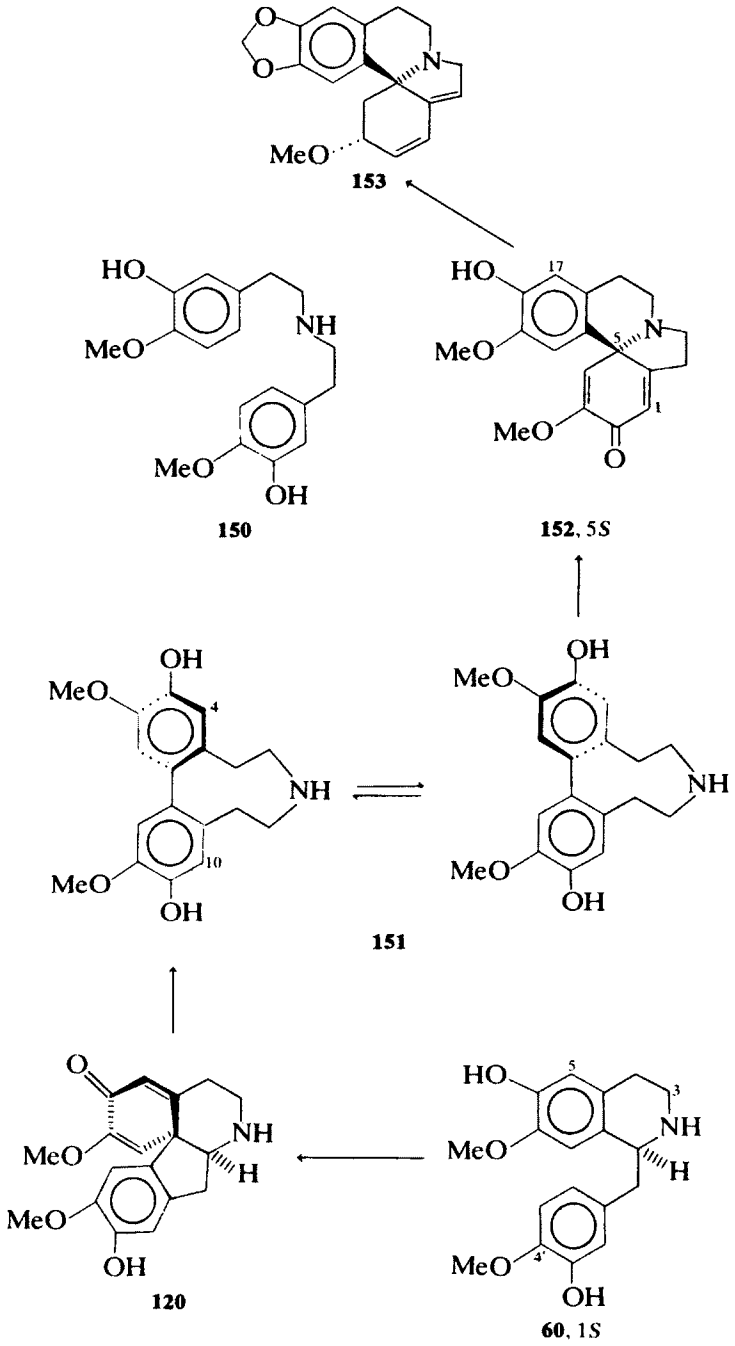
In an early study of *Erythrina* alkaloid biosynthesis, [2-^{14}C]tyrosine (**4**) was fed to *E. berteroana* and radioactive α- and β-erythroidine (**148**) and (**149**) were isolated.[77] α-Erythroidine (**148**) was isomerized to β-erythroidine (**149**), and both radioactive samples were degraded[77] as shown (Scheme 21), proving that the total radioactivity was distributed approximately equally between C-8 and C-10. The result was taken to indicate that the erythroidines are biosynthesized by using two C_6–C_2 units provided by tyrosine. This is almost certainly correct, but subsequent biosynthetic studies have revealed that there is a symmetrical intermediate that will inevitably result in equal labeling at C-8 and C-10 even if [2-^{14}C]tyrosine (**4**) provided only one C_6–C_2 unit.

[2-^{14}C]Tyrosine (**4**) was also incorporated[68] into erythraline (**153**) by *E. crista-galli* and *E. rubrinervia*, but as the incorporation by the former plant was higher, it was used for subsequent studies in which the hypothetical



Scheme 21. Degradation of α- and β-erythroidine.

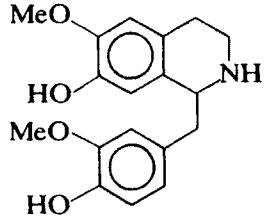
precursors [*aryl*-^{3}H]bis-phenethylamine (**150**) and [1,17-$^3H_2$]dienone **152** were fed. The dienone **152** was incorporated well into erythraline (**153**); therefore, it was surprising that the assumed precursor **150** gave only negative results. The mystery was cleared up when [*aryl*-^{3}H] norprotosinomenine (**60**) was shown[78] to be a good precursor of erythraline (**153**).


O
O
N
MeO
153
HO
MeO
NH
MeO
OH
150
HO
17
MeO
5
N
1
MeO
O
152, 5S
OH
MeO
4
NH
MeO
10
OH
151
OH
MeO
NH
MeO
OH
O
MeO
NH
H
MeO
OH
120
HO
5
3
NH
MeO
H
MeO
4'
OH
60, 1S

The pathway to the *Erythrina* alkaloids that is consistent with these results involves oxidative phenol coupling of norprotosinomenine (**60**) to the dienone **120** that fragments to the amine **147**. Reduction of **147** would give the dibenzazonine **151**, and this would lead on oxidation to the parent Erythrina dienone **152**. There is now excellent experimental support for this biosynthetic pathway. Thus [3-^{14}C,5-^{3}H] and [5-^{3}H,4′-*O*-*methyl*-^{14}C]norprotosinomenine (**60**) gave[79] erythraline (**153**) and erythratine (**154**) without alteration of the ^{3}H:^{14}C ratio, thus indicating the intact incorporation of the 1-benzylisoquinoline. Good incorporations into both alkaloids without tritium loss were also obtained[79] on feeding [4,10-$^{3}H_2$,*O*-*methyl*-^{14}C]dibenzazonine **151** and [1,17-$^{3}H_2$,*O*-*methyl*-^{14}C]erysodienone (**152**), and in each case degradation of the erythraline (**153**) and erythratine (**154**) revealed that half of the ^{14}C radioactivity was in the methylenedioxy bridge and the remainder, in the *O*-methyl group. Therefore, the methylenedioxy bridge is built up directly from an *o*-methoxyphenol as shown for several other classes of alkaloid.

Feeding experiments with resolved norprotosinomenine showed that the (+)-(1*S*)-enantiomer is incorporated[79] far more effectively than is the (−)-(1*R*)-enantiomer into both erythraline and erythratine. Now if the chirality of (+)-norprotosinomenine (**60**) were retained in the twisted biphenyl intermediate **151**, subsequent ring closure would give (5*R*)-erysodienone (**152**), which is the *opposite* configuration to that of erythraline and erythratine; thus a change of absolute configuration must occur at some point. An optically active sample of dibenzazonine (**151**) was prepared and $t_{1/2}$ for racemization at 20°C was found[80] to be only 1.2 min; hence it seems likely that this compound is formed as a free intermediate *in vivo* and that after racemization the appropriate enantiomer is selected and enzymically oxidized to give (5*S*)-erysodienone (**152**). Indeed, (−)-(5*S*)-erysodienone (**152**) is a far better precursor[80] than its enantiomer, both of erythraline in *E. crista-galli* and of α- and β-erythroidine (**148** and **149**) in *E. berteroana*.

Feeding experiments[81] with labeled (±)-norreticuline (**67**) and (+)-nororientaline (**161**) gave no support for an alternative pathway[81] to the

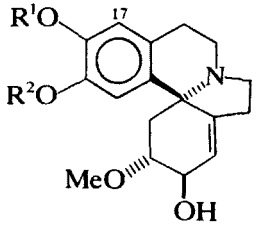


161

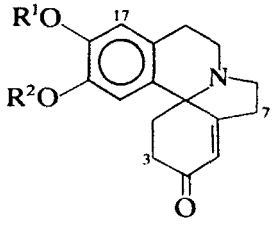
Erythrina alkaloids. The later stages of *Erythrina* alkaloid biosynthesis were investigated[79] by feeding [1,3,7-^{3}H]erythratinone (**156**) and [17-^{3}H] samples of erysotinone (**157**), erysotine (**155**), erysodine (**158**), and erysopine (**159**) to *E. crista-galli*. *All* these compounds were incorporated to a similar

degree into erythraline (**153**), thus indicating that alkylation and dealkylation of the phenolic oxygen does not follow a rigid order in this plant.

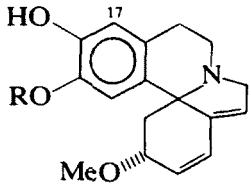
[17-^{3}H]Erysodine (**158**) was also incorporated[79] into α- and β-erythroidine (**148**, **149**) in *E. berteroana*. Degradation of these compounds to the radioinactive isomer **160** showed that the tritium was specifically located at C-17, thereby proving that the lactone ring of the erythroidines is formed by degradation of an aromatic precursor.



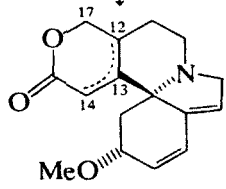
154, $R^1R^2 = CH_2$
155, $R^1 = H$; $R^2 = Me$



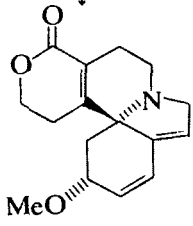
156, R^1, $R^2 = CH_2$
157, $R^1 = H$; $R^2 = Me$



158, R = Me
159, R = H



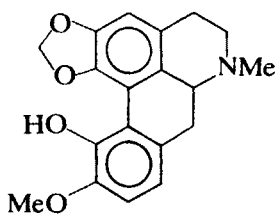
148, $\Delta^{13,14}$
149, $\Delta^{12,13}$



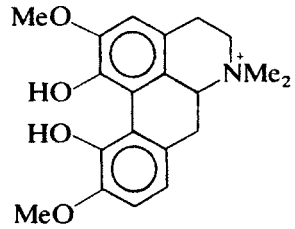
160

(d) *Aporphines by Direct Phenol Coupling*

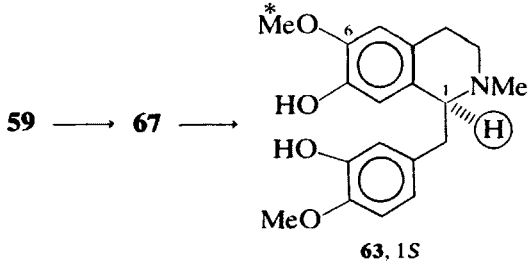
It was pointed out earlier that oxidative coupling of norreticuline (**67**) and its derivatives can generate the aporphine skeleton directly. Such a pathway is apparently utilized for the biosynthesis of bulbocapnine (**162**)[82] in *Corydalis cava*, of magnoflorine (**163**)[83] in *Aquilegia*, of isoboldine (**164**)[84] in *P. somniferum*, and of boldine (**165**)[85] in *Litsea glutinosa*. The evidence in



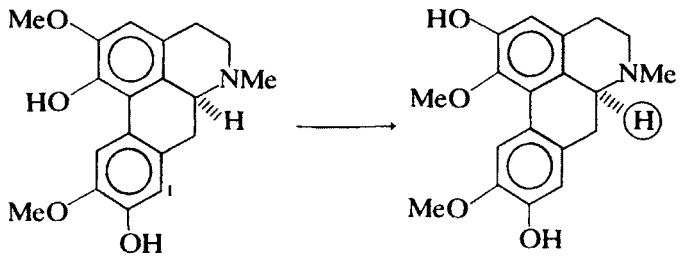
162



163



63, 1*S*



164 **165**

the first three cases is based on the specific incorporation of [*N-methyl*-^{14}C] reticuline (**63**) into the aporphine alkaloids bulbocapnine (**162**), magnoflorine (**163**), and isoboldine (**164**), but more detailed information is available concerning the biosynthesis of boldine (**165**). Thus [1-^{3}H]4′-*O*-methylnorlaudanosoline (**59**) and [*aryl*-^{3}H]norreticuline (**67**) were shown[85]

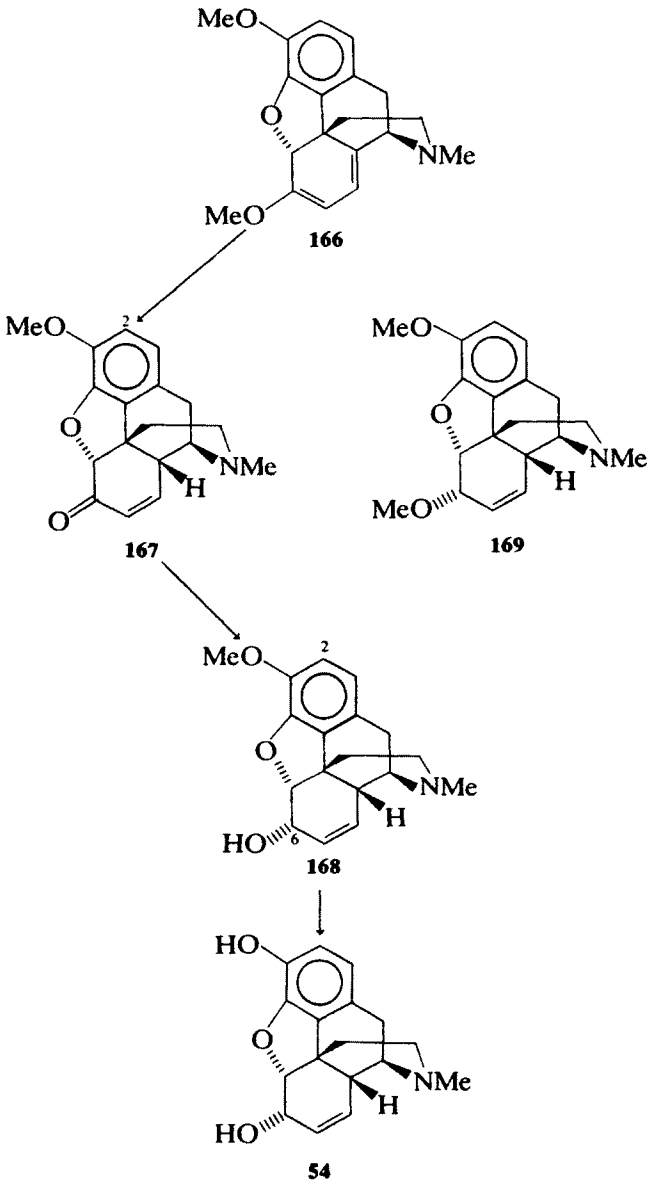
to give rise to radioactive boldine (**165**), and (+)-reticuline (**63**) was incorporated far better than was the (−)-enantiomer. Norprotosinomenine (**60**) has the same pattern of oxygen substituents as boldine (**165**), but neither it nor nororientaline (**161**) were effectively incorporated. The pathway clearly involves direct coupling, but some sort of transmethylation must take place en route to boldine, and this was investigated[85] by feeding [1-^{3}H,6-*O*-*methyl*-^{14}C]reticuline (**63**) to *L. glutinosa*. The labeling ratio in the resultant aporphine corresponded to a loss of 64% of the ^{14}C radioactivity, thus showing that the methyl group is not transferred in an intramolecular fashion. These results support a pathway in which direct oxidative coupling of reticuline leads to isoboldine (**164**), which then undergoes demethylation–remethylation to afford boldine (**165**). In agreement with this theory, (+)-[1-^{3}H]isoboldine (**164**) was efficiently incorporated into boldine.

(e) *Morphine Alkaloids*

Morphine (**54**) is a particularly fascinating compound for the organic chemist. The pure crystalline alkaloid was first isolated from opium in 1804, and the research that began then and continues today exemplifies the greatest achievements of organic chemistry. The biosynthetic studies on morphine that appeared during the 1960s achieved a degree of excellence, and the publications are of wide general interest since they frequently recall the more interesting aspects of the chemistry of morphine, reactions that were largely discovered prior to Robinson's brilliant proposal of the correct structure in 1925.

(i) Morphine, Codeine, and Thebaine. The three morphinan alkaloids morphine (**54**), codeine (**168**), and thebaine (**166**) were found[86] to be radioactive when isolated from poppy plants that had been exposed to an atmosphere of $^{14}CO_2$ for 2 days. Each alkaloid was demethylated,[86] and the specific activities of the resultant products were in the order thebaine > codeine > morphine. This is the order expected for the biosynthetic pathway thebaine → codeine → morphine, and this sequence was confirmed[86] by feeding a ^{14}C-labeled sample of each alkaloid to *Papaver somniferum* and, after a period of growth, by extracting the three alkaloids and monitoring the radioactivity in each one. From the [^{14}C]morphine feeding only the reisolated morphine was radioactive, from the [^{14}C]codeine feeding both morphine and codeine were radioactive, and from the [^{14}C]thebaine feeding all three alkaloids were found to be radioactive.

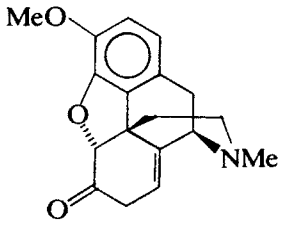
These early biosynthetic results defined the sequence for the late stages of the biosynthetic pathway with respect to the three major morphinan alkaloids. The conversion of codeine into morphine involves a simple demethylation reaction, but the thebaine → codeine transformation requires at least two steps, demethylation and reduction. Two intermediates have been



considered, codeinone (**167**) and codeine methyl ether (**169**), and their involvement was tested by a refined version of the experiments described earlier. Poppy plants were once again exposed to $^{14}CO_2$ for 4 hr and the nonphenolic alkaloid fraction was isolated. Since only vanishingly small quantities of the possible intermediates (**167**) and (**169**) were present, the specific activity of these intermediates could not be determined after conventional crystallization. Instead, the alkaloid fraction was separated by

gas-liquid chromatography (after silylation), and the radioactivity of each component was measured in a gas-flow counter. The codeine methyl ether fraction was found[87] to be radioinactive (even when inactive carrier was added), whereas the codeinone (**167**) fraction had a specific activity midway between the values for thebaine (**166**) and codeine (**168**). Hence codeinone (**167**) appears to be the key intermediate, and this was confirmed by conventional feeding experiments. Thus [U-^{14}C][87] and [2-^{3}H]codeinone (**157**)[88] were efficiently incorporated[87,88] into codeine (**168**) and morphine (**54**). Furthermore, [2,6-$^{3}H_2$]codeine (**168**) was converted by *P. somniferum* into morphine (**54**) without alteration of the labeling ratio, thus showing that the pathway is effectively irreversible.[88]

The role of another possible intermediate, neopinone (**170**), has not yet been reported.

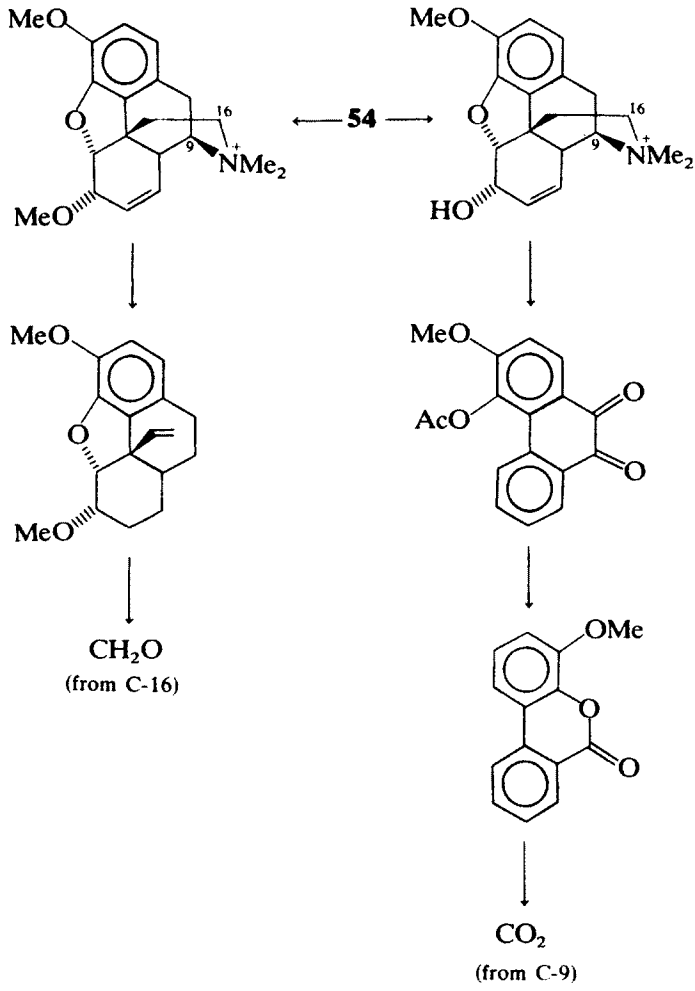


170

(1) *Enzymic Aspects.* Very little progress has yet been made in the isolation from plants of the enzymes that catalyze the various reactions in alkaloid biosynthesis, and hence little is known about them. However, a recent piece of research illustrates how the substrate specificity of an enzyme can be examined by feeding experiments using whole plants. In this example the enzyme investigated was the one that catalyzes the demethylation of codeine (**168**) to give morphine (**54**).

A series of codeine analogues (C′) were prepared[89] by labeling with tritium, and each was mixed with [*N-methyl*-^{14}C]codeine (a much smaller weight to allow for dilution by endogenous codeine), and the mixture administered to *P. somniferum*. The corresponding morphine analogues (M′) were also prepared to assist in the isolation and purification of any tritiated M′ that might be formed enzymically from C′. After a suitable time had elapsed the plants were harvested, and in each case codeine (**168**), morphine (**54**), C′, and M′ were isolated and purified. Therefore, incorporation of **168** into **54** and C′ into M′ could be determined, and the ratio of these incorporations provided a measure of the effectiveness of C′ as a substrate for the demethylation enzyme. It was found[89] that dihydrocodeine, codeine methyl ether (**169**), and dihydrodeoxycodeine were all demethylated almost as effectively as was codeine (**168**) itself. Therefore, it can be concluded that neither the hydroxyl group nor the double bond in codeine is essential for binding to the demethylation enzyme.

(ii) ORIGIN OF CARBON SKELETON. Early biosynthetic studies revealed that [U-^{14}C][90] and [2-^{14}C]tyrosine[33,91] (**4**) were incorporated into morphine (**54**), codeine (**168**), and thebaine (**166**) by *P. somniferum* and also established that the highest incorporations are achieved when aqueous solutions of precursors are injected into young seed capsules of the plants. The radioactive morphine (**54**) from these experiments was degraded[33,91] to determine the radioactivity at C-9 and at C-16 (Scheme 22), and the results showed

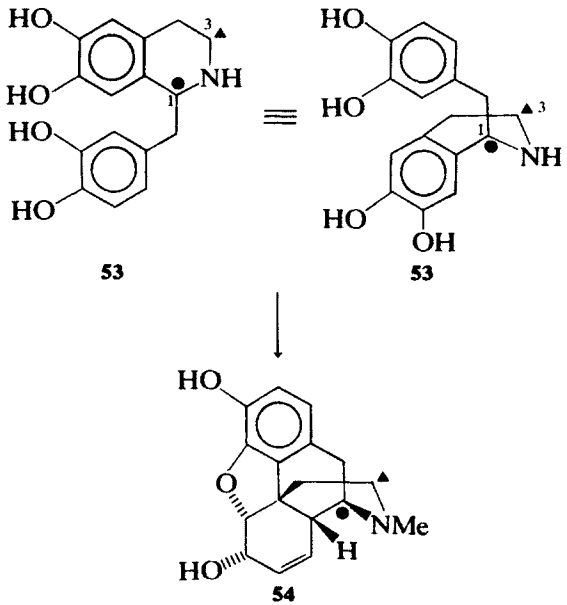


Scheme 22. Degradation of morphine.

that these two carbon atoms are equally labeled, thus proving that the morphine skeleton is built up from two C_6–C_2 units, each provided by tyrosine.

[1-^{14}C]Dopamine (**1**) was also incorporated into morphine, but this time degradation revealed[35,59] that *all* the radioactivity was located at C-16.

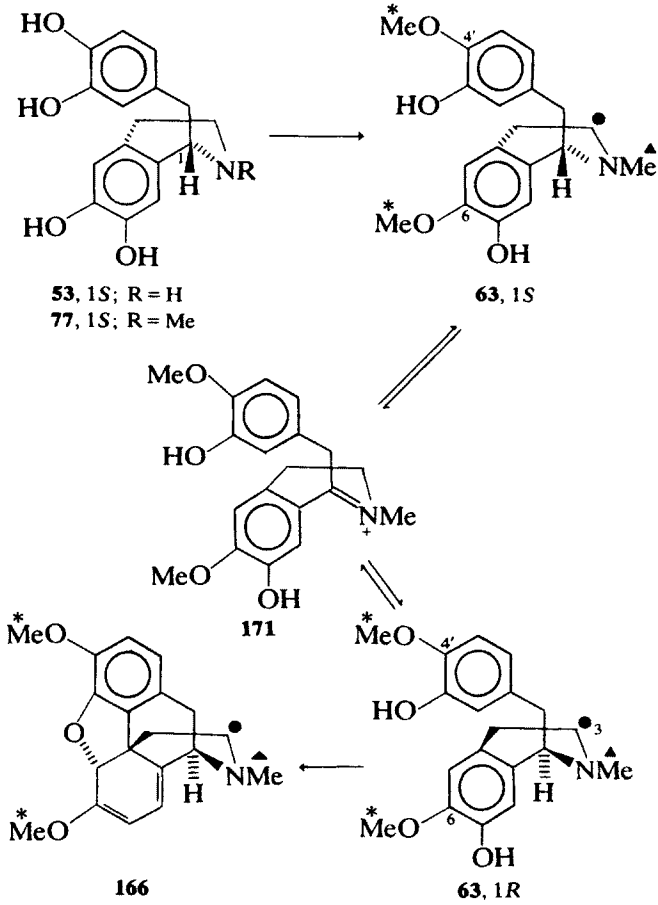
(iii) 1-Benzylisoquinoline Precursors. In 1925 Robert Robinson had brilliantly deduced[92] that morphine might be structurally related to the 1-benzylisoquinolines, and he went on to propose[5] that norlaudanosoline (**53**) should be the *in vivo* precursor of the morphine alkaloids. These ideas were emphatically confirmed in 1960, when it was reported[93] that [1-^{14}C]- and [3-^{14}C]norlaudanosoline (**53**) were incorporated[31] specifically into morphine, codeine, and thebaine (and papaverine) by *Papaver somniferum*.



At that time labeled precursors of such complexity had not been introduced into higher plants, but these successful results were soon followed up, and both [3-^{14}C]norreticuline (**67**) and [3-^{14}C]reticuline (**63**) were also shown[31] to serve as effective and specific precursors of the morphine alkaloids. This was a very important and exciting result because these two compounds have precisely the *O*-methylation pattern required for directed oxidative phenol coupling[66] to the morphinan skeleton. However, it was conceivable that the compounds were suffering demethylation prior to incorporation [e.g., by way of norlaudanosoline (**53**)]. To check for this possibility, multiply labeled samples of reticuline were prepared and tested[94] as precursors of the morphine alkaloids in the opium poppy. Thus samples of [*N*-*methyl*-^{14}C]-, [4′-*O*-*methyl*-^{14}C]-, [6-*O*-*methyl*-^{14}C]-, and [3-^{14}C]reticuline were prepared, mixed in a known ratio and administered to poppy plants. Radioactive thebaine (**166**) was isolated and degraded by the Zeisel method to determine the radioactivity present in the *O*-methyl and *N*-methyl groups

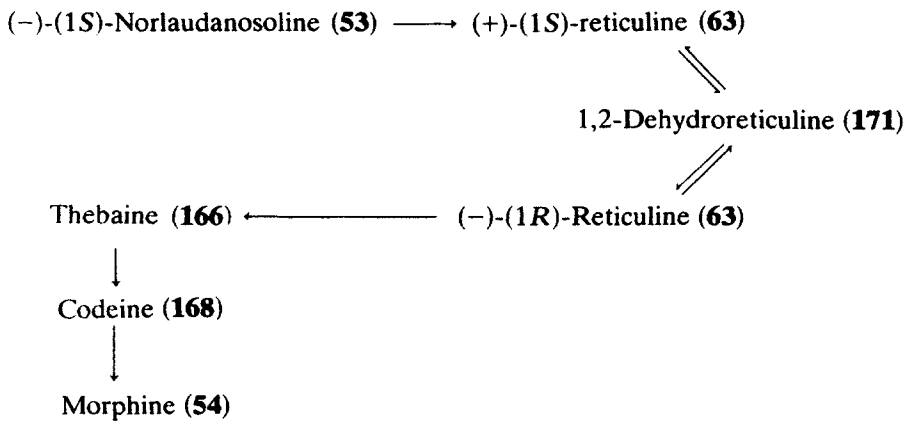
respectively. The skeletal radioactivity was obtained by difference, and the results[94] revealed that the multiply labeled reticuline had been incorporated intact into thebaine.

Subsequent studies focused attention on the configuration at C-1 of the 1-benzylisoquinoline precursors by testing the incorporation of optically active precursors. (−)-(1*S*)-Norlaudanosoline (**53**)[95] and (−)-(1*S*)-laudanosoline (**77**)[40] were found to be much better precursors of morphine than were the (1*R*)-enantiomers, despite the fact that they have a configuration at C-1 opposite to that found at the corresponding atom C-9 in the morphine alkaloids. On the other hand, (+)- and (−)-reticuline were incorporated[95] equally well into thebaine, codeine, and morphine. A valuable clue to the interpretation of these results was the finding that (+)-(1*S*)-[1-^{3}H]reticuline (**63**) loses most (82 to 99%) of its tritium during conversion to the morphine alkaloids whereas (−)-(1*R*)-[1-^{3}H]reticuline is incorporated with a significantly higher retention (32 to 58%) of tritium.[95] It



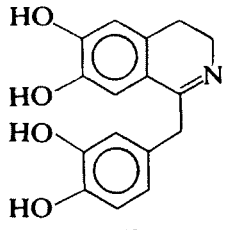
Scheme 23. Biosynthesis of thebaine from recticuline.

seemed, therefore, that (+)- and (−)-reticuline were being interconverted with removal of the hydrogen atom at C-1, probably through a redox reaction with 1,2-dehydroreticuline (**171**) as an intermediate (Scheme 23). In agreement with this hypothesis, [3-^{14}C]1,2-dehydroreticuline (**171**) was transformed into morphine by the opium poppy, and the incorporation[95] of 10.5% was a record at that time. The pathway consistent with these results is as follows:

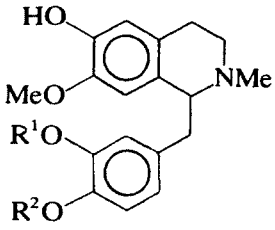


The poor incorporation of (+)-(1*R*) norlaudanosoline (**53**) shows that this compound is not converted by the plant into (−)-(1*R*)-reticuline (**63**) (i.e., the enzymes that catalyze *O*- and *N*-methylation are specific for the (1*S*) enantiomer) and that norlaudanosoline cannot be racemized by a reversible redox reaction. Indeed, 1,2-dehydronorlaudanosoline (**172**) is not a precursor of morphine in *P. somniferum*.[96] Finally, the lack of incorporation of labeled samples of (1) the three structural isomers[95] of reticuline, namely, orientaline (**61**), protosinomenine (**173**), and **174**, (2) the *N*-methyl derivative tembetarine (**175**)[96], and (3) the *O*-methyl derivative codamine (**176**)[96] emphasizes the fact that (1*R*)-reticuline uniquely possesses the structural features necessary for further transformation to the morphine alkaloids.

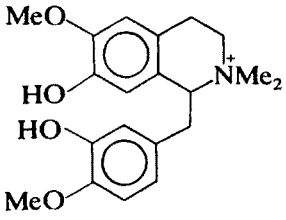
(iv) Conversion of (1*R*)-Reticuline to Thebaine. The experimental proof that (1*R*)-reticuline (**63**) is the unique precursor of thebaine (**166**) strongly supported the hypothesis[66] that oxidative phenol coupling is a key step in the biosynthesis of the morphine alkaloids and reinforced the expectation that the dienone **177** should be the next intermediate in the pathway. Dienone **177** was therefore synthesized[94] from thebaine (**166**) and the product was soon shown to be identical with a new alkaloid, salutaridine (**177**), isolated from *Croton salutaris*. Borohydride reduction of salutaridine (**177**) gave[94] a mixture of salutaridinols I and II, and their relative stereochemistries were later elegantly demonstrated[97] to correspond to **178** and **179**, respectively.



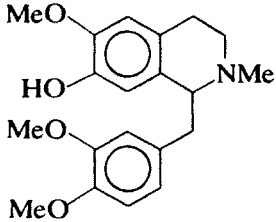
172



173, $R^1 = H$; $R^2 = Me$
174, $R^1 = Me$; $R^2 = H$



175



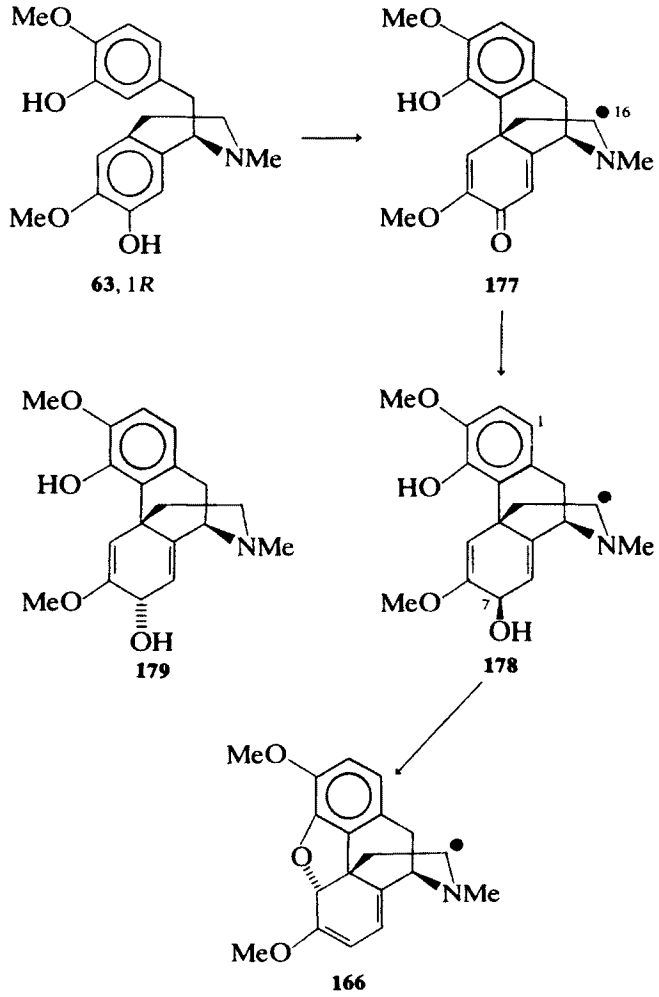
176

[16-^{14}C]Salutaridine (**177**), prepared from biosynthetically labeled thebaine, was efficiently incorporated into the morphine alkaloids, and salutaridinol I (**178**) was a better precursor than was its epimer **179**, as shown by feeding experiments with [1,7-$^3H_2$]- and [7-^{3}H,6-^{14}C]salutaridinols. Furthermore, the latter experiment showed that the tritium at C-7 was retained in thebaine whichever epimer acted as precursor, thus indicating that the epimers cannot be interconverted *in vivo* through salutaridine. The loss of tritium from C-7 (14 to 18%) that apparently occurs during the transformation of thebaine (**166**) into codeine (**168**) and morphine (**54**) can perhaps occur by enolization of codeinone (**167**) through neopinone (**170**).

These results nicely define the key steps in the biosynthesis of the morphine alkaloids from the ubiquitous precursor reticuline as regiospecific ortho–para oxidative phenol coupling of (1*R*)-reticuline (**63**) to give salutaridine (**177**) followed by stereospecific reduction of salutaridine to give salutaridinol I (**178**), and subsequent dehydration of salutaridinol I with simultaneous formation of the cyclic ether of thebaine (**166**). This last reaction is essentially an S_N2' substitution of an allylic alcohol. However, there is no evidence that this is a one-step process.

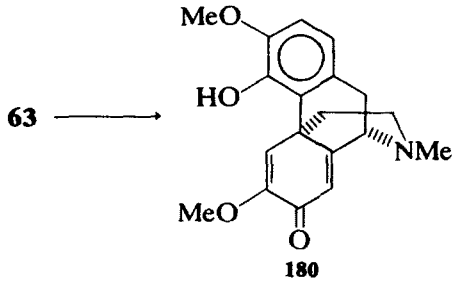
(f) *Alkaloids Related to Morphine*

(i) Sinomenine. The alkaloid sinomenine (**181**) possesses the same carbon skeleton as the morphine alkaloids, although it belongs to the enantiomeric

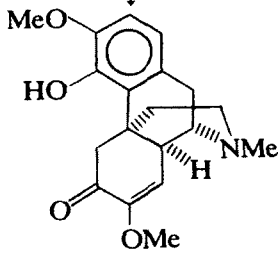


series. [*Aryl*-^{3}H]Reticuline (**63**) was incorporated[98] by *Sinomenium acutum* plants into sinomenine, as was (−)-(1-^{3}H]-sinoacutine (**180**), the enantiomer of salutaridine (**177**). In comparable experiments [*aryl*-^{3}H]norprotosinomenine (**60**) was not significantly incorporated, and so these results support the pathway (1*S*)-reticuline (**63**) → sinoacutine (**180**) → sinomenine (**181**). The late stages of the biosynthesis have not been defined, although the negative results from feeding experiments with labeled sinoacutinols (**182**) and isosinomenine (**183**) do restrict the possible pathways.[98]

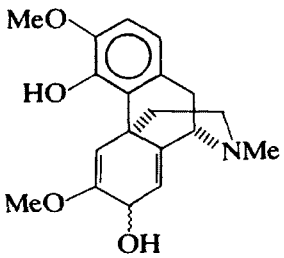
(ii) Flavinantine. Flavinantine (**184**) is an isomer of salutaridine (**177**). In accord with the principle of oxidative phenol coupling, it was found[99] that [*N-methyl*-^{14}C]reticuline (**63**) was incorporated far better than was [*N-methyl*-^{14}C]orientaline (**61**) in *Croton flavens*. Presumably, isosalutaridine



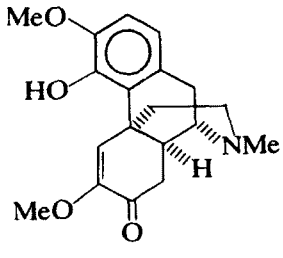
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181



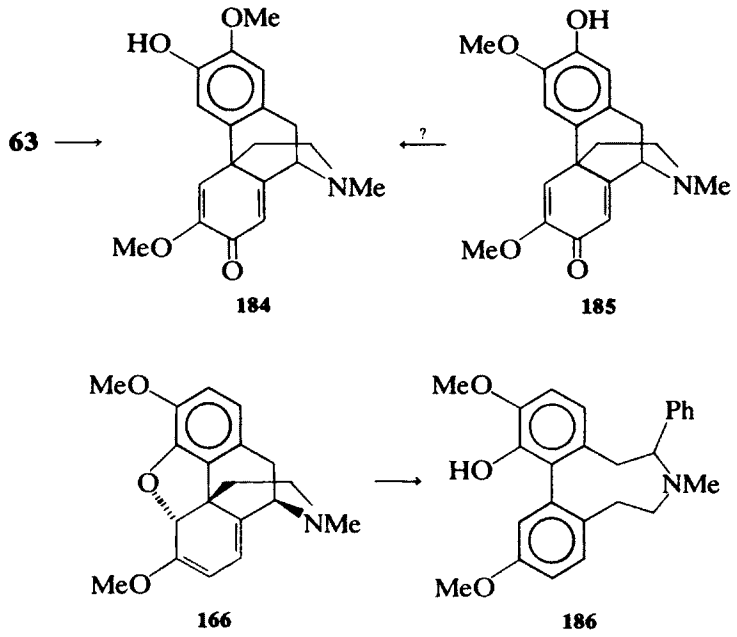
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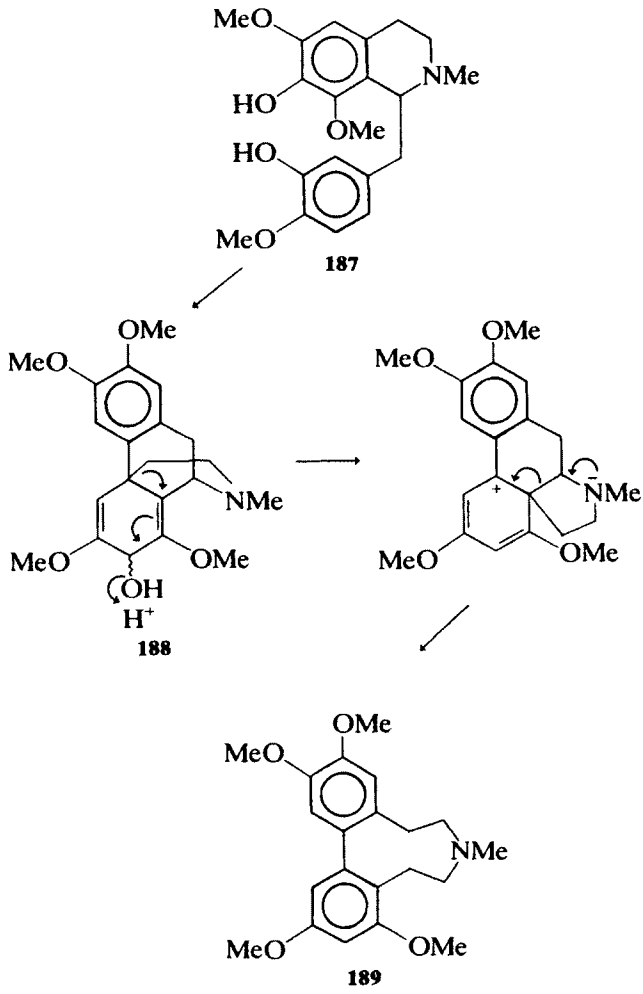
183

(**185**) is an intermediate that suffers demethylation–remethylation analogous to the biosynthesis of crotonosine [Section VII.B(b)].

(iii) PROTOSTEPHANINE. Protostephanine (**189**) is a minor alkaloid of *Stephania japonica* with the dibenzazonine skeleton. Speculation concerning the biosynthesis of protostephanine was influenced by the knowledge that the dibenzazonine (**186**) is produced[100] by reaction of thebaine (**166**) with phenyl magnesium bromide. By analogy, the biosynthesis of protostephanine might involve rearrangement, fragmentation, and subsequent reduction of the morphinandienol (**188**) whose precursor would be the 1-benzylisoquinoline **187**. This hypothesis (Scheme 24) was tested by feeding radioactive **187** and several related isoquinolines to *S. japonica*, but in each case the isolated protostephanine had incorporated an insignificant



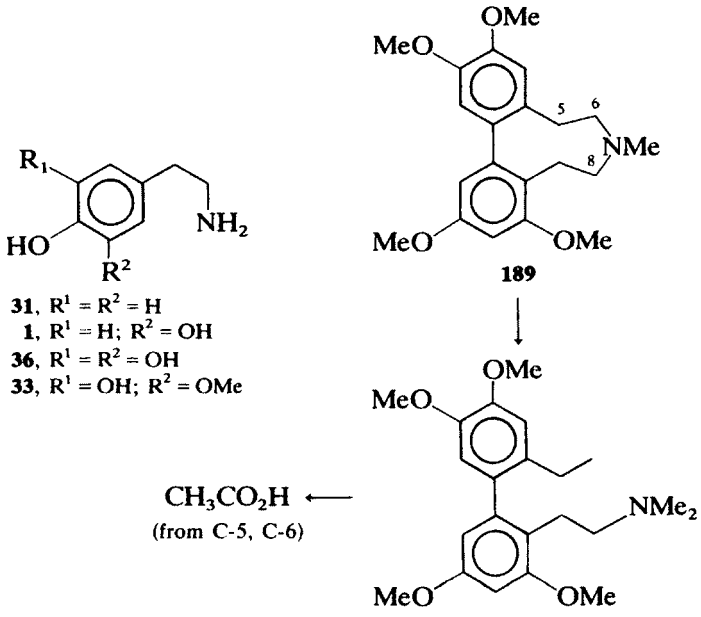
amount of radioactivity. Even if it is assumed that the administered precursors were reaching the appropriate location in the plant, these negative results did not disprove the *essence* of the hypothesis, since a similar mechanistic scheme might operate on a less highly oxygenated or methylated 1-benzylisoquinoline with the necessary adjustments taking place at a late stage in the biosynthetic pathway. Therefore, it seemed important at this point to identify the primary precursors from which protostephanine (**189**) is built up. [2-^{14}C]Tyrosine (**4**) was incorporated[101] into protostephanine, and the degradation shown in Scheme 25, revealed that *half* the radioactivity was located at C-6, with the remainder presumably at C-8. [1-^{14}C]Tyramine (**31**), dopamine (**1**), and trioxygenated phenethylamines **36** and **33** were also incorporated but only into the lower C_6–C_2 unit, with the radioactivity presumably residing at C-8. From these results it became clear that if tyrosine and the phenethylamine **33** are incorporated into protostephanine (**189**) by way of a 1-benzylisoquinoline, the precursor must have *at least* the oxygenation pattern of **190** or **191**. Subsequently, a second oxygen atom must be introduced into ring *C*, and *O*-methylation may occur before oxidative phenol coupling. To obtain a definitive answer concerning the biosynthesis of protostephanine, *all* the 1-benzylisoquinolines which match these requirements were prepared, each one carrying a ^{14}C-label at C-3. In addition, a complete set of ^{14}C-labeled bisphenethylamines related to **192** was prepared, and both series of compounds were tested as precursors of protostephanine in *S. japonica*. The results[102] clearly imply that the sequence shown in Scheme 26 represents the major pathway to



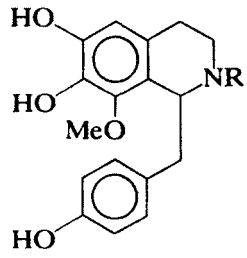
Scheme 24. Hypothetical pathway to protostephanine from a 1-benzylisoquinoline.

protostephanine. Note, however, that experiments with multiply labeled isoquinolines and with the hypothetical dienone **194** have yet to be carried out. None of the bisphenethylamines was effectively incorporated.

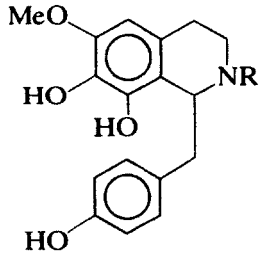
(iv) HASUBANONINE. Hasubanonine (**196**) is a representative member of a novel class of alkaloids whose skeleton differs from that of the morphine alkaloids only in the position of attachment of the bridge nitrogen atom. Since hasubanonine (**196**) occurs alongside protostephanine (**189**) in *S. japonica*, biosynthetic studies on both alkaloids have been made in parallel,[101] and the results[102] show that both alkaloids share a common pathway as far as the isoquinoline **193**. Two modes of oxidative phenol



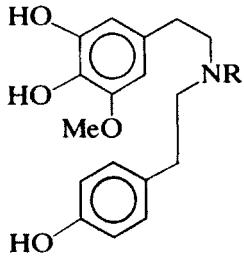
Scheme 25. Degradation of protostephanine.



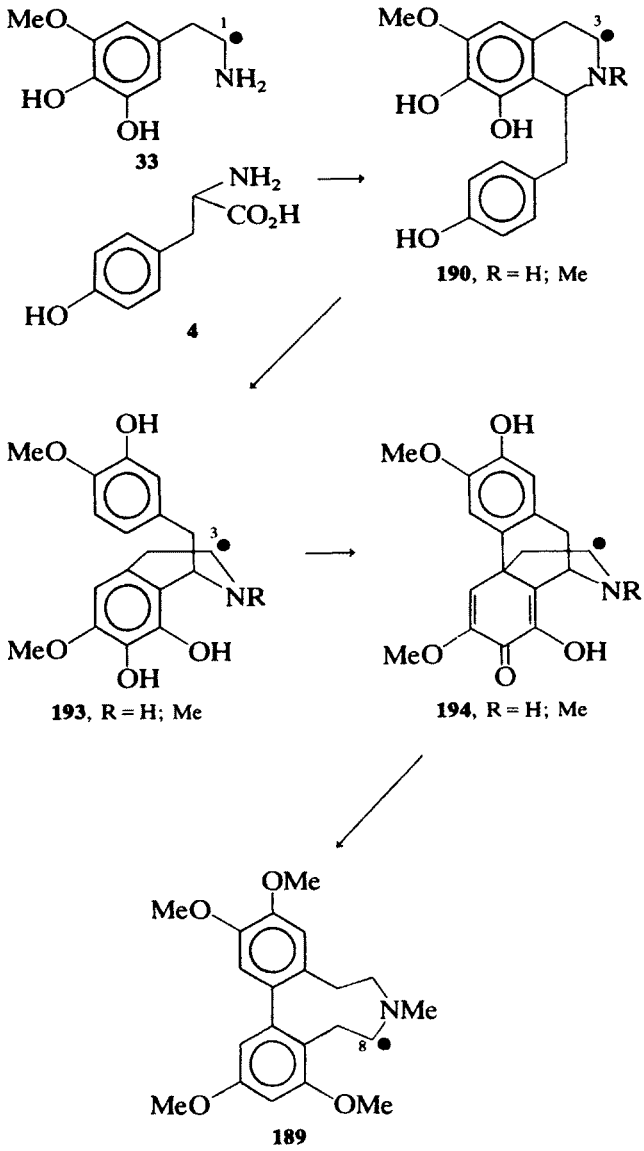
190, R = H; Me



191, R = H; Me

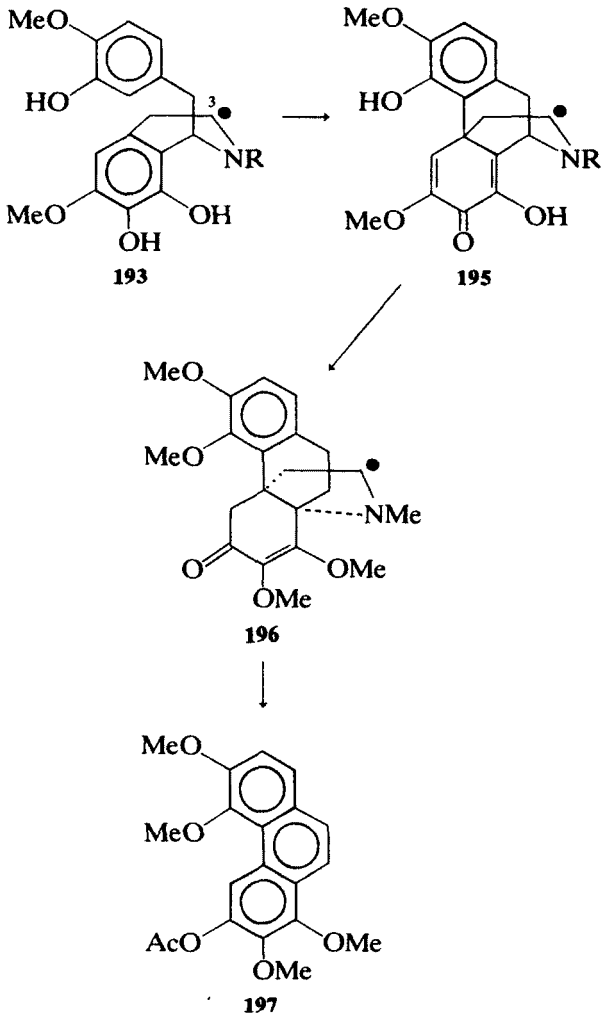


192, R = H; Me



Scheme 26. Biosynthesis of protostephanine in *S. japonica*.

coupling are, in principle, open to **193**, one leading to protostephanine (**189**) through the dienone (**194**) and the other, to hasubanonine (**196**) by way of the isomeric dienone **195**. The late stages of this pathway have not yet been studied, but it is likely that the degradation of hasubanonine (**196**) to the phenanthrene **197** will serve a useful function for future studies as it has already done in earlier work.[101]



VIII. 1-PHENETHYLISOQUINOLINE ALKALOIDS

A. Colchicine

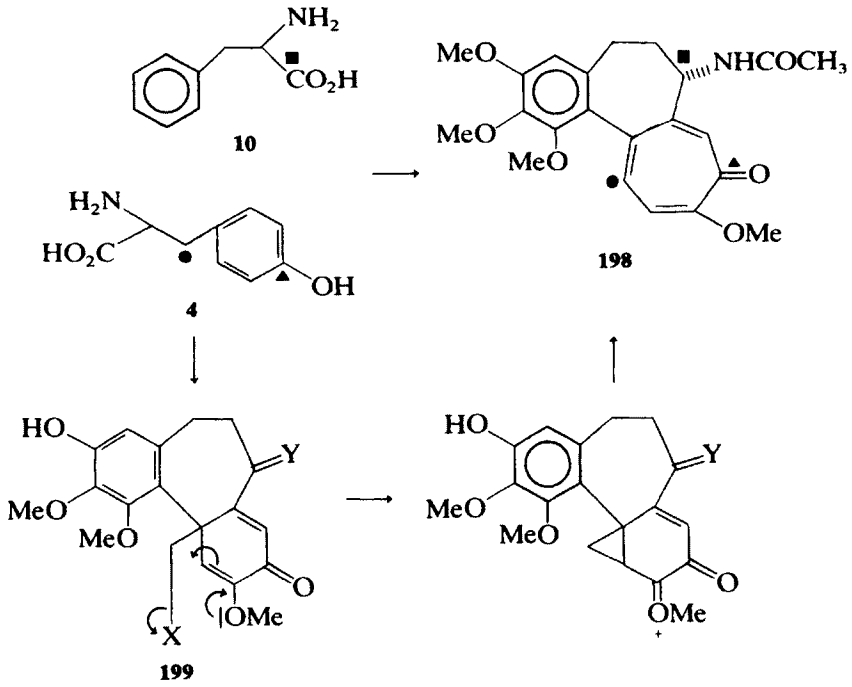
Colchicine (**198**) is now known to be the end product of a remarkable biosynthetic pathway in which a 1-phenethylisoquinoline is so extensively modified that it is difficult to discern the essential structural relation between colchicine and other isoquinoline alkaloids. The story of the elucidation of the biosynthesis is an instructive one, and it is given in outline first, with the detailed evidence following in later sections.

(a) *Outline of Biosynthetic Studies*

At the outset of research on colchicine biosynthesis no naturally occurring 1-phenethylisoquinolines were known, and no clue was available to its true origin. Hence the early work attempted to identify the primary precursors of the colchicine skeleton by feeding labeled phenylalanine (**10**), tyrosine (**4**), and acetate to *Colchicum* plants. The aromatic amino acids might reasonably provide all or part of the C_6–C_3 unit, and acetate was regarded as a potential precursor of the tropolone ring by analogy with fungal tropolone biosynthesis.[103]

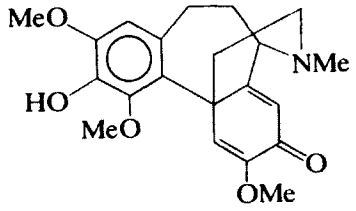
These experiments eventually revealed that the C_6–C_3 unit is derived intact from phenylalanine (**10**),[104–106] that acetate is incorporated only into the *N*-acetyl group of colchicine,[106,107] and that the tropolone ring is formed by ring expansion of a C_6–C_1 unit provided by tyrosine (**4**).[106,108]

It was far from obvious how these pieces were assembled *in vivo* for further transformation into colchicine (**198**), but a key step is clearly the ring expansion of the C_6–C_1 unit, and it was postulated that this might take place through the dienone **199** generated by oxidative phenol coupling as shown in Scheme 27. To test this hypothesis, it would be necessary to synthesize a variety of dienones of type **199** with different substituents X and Y in labeled form for feeding experiments to *Colchicum* plants. Indeed, the



Scheme 27. Hypothetical pathway to colchicine.

synthetic program was in progress[109] when it was reported that a dienone alkaloid (androcymbine) had been found to occur alongside colchicine (**198**) in *Androcymbium melanthiodes*. The structure of androcymbine was defined[110] as **200**, its structural relationship to the hypothetical dienone **199** was immediately evident, and *O*-methylandrocymbine (**202**) was soon shown[111] to be a precursor of colchicine (**198**).



200

The *O*-methylandrocymbine result provided the key to the whole problem of colchicine biosynthesis, and it was now possible to consider logically the likely nature of the earlier intermediates in the biosynthetic pathway (Scheme 28). Thus the principles of oxidative phenol coupling applied to *O*-methylandrocymbine (**202**) suggested that its biosynthetic precursor should be the diphenolic 1-phenethylisoquinoline **201**. Feeding experiments with multiply labeled samples of **201** (autumnaline) conclusively confirmed this hypothesis and firmly established[111-113] the isoquinoline origin of colchicine and related alkaloids.

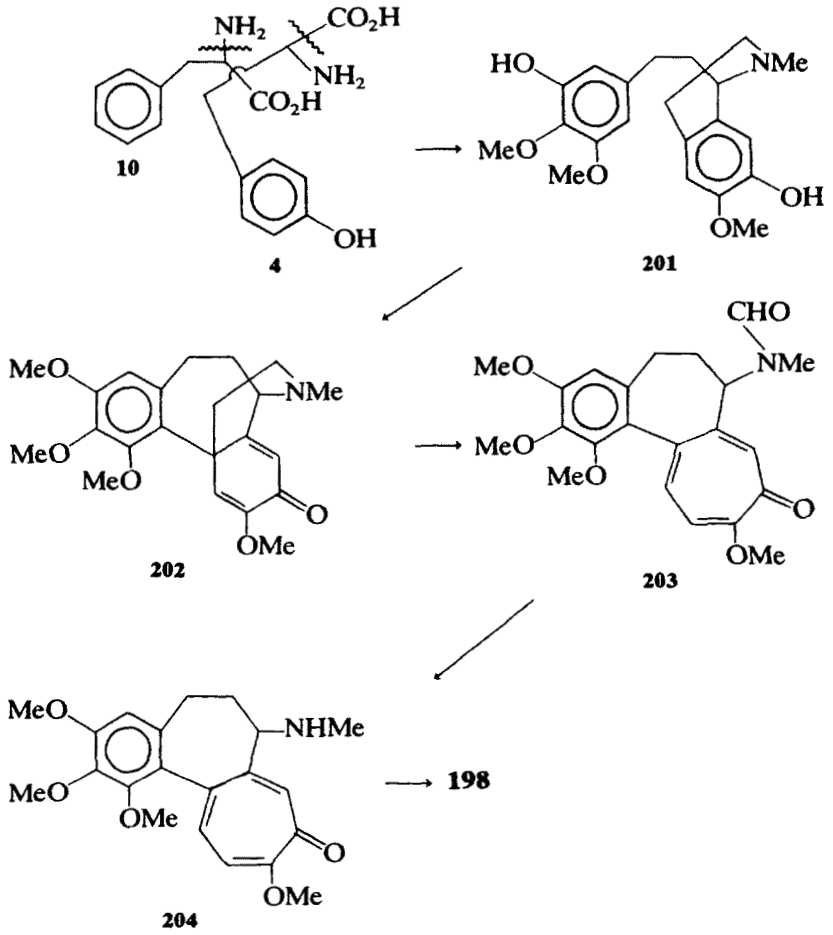
The results with *O*-methylandrocymbine (**202**) and with autumnaline (**201**) also led to constructive speculation concerning the late stages of colchicine biosynthesis. In particular, they focused attention on the significance of minor *Colchicum* alkaloids carrying substituents other than acetyl on the exocyclic amino group, and it was soon shown[114] that the *N*-methyl group of autumnaline (**201**) is *retained* in the alkaloid demecolcine (**204**) and that demecolcine is an efficient precursor of colchicine (**198**).

A search was subsequently made for an intermediate retaining *all* the carbon atoms of *O*-methylandrocymbine (**202**), and this succeeded when *N*-formyldemecolcine (**203**) was identified[114] as an obligatory intermediate en route to colchicine (**198**).

Having summarized the key stages in the elucidation of the pathway to colchicine, I now describe in detail the evidence for each individual stage.

(b) *Origin of* C_6–C_3 *Unit*

The degradations used for locating the site of any radioactivity in the C_6–C_3 unit of colchicine (**198**) are summarized in Scheme 29. In this way it was shown that [1-^{14}C]-,[106] [2-^{14}C]-,[105] and [3-^{14}C]phenylalanine (**10**) are incorporated by *Colchicum* plants specifically into C-7, C-6, and C-5,

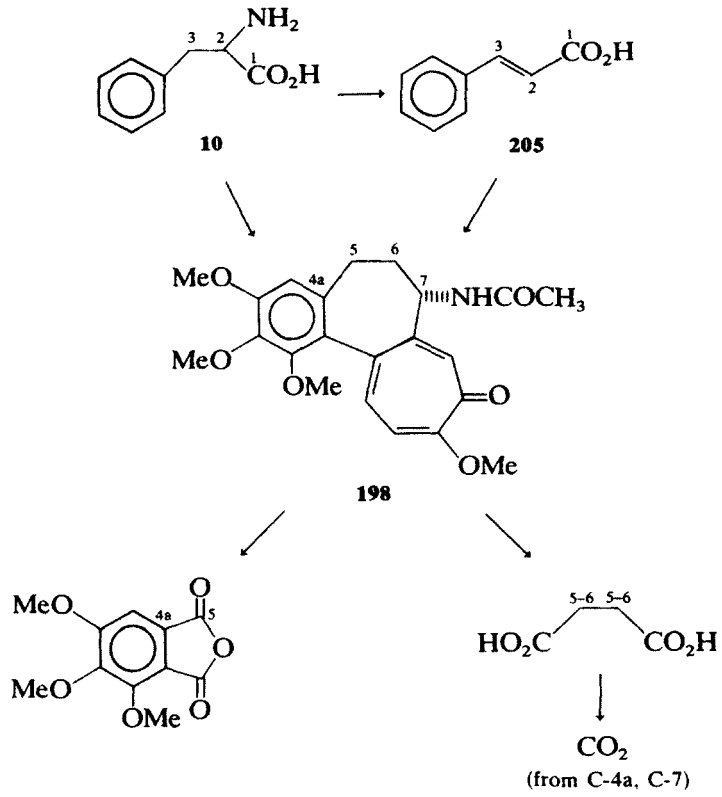


Scheme 28. Biosynthesis of colchicine.

respectively. [2-^{14}C]Tyrosine (**4**) also afforded radioactive colchicine, but in this case the labeling was not specific; most of the radioactivity appeared to be located in the *N*-acetyl group and in the *O*-methyl groups, and C-6 was labeled to only a negligible extent. Furthermore, [1-^{14}C]tyrosine (**4**) afforded radioinactive colchicine.[106]

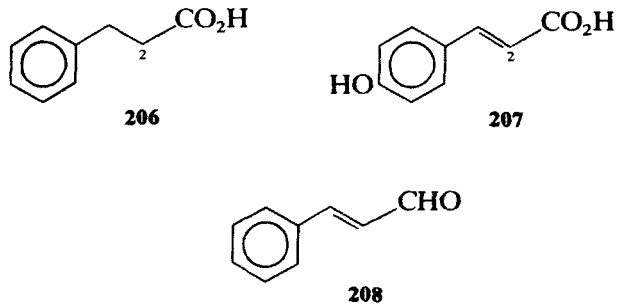
Since ring *A* of colchicine is highly oxygenated, the incorporation of phenylalanine but not tyrosine was surprising. However, the same situation was found[115] for the biosynthesis of the C_6–C_1 unit of the *Amaryllidaceae* alkaloids, and in both cases it has now been shown that phenylalanine is converted[116] into *trans*-cinnamic acid (**205**) before oxygenation of the aromatic ring. Thus [2-^{14}C]-[106] and [3-^{14}C][106,117] cinnamic acid (**205**) afforded [6-^{14}C]- and [5-^{14}C]colchicine (**198**), respectively.

The next stage in the biosynthetic pathway has not yet been established,



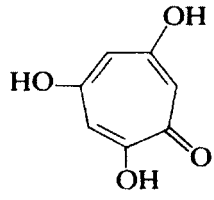
Scheme 29. Degradation of colchicine derived from labeled cinnamate.

but neither [2-^{14}C]hydrocinnamic acid (**206**) nor [2-^{14}C]*para*-hydroxycinnamic acid (**207**) were incorporated into colchicine by *C. Autumnale*. Although these negative results[111] must be interpreted with caution, they imply that the carboxyl group of cinnamic acid must be modified, probably to give cinnamaldehyde (**208**), prior to reduction of the double bond or hydroxylation of the aromatic ring.



(c) *Origin of Tropolone Ring*

Since the fungal tropolone stipitatic acid (**209**) had been shown[103] to be acetate derived, [1-^{14}C]acetate was fed to *Colchicum* plants. Although radioactive colchicine was isolated, only the *N*-acetyl group was labeled.[106,107]



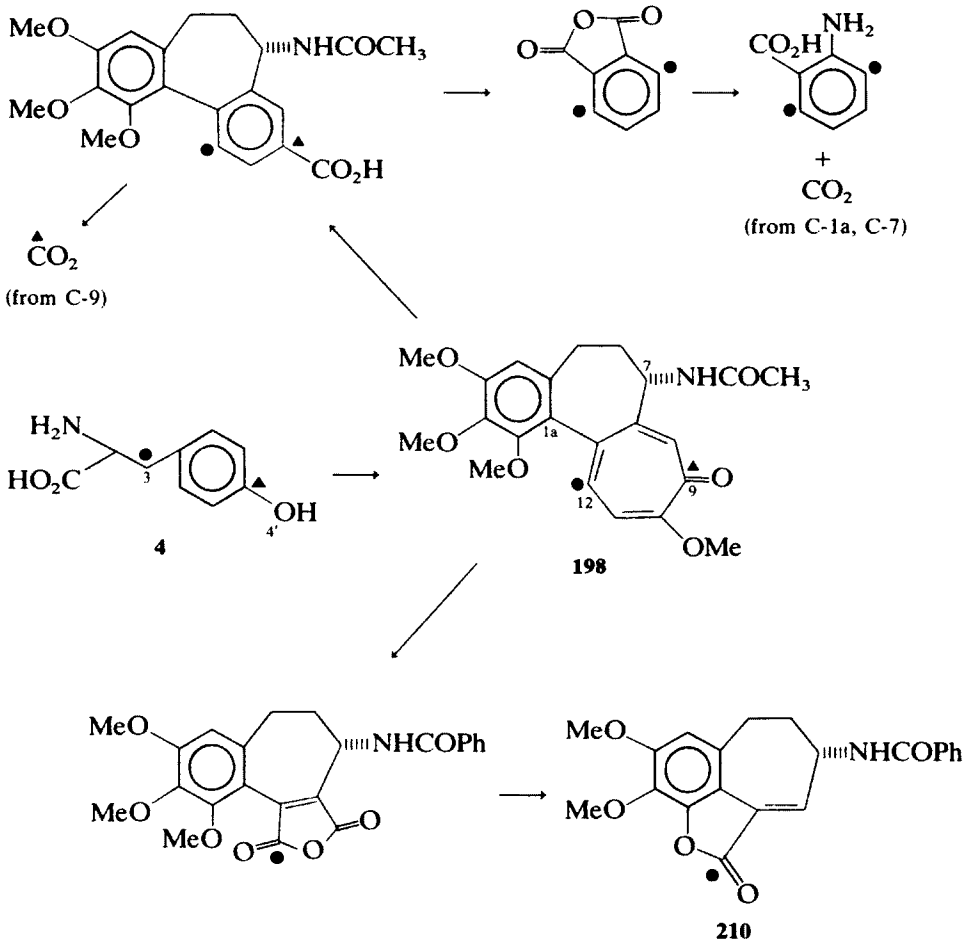
209

A second hypothesis—namely, that the tropolone ring might be derived from a C_6–C_1 unit by ring expansion—was tested[106] by feeding [3-^{14}C]tyrosine. Radioactive colchicine was isolated, and this was degraded as shown in Scheme 30 to give phthalic acid with 81% of the radioactivity. Subsequent Schmidt degradation yielded radioinactive CO_2, and it follows that the tropolone ring must carry all the radioactivity.[106] A second degradation[111] (Scheme 30) afforded lactone **210** with 81% of the specific radioactivity of the colchicine sample. Taken together, these degradations prove that [3-^{14}C]tyrosine is specifically incorporated into C-12 of colchicine (**198**). [4′-^{14}C]Tyrosine (**4**) was also incorporated[108] into colchicine (**198**), and the degradation shown in Scheme 30 yielded radioactive CO_2, thus showing that the colchicine was labeled at C-9.

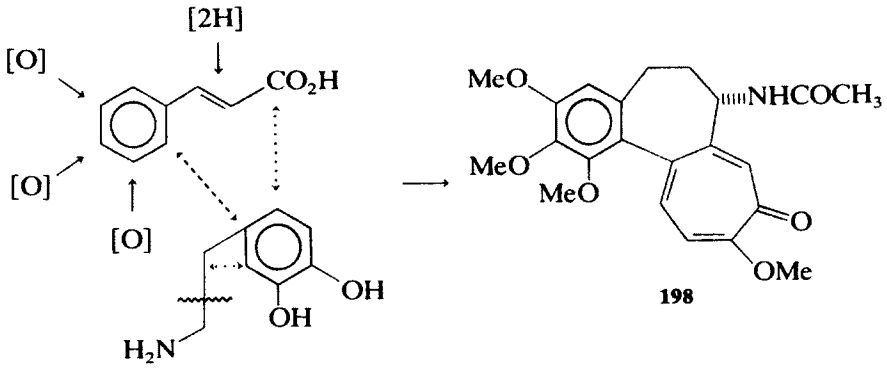
[2-^{14}C]Tyramine (**31**) and [*aryl*-^{3}H]dopamine (**1**) were incorporated well[111] into colchicine, and they presumably contribute the same C_6–C_1 unit as does that provided by tyrosine (**4**). Since the tyrosine results define the *mode* of incorporation of the C_6–C_1 unit, it is clear that the two primary building blocks must eventually become attached as shown in Scheme 31.

(d) *Discovery of Key Intermediate*

The primary precursors cinnamic acid and dopamine undergo extensive modification en route to colchicine (Scheme 31). At this stage the timing of the various changes was not at all evident and various speculations were tested without success.[109,118] Progress was subsequently furthered enormously by contemporary studies on the alkaloids of *Androcymbium melanthioides*. Androcymbine (**200**)[100] strongly resembled the hypothetical intermediate **199**, and so a radioactive derivative was prepared by treating the natural alkaloid with diazomethane-tritiated water. The resultant [*O*-*methyl*-^{3}H]*O*-methylandrocymbine (**201**) was administered[111] to *C. autumnale*, and a remarkable 15% of the radioactivity was incorporated into



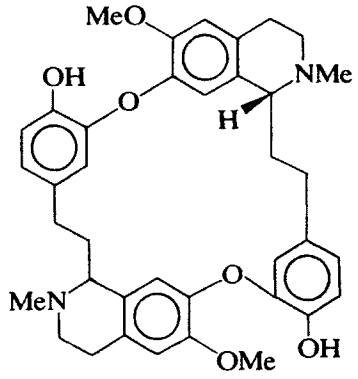
Scheme 30. Degradations of colchicine derived from labeled tyrosine.



Scheme 31. Cinnamic acid and dopamine as building blocks for colchicine biosynthesis.

colchicine. Degradation to trimethoxyphthalic anhydride (Scheme 29) showed that the radioactivity was specifically located in a ring-*A* methoxyl group.

It was at once evident that the skeleton of *O*-methylandrocymbine (**201**) should be formed by oxidative phenol coupling of a suitably substituted 1-phenethylisoquinoline (e.g., **202**), and circumstantial evidence in favor of this hypothesis was soon available when structure **211** was assigned[119] to melanthioidine, a second alkaloid from *A. melanthioides*. Attention then turned toward the synthesis of labeled 1-phenethylisoquinolines.



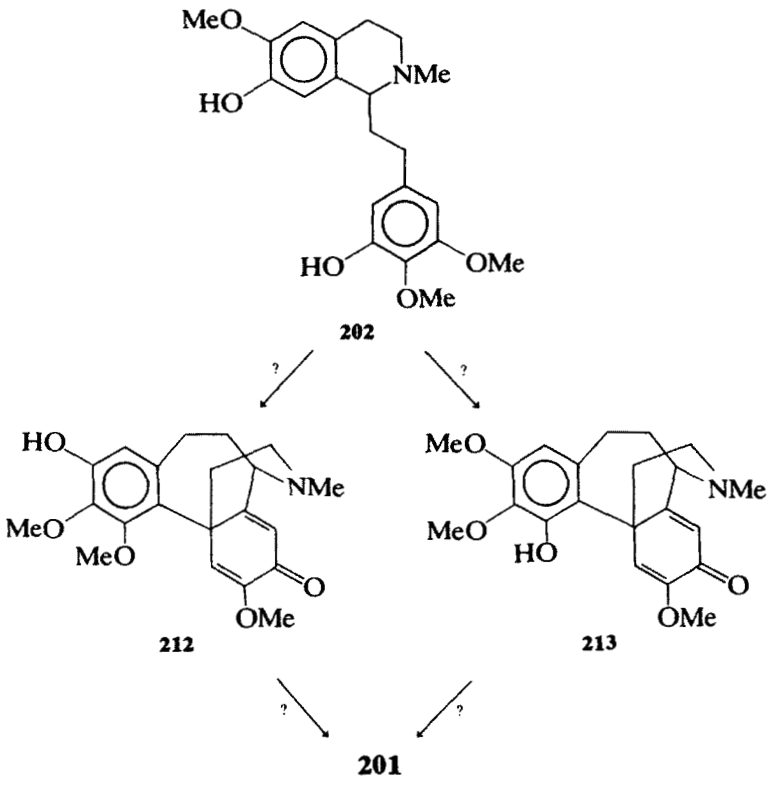
211

(e) 1-*Phenethylisoquinoline Precursors*

(i) AUTUMNALINE. If *O*-methylandrocymbine (**201**) is formed *in vivo* by oxidative coupling, the logical precursor is the diphenolic 1-phenethylisoquinoline autumnaline (**202**).

Autumnaline (**202**) might undergo oxidative cyclization with either ortho-para coupling to **213** or para–para coupling to **212**, and *O*-methylation could in each case afford *O*-methylandrocymbine (**201**). This hypothesis has been subjected to the closest scrutiny by feeding a variety of multiply labeled and resolved samples of autumnaline (**202**) to *Colchicum* plants and determining by degradation the labeling pattern in the resultant colchicine (**198**) and demecolcine (**204**). The results that follow are summarized in Scheme 32.

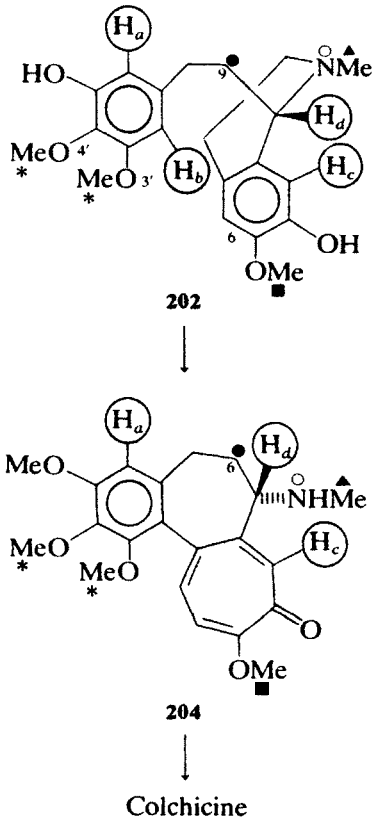
The high incorporation[111] (ca. 10%) of [9-^{14}C]autumnaline (**202**) into colchicine at once confirmed that the tropolone alkaloids are, indeed, modified 1-phenethylisoquinolines. Degradation (Scheme 29) proved that the colchicine was specifically labeled at C-6, and so this skeletal label could now be used as a reference to test whether autumnaline remains intact during its bioconversion into colchicine. By choosing suitable combinations



of labels, it was thus shown[112] that:

1. One of the aryl-hydrogen atoms of ring *A* (H_b) is lost as expected.
2. The N-atom of autumnaline is completely retained.
3. The 6-*O*-methyl group is completely retained.
4. The 3′- and 4′-*O*-methyl groups are also completely retained, and the degradations shown in Scheme 33 prove that they correspond to the *O*-methyl groups at C-1 and C-2 in colchicine. This result thus proves that autumnaline cyclizes exclusively by para–para coupling.
5. The *N*-methyl group of autumnaline is completely retained in demecolcine (**204**) but is completely absent in colchicine (**198**) itself. This result strongly suggested that demecolcine (**204**) is a precursor of colchicine (**198**).
6. (−)-(1*S*)-Autumnaline, whose configuration corresponds to that at C-7 in colchicine, was incorporated 180 times better than the (1*R*)-enantiomer. However, (1*S*)-[1-^3H]autumnaline gave colchicine with retention of only 65% of the tritium activity.

The loss of tritium might occur through a redox equilibrium with



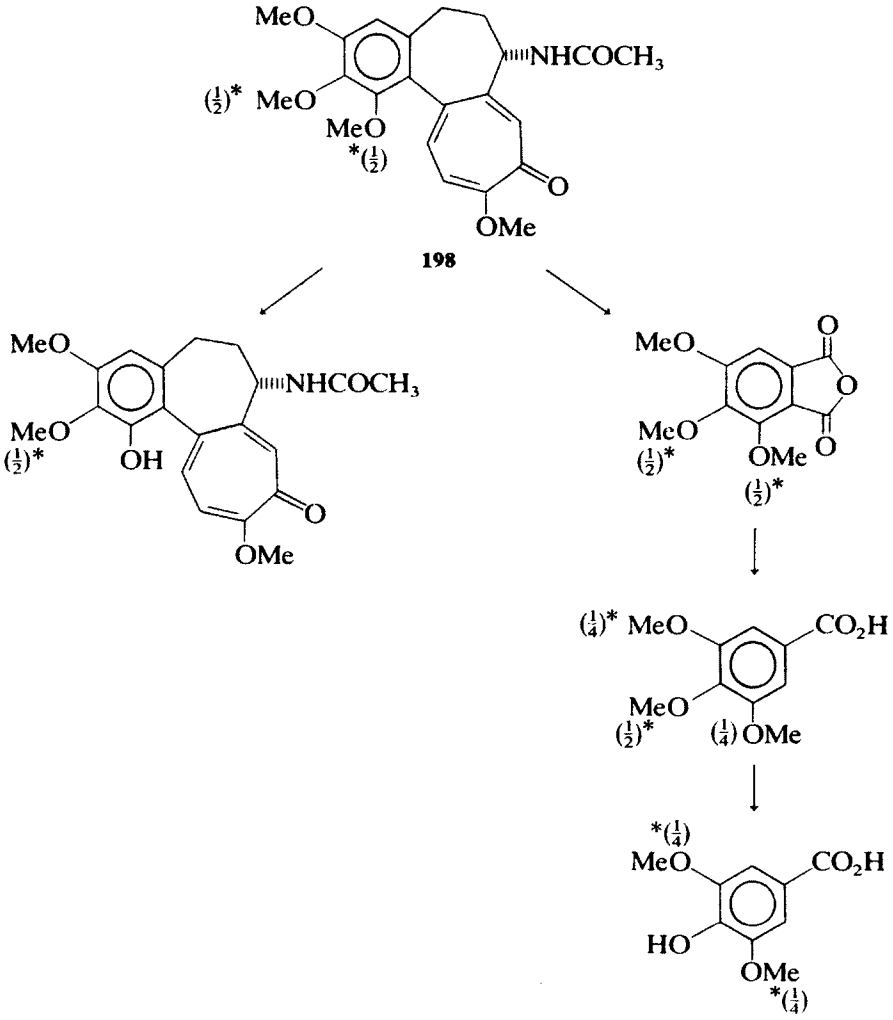
Scheme 32. Biosynthesis of colchicine from multiply labeled autumnaline.

1,2-dehydroautumnaline (**214**), and, indeed, [9-^{14}C] **214** was efficiently incorporated into colchicine. The situation here is similar to that found in *Papaver somniferum* [Section VII.B(e)(iii)], except that whereas the *Colchicum* redox enzyme appears to operate *only* on (1*S*)-autumnaline, the poppy enzyme(s) accepts (accept) both (1*S*)- and (1*R*)-reticuline.

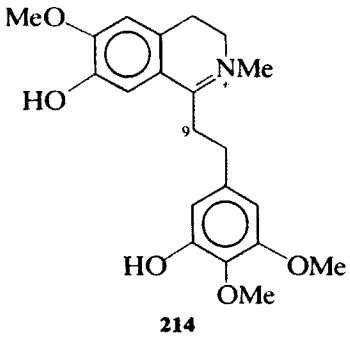
In total, these results highlight the crucial role of (1*S*)-autumnaline (**202**) in the biosynthesis of the tropolone alkaloids demecolcine and colchicine by way of *O*-methylandrocymbine (**201**).

(1) *Incorporation of* [^{13}*C*]*Autumnaline.* Section II.B emphasizes the need for chemical degradation of each radioactive alkaloid to establish the precise labeling pattern, and many examples can be seen throughout this chapter. The potential advantages of ^{13}C-labeling are also discussed in Section II.B, but it is emphasized that this new technique can only be used when incorporation levels are high.

At present only one example has been reported[113] of the use of ^{13}C-labeling in the study of isoquinoline alkaloid biosynthesis. An aqueous



Scheme 33. Degradation of colchicine derived from 3',4'-*O*,*O*-dimethyl-^{3}H autumnaline.



214

solution of [1-^{13}C]autumnaline (90 atom % ^{13}C) (300 mg) was injected into 300 seed capsules of healthy intact *C. autumnale* plants. After 2 weeks the capsules were cut off and colchicine (1.24 g) was isolated. When the ^{13}C nmr spectrum of the labeled alkaloid was run and compared with the spectrum of unlabeled colchicine, a signal at δ 52.4 was found to be enhanced in intensity by about 2.5. Previously the signal at δ 52.4 had been unambiguously assigned as that due to C-7 of colchicine, and so the experiment[113] confirms the specific incorporation of autumnaline (**202**) into colchicine (**198**).

The ^{13}C enrichment of the isolated colchicine corresponded to an incorporation of approximately 6% of the autumnaline fed, and the experiment demonstrates the value of ^{13}C in biosynthetic studies when such incorporation levels can be achieved.

(ii) Intermediates Leading to Autumnaline. The early research on colchicine biosynthesis had identified the primary precursors as *trans*-cinnamic acid and dopamine. Now that autumnaline (**202**) had been identified as a key intermediate, it was possible to study the sequence of the various transformations in a systematic way. Since neither the oxygenated cinnamic acids nor hydrocinnamic acid are precursors of colchicine, it seemed likely that sequential oxidation of the C_6–C_3 unit might take place at the isoquinoline level. This was confirmed when each [9-^{14}C]1-phenethylisoquinoline (**215–217**), was found to be incorporated[111] into colchicine. Subsequent studies[112] with multiply labeled **215** and **216** revealed that these precursors retain their *O*-methyl groups during their intact bioconversion into colchicine.

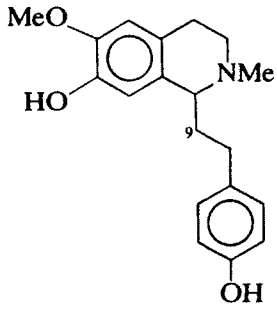
The isoquinoline (**218**) was *not* incorporated into colchicine, and so the timing of the initial oxygenation of the C_6–C_3 unit remains to be established.

(f) *Sequence of Tropolone Intermediates*

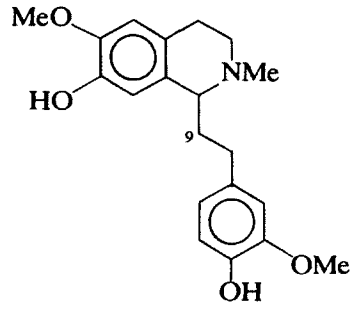
Since the *N*-methyl group of autumnaline (**202**)—and hence of *O*-methylandrocymbine (**201**)—is wholly retained during the biosynthesis of demecolcine (**204**) but is totally lost en route to colchicine (**198**), it seemed likely that demecolcine (**204**) might be a precursor of colchicine (**198**). This was confirmed[112] by feeding experiments with [3-*O*-*methyl*-^{3}H] samples of demecolcine (**204**) and colchicine (**198**). These and related labeled tropolones were prepared from the naturally occurring phenolic alkaloids by using diazomethane tritiated water.

The intermediates between demecolcine (**204**) and colchicine (**198**) could now be guessed at, and both incorporation and trapping experiments[114] supported the sequence **204** → **219** → **220** → **198**.

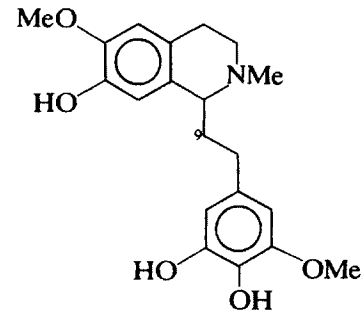
In the *Colchicum* plants studied, *N*-formyldesacetyl colchicine (**219**) is produced in part by formylation of desacetylcolchicine (**220**), but with this



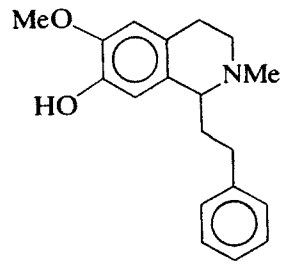
215



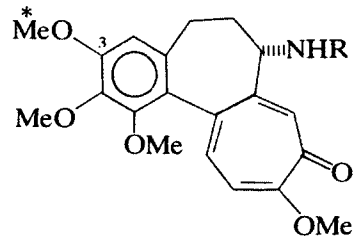
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217



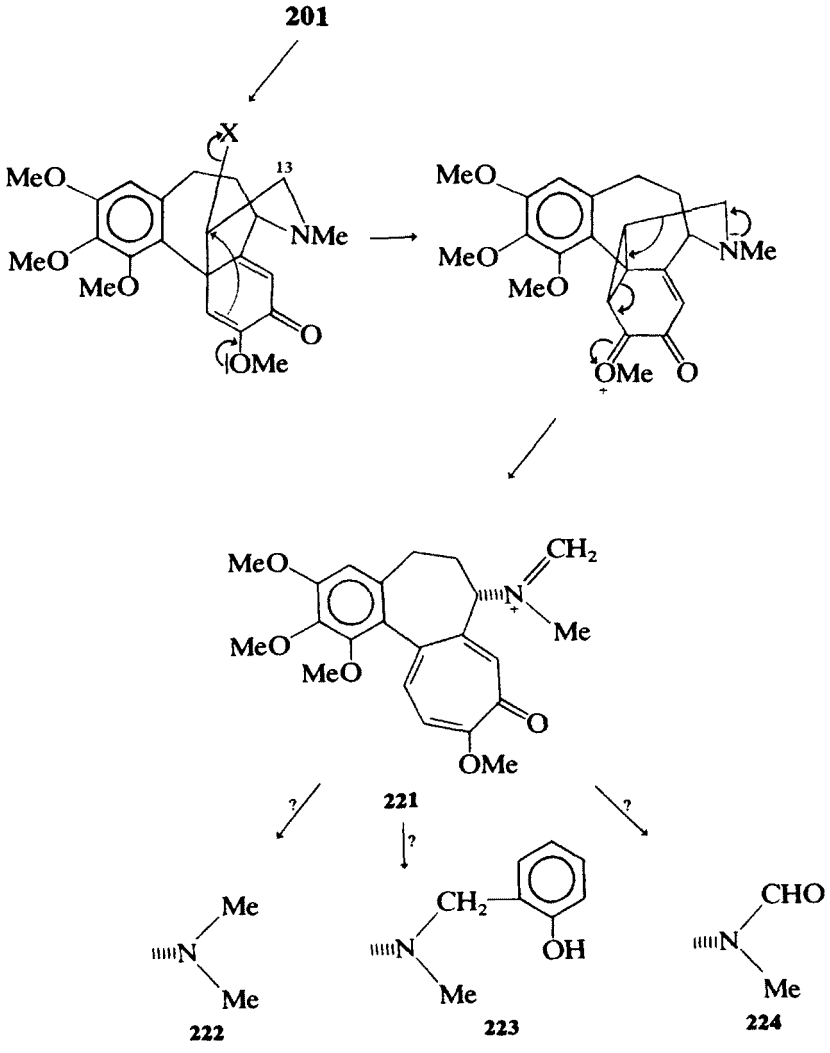
218



204, R = Me
219, R = CHO
220, R = H
198, R = $COCH_3$

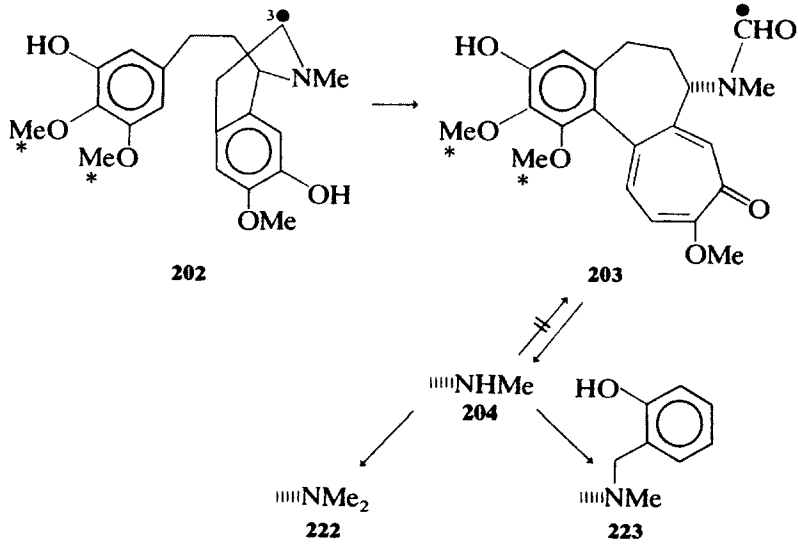
exception the late stages of colchicine biosynthesis are not significantly reversible.

Since C-13 of *O*-methylandrocymbine (**201**) is lost during its bioconversion into demecolcine (**204**), a search was made for any tropolone alkaloids that might retain C-13 and thereby permit a study of the mechanism of tropolone ring formation. *N*-methyldemecolcine (**222**), speciosine (**223**), and *N*-formyldemecolcine (**224**) are all naturally occurring alkaloids that might be biosynthesized through the hypothetical intermediate (**221**) as shown in Scheme 34. Each compound was found[114] to be tritium labeled when



Scheme 34. Biosynthesis of *N*-demethylcolcine, speciosine, and *N*-formyldemecolcine.

biosynthesized from [3-^{14}C,3′,4′-*O*-*methyl*-^{3}H]autumnaline (**202**), but only *N*-formyldemecolcine (**203**) had an unaltered $^{3}H:^{14}C$ ratio. It seems, therefore, that *N*-methyldemecolcine (**222**) and speciosine (**223**) are biosynthesized largely by alkylation of demecolcine (**204**), this has been confirmed[114] by feeding experiments with labeled demecolcine. In contrast, demecolcine was *not* incorporated into *N*-formyldemecolcine (**203**).



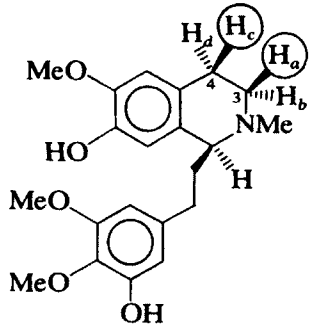
Clearly, *N*-formyldemecolcine (**203**) is a precursor of demecolcine (**204**) that retains all the carbon atoms of *O*-methylandrocymbine (**201**), thus affording an excellent and unique opportunity to study the changes in the oxidation level that occur at C-3 of autumnaline (**202**) during tropolone alkaloid biosynthesis.

(g) *Mechanism of Ring Expansion—Stereochemical Studies*

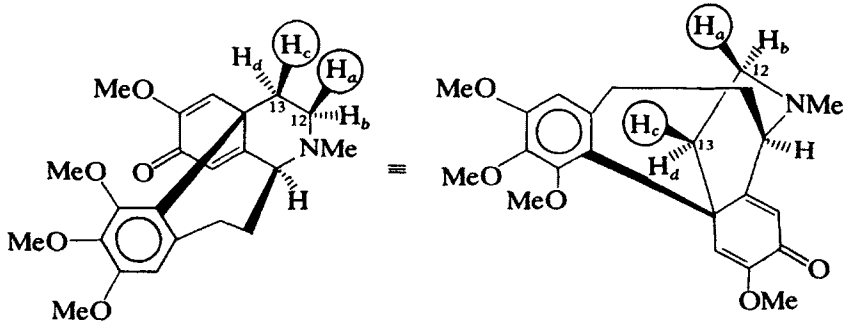
The most fascinating problem in colchicine biosynthesis is the mechanism of the transformation of *O*-methylandrocymbine (**201**) to *N*-formyldemecolcine (**203**). No intermediates have been identified—despite a search for bridge-functionalized derivatives of **201**—but stereochemical studies of the changes in oxidation level at C-12 and C-13 of *O*-methylandrocymbine (**201**) have allowed clear mechanistic proposals to be made for this key transformation.

(3*R*)-[3-^{3}H,3-^{14}C]Autumnaline (**202**) was incorporated[120] by *C. autumnale* into *N*-formyldemecolcine (**203**) without alteration of the $^{3}H:^{14}C$ ratio. In contrast, the (3*S*)-enantiomer lost virtually all of its tritium en route to (**203**). Clearly, the (3-*pro*-*S*)-hydrogen (H_b) is removed in a highly stereospecific manner.

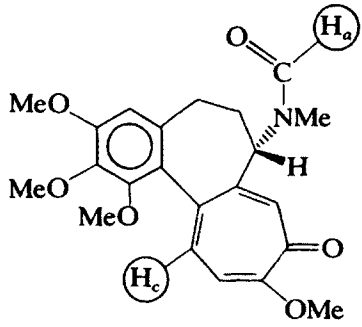
(4*R*)-[4-^{3}H,9-^{14}C]Autumnaline (**202**) was incorporated[120] into colchine (**198**) with approximately 75% retention of tritium relative to the skeletal ^{14}C label. Under the same conditions the (4*S*)-enantiomer lost virtually all its tritium. This result shows that the (4-*pro*-*S*)-hydrogen (H_d) is specifically removed but that H_c also suffers some incidental loss, probably by chemical exchange with the medium.



202



201 **201**



203

Scheme 35. Stereospecificity in biosynthesis of N-formyldemecolcine from autumnaline.

It seems highly likely that these stereospecific reactions occur during oxidative attack at C-13 and C-12 of the androcymbine skeleton **201** *prior to* fragmentation of the C-12–C-13 band. (Scheme 35). The stereochemical results are consistent with either hydroxylation with retention of configuration[121] at both C-13 and C-12 leading to the diol **224** or cis dehydrogenation to the enamine **225**. It is noteworthy that attack in both cases is from the least-hindered side of the dienone. The intermediate **224** is suitably activated for ring expansion and fragmentation leading to *N*-formyldemecolcine (**203**) through **226**.

An attractive mechanism can also be written for the conversion of the enamine **225** into *N*-formyldemecolcine (**203**) through the intermediates **227** and **228**. The final oxidative step might require the biological hydride receptor NAD^+ as a cofactor. Both pathways (Scheme 36) deserve further consideration, but that involving the enamine **225** has the merit of allowing a rationale for the partial loss of H_c by chemical exchange with the medium through enamine–iminium tautomerism.

The investigation of colchicine biosynthesis has been an exciting one, with many surprises as nature's beautiful route was gradually revealed. Even now some mysteries remain, especially concerning the ring expansion, and *in vitro* analogies for this process have yet to be discovered.

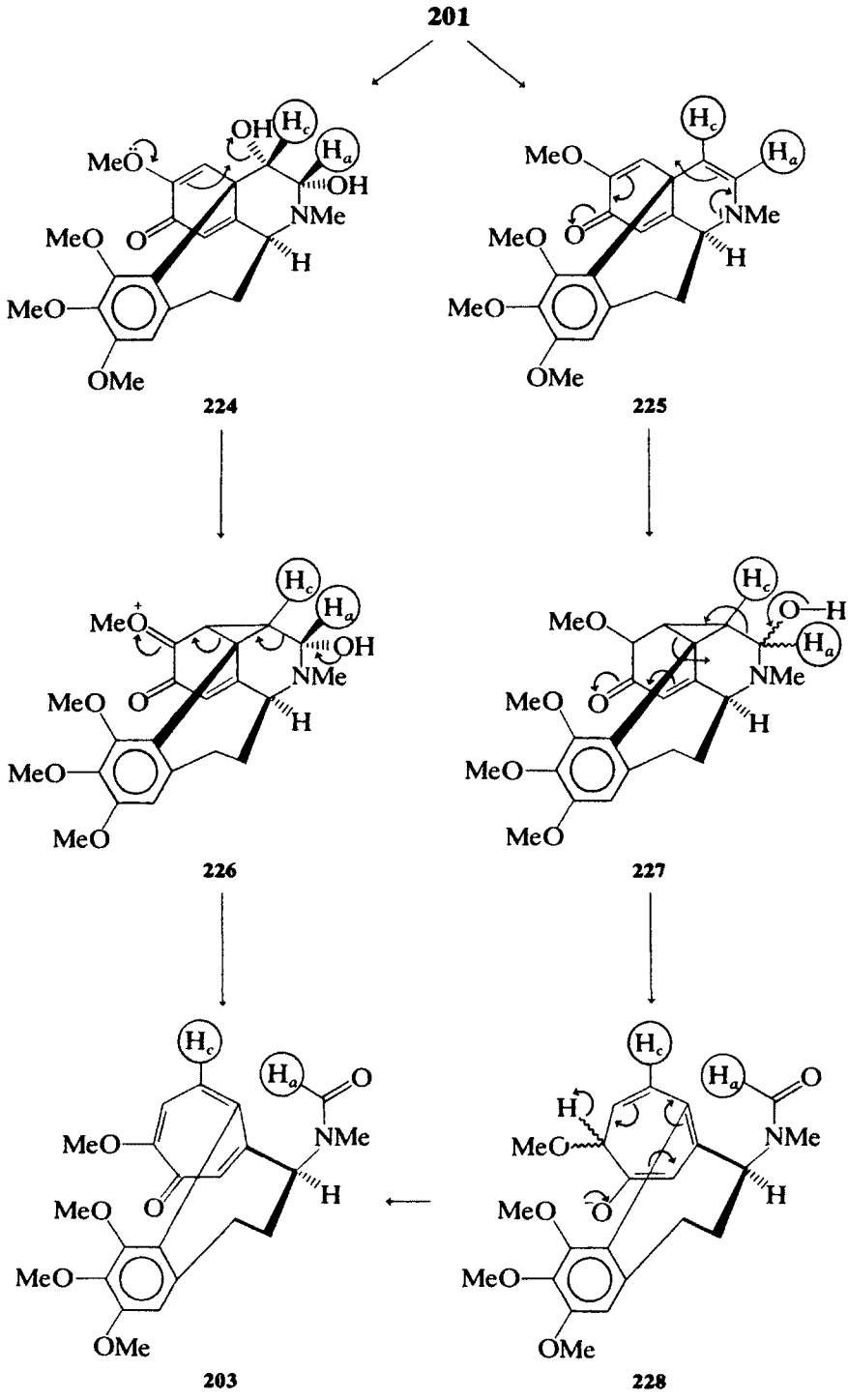
B. *C*-Homoaporphines

Shortly after the discovery of the first phenethylisoquinoline alkaloids androcymbine (**200**) and melanthiodine (**211**) and the recognition that colchicine (**198**) is an extensively modified 1-phenethylisoquinoline, several other structural types were discovered. In particular, the C-homoaporphines floramultine (**229**), multifloramine (**230**), and kreysigine (**231**) were found[122] alongside colchicine (**198**) in *Kreysigia multiflora*. This plant, like *A. melanthioides* and *Colchicum*, belongs to the *Liliaceae*.

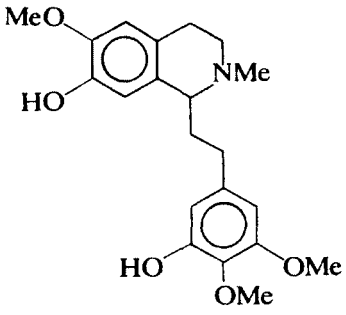
Biosynthetic studies using *K. multiflora* have now shown[123] that [3-^{14}C]autumnaline (**202**) is efficiently and specifically incorporated into the *C*-homoaporphine alkaloids at least 100 times better than the isomeric isoquinoline **232**. The *C*-homoaporphines seem, therefore, to be biosynthesized by direct oxidative phenol coupling rather than through a dienone intermediate such as **233**. It is interesting, however, that small amounts of the related dienone alkaloid kreysiginone (**234**) are present in *K. multiflora*.

C. Homoerythrina Alkaloids

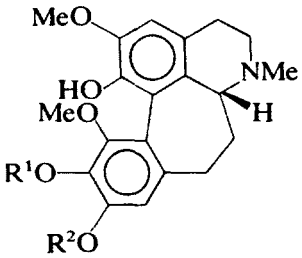
A series of homoerythrina alkaloids has been isolated[124] from the Australian tropical plant *Schelhammera pedunculata* (Liliaceae). Preliminary biosynthetic experiments have been carried out[125] and [2-^{14}C]tyrosine (**4**)



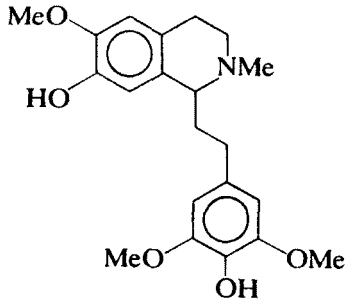
Scheme 36. Suggested pathway for biosynthesis of *N*-formyldemecolcine from *O*-methylandrocymbine.



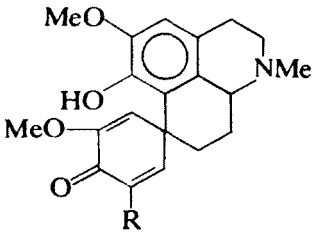
202



229, $R^1 = R^2 = Me$
230, $R^1 = Me$; $R^2 = H$
231, $R^1 = H$; $R^2 = Me$



232

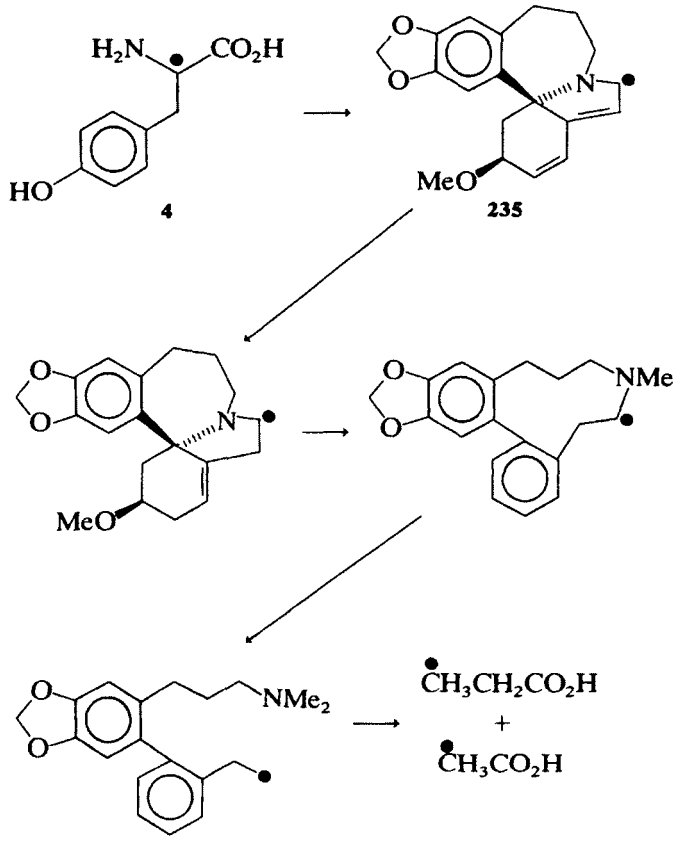


233, R = OMe
234, R = H

was specifically incorporated into the C_6–C_2 unit of schelhammeridine (**235**), as shown by the degradation in Scheme 37. Incorporations of [2-^{14}C]phenylalanine (**10**), [2-^{14}C]cinnamic acid (**205**), and [1-^{14}C]dopamine (**1**) were significant but too low to permit location of the radioactivity by degradation. However, the results suggest that the C_6–C_3 unit is derived from phenylalanine, and it seems highly probable that the *Schelhammera* alkaloids are biosynthesized from a 1-phenethylisoquinoline essentially as in Scheme 38, in complete analogy with their "junior" cousins in *Erythrina* plants [Section VII.B(c)(ii)]. Syntheses of all the key hypothetical intermediates have been reported.[126–128]

IX. SYNTHESIS OF LABELED ISOQUINOLINE PRECURSORS

Little mention was made in earlier sections of the synthesis of the labeled precursors used to trace the various biosynthetic pathways. The methods are, in fact, quite general and may be exemplified by considering the synthesis of a variety of labeled samples of autumnaline **202**.



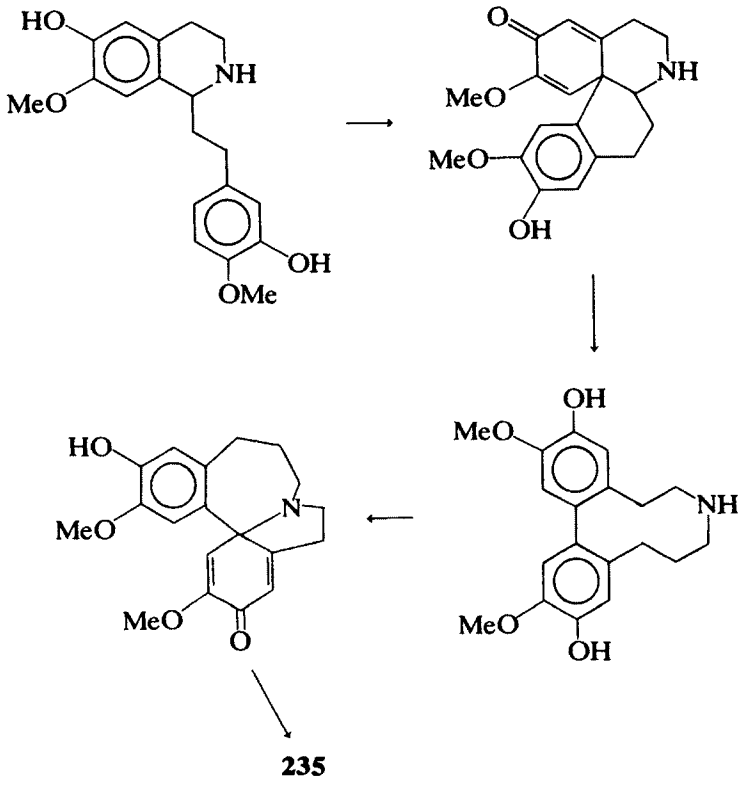
Scheme 37. Degradation of schelhammeridine.

A. Radioinactive Autumnaline

Radioinactive autumnaline (**202**) was prepared by the route outlined in Scheme 39. The phenethylamine **236** and the phenylpropionic acid **237** were condensed to form the amide **238**, and Bischler–Napieralski cyclization gave the 3,4-dihydroisoquinoline **239**. Methylation followed by borohydride reduction and hydrogenolysis gave (*R,S*)-autumnaline (**202**).[111] The route is a standard one for 1-benzyl and 1-phenethylisoquinolines.

B. [Aryl-^{3}H]Autumnaline

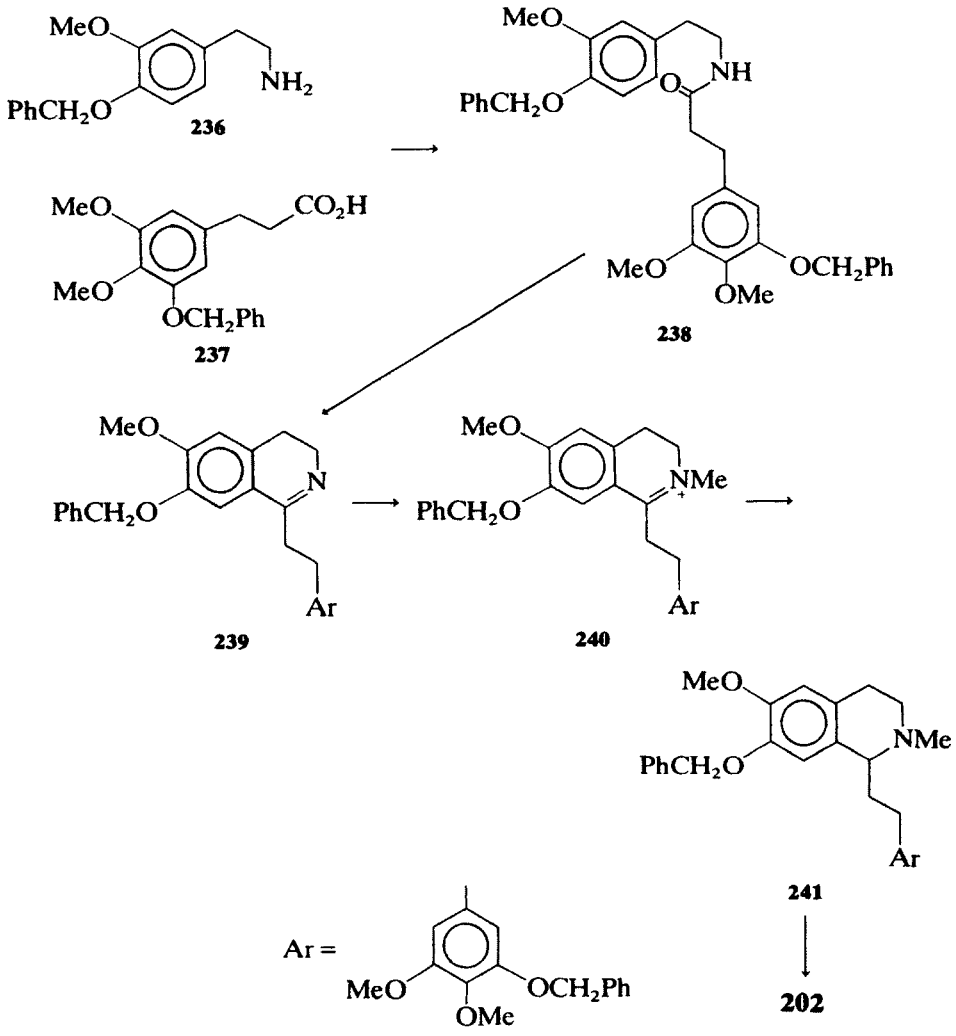
A solution of autumnaline (free base) in dry dimethylformamide containing one drop of tritiated water was heated[111] in a sealed tube for 72 hr at



Scheme 38. Suggested pathway for biosynthesis of schelhammeridine from a 1-phenethyl isoquinoline.

100°C. Under these conditions it has been shown[129] that the aryl hydrogens ortho and para to the free phenolic hydroxyl groups are exchanged to an approximately equal extent. Of course, the hydroxylic protons also become tritiated, but they exchange so rapidly in a hydroxylic solvent that the unwanted tritium can be removed by repeatedly dissolving the isolated autumnaline in methanol and evaporating to dryness. The specific radioactivity of the autumnaline depends on that of the tritiated water used, and high levels can be achieved.

The method is a general one for all phenolic compounds that will survive these reaction conditions. It is probably the simplest and cheapest way of preparing a labeled precursor and is most useful when a compound has been isolated from a plant but not yet synthesized. Although [*aryl*-^{3}H] compounds may be used for a preliminary study of a biosynthetic pathway, it may be unwise to place too much significance on a low incorporation since it is conceivable that tritium might be released by exchange *in vivo* and then incorporated into a variety of plant products in a nonspecific way.



Scheme 39. Synthesis of autumnaline.

C. [1-^{3}H]Autumnaline

Reduction of the salt **240** with sodium borotritiide in dry dimethylsulfoxide introduced[130] a tritium label specifically at C-1. The method is a general one[95] for the preparation of [1-^{3}H]tetrahydroisoquinolines.

To achieve the highest possible *radiochemical* yield, such reactions are best run in two stages. Initially, an *excess* of the iminium salt is used, and the reaction is allowed to proceed for a day or more so that as much borotritiide

as possible is consumed. Because of the kinetic isotope effect, this reaction will be much slower than any trial that has been run with normal borohydride. Finally, radioinactive borohydride is added to quickly complete the reaction.

D. [*N*-Methyl-^{14}C]Autumnaline

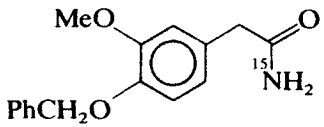
Methylation of the imine **239** with [^{14}C]methyl iodide served[130] to introduce an *N*-methyl-^{14}C label, and again the method is a general one[94] for *N*-methyl tetrahydroisoquinolines. To achieve high radiochemical yields, the labeled methyl iodide is transferred under high vacuum in a sealed system. The reaction is allowed to proceed with excess imine in a sealed tube for a long period before it is completed by adding excess radioinactive methyl iodide.

E. Autumnaline from Labeled Building Blocks

The following samples of autumnaline were prepared from the appropriately labeled building block **236** or **237** as in Scheme 39.

(a) *From Labeled Phenethylamines*

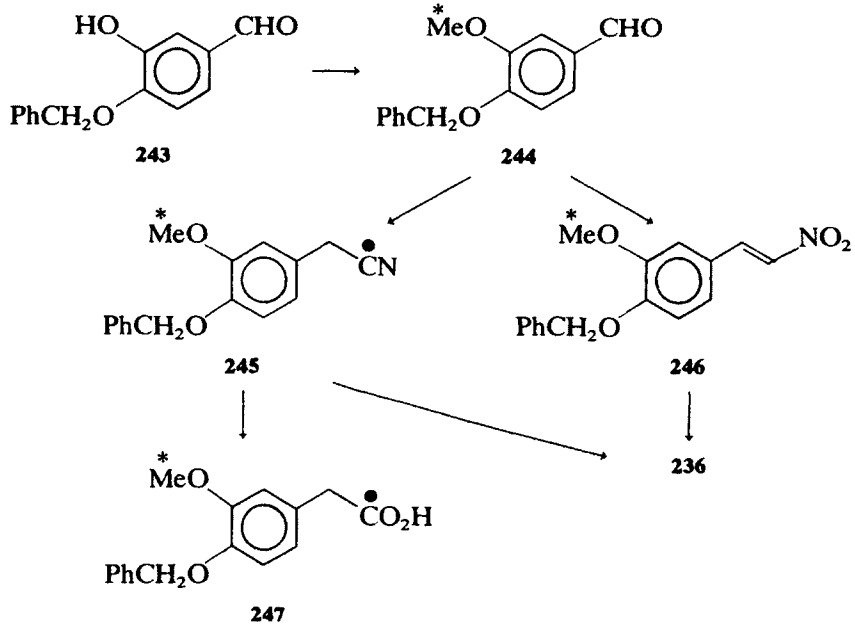
(i) [^{15}N]Autumnaline. The [^{15}N]amide **242** was prepared[131] from [^{15}N]ammonia and the appropriate acid chloride, and subsequent reduction afforded the [^{15}N]phenethylamine **236**.



242

(ii) [6-*O*-*Methyl*-^{3}H]Autumnaline. A solution of the phenolic aldehyde **243** in dry tetrahydrofuran containing one drop of tritiated water was treated with excess ethereal diazomethane, and the reaction[131] was allowed to proceed to completion at 5°C. The resultant tritium-labeled aldehyde **244** was converted to the [3-*O*-*methyl*-^{3}H]phenethylamine **236** either through the nitrile **245** or by way of the nitrostyrene **246** (Scheme 40).

(iii) [3-^{14}C]Autumnaline. Potassium [^{14}C]cyanide was converted[31] into the labeled nitrile **245** by using the appropriate benzylic halide, and reduction afforded the [1-^{14}C]phenethylamine **236**. Hydrolysis of the nitrile **245** provides phenylacetic acid **247** suitable for the preparation of [1-^{14}C]1-benzylisoquinolines.



Scheme 40. Synthesis of labeled β-phenethylamine.

(b) *Labeled Phenylpropionic Acids* (*237*)

(i) [3′,4′-*O*,*O*-*Dimethyl*-^{3}H]Autumnaline. The catechol aldehyde **248** was methylated[130] with diazomethane-tritiated water and the product **249** converted by a standard route[111] (Scheme 41) into the corresponding phenyl propionic acid **237**.

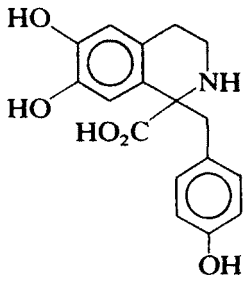
(ii) [9-^{14}C]Autumnaline. Knoevenagel condensation[111] of the aldehyde **249** with [2-^{14}C]malonic acid gave the required [2-^{14}C]cinnamic acid **252**. Catalytic hydrogenation then gave the corresponding phenylpropionic acid **237**.

(iii) [1-^{13}C]Autumnaline. The labeled nitrile **251** prepared[113] from potassium [^{13}C]cyanide and the appropriate mesylate, on hydrolysis afforded the required [1-^{13}C]phenylpropionic acid **237**.

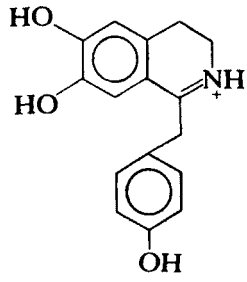
F. Stereospecifically Tritiated Isoquinolines

Stereospecific tritium labels have been introduced at C-1 and C-2 of several phenethylamines, and these have been used[120] to prepare isoquinolines stereospecifically labeled at C-3 and C-4. The available methods have been recently reviewed elsewhere.[132]

V. Coclaurine (**111**) is biosynthesized[135] by *Anona reticulata* from dopa (isoquinoline portion only) and tyrosine (both aromatic rings) by way of the 1-carboxylic acid (**255**) and the imine (**256**) (cf. biosynthesis of norlaudanosoline, Section V.A).

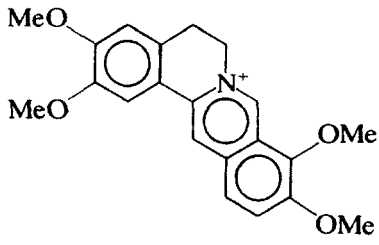


255



256

VI.E. Palmitine (**257**) was incorporated more effectively than tetrahydropalmitine (**258**) into corydaline (**86**) in *Corydalis solida*. It is assumed that reduction *in vivo* yields the key intermediate **79**.



257

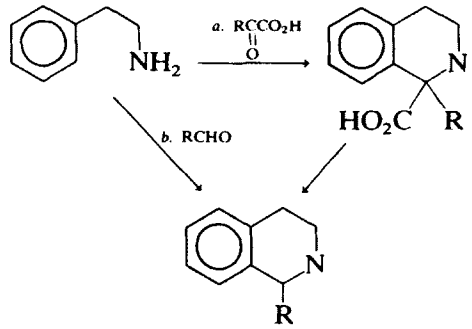
258, tetrahydro derivative

VI.F. A report[137] that [N-$^{13}CH_3$]protopine (**74**) is "incorporated" into chelidonine (**76**) and sanguinarine (**97**) emphasizes the need to demonstrate *specificity* of incorporation, since it seems to the reviewer highly probable that the labeling arises *indirectly* from the C_1-pool after metabolic degradation of the precursor.

VII.A(b). Biosynthetic studies have now been reported for several bisbenzylisoquinoline alkaloids *viz.* cocsulin,[138] cocsulinin,[139] oxyacanthine,[140] and tetrandrine[141] in *Cocculus laurifolius* and tiliacorine[142] in *Tiliacora racemosa*.

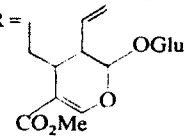
VII.B(c)(ii). In *Cocculus laurifolius* isococculidine (**259**) is derived[143] from norprotosinomenine (**60**) probably through intermediates (**260**) and (**261**). Minor metabolic changes then produce cocculidine and cocculine.[144]

VII.B(d). Isocorydine (**262**) is another aporphine that is derived by direct coupling (ortho–ortho) of reticuline: further, (+) norreticuline is incorporated 90 times better than the (−) enantiomer, in *Anona squamosa*.[145]



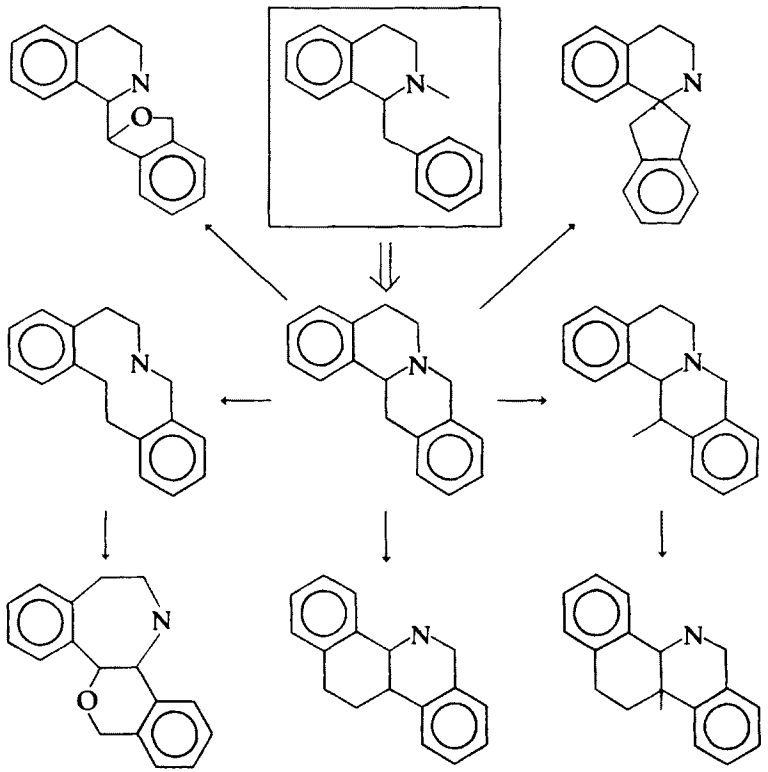
Path *a*: R = H,Me,$ArCH_2$

Path *b*: R =

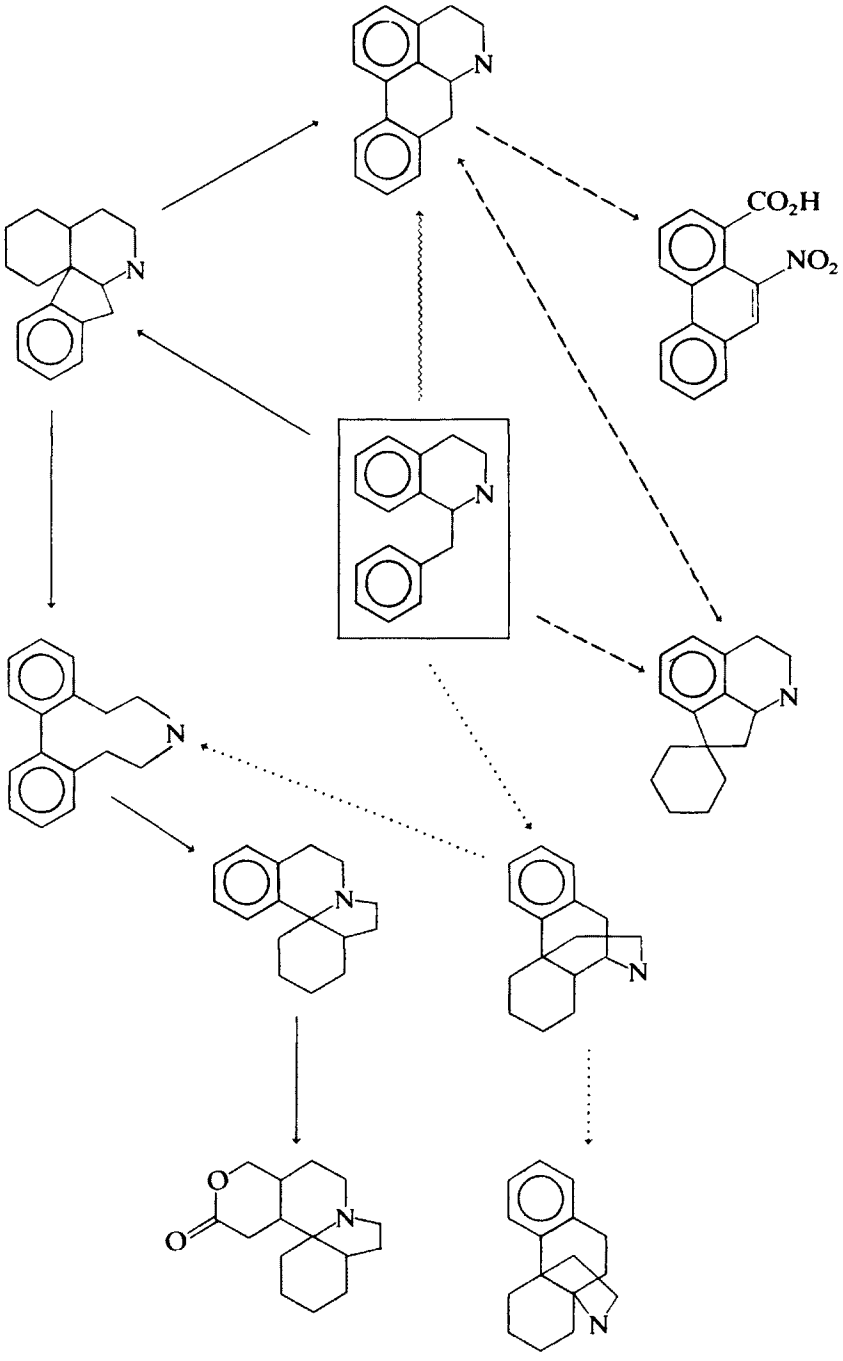


Path *b* is likely for: R = *i*-$PrCH_2$, Ar, $ArCH_2CH_2$

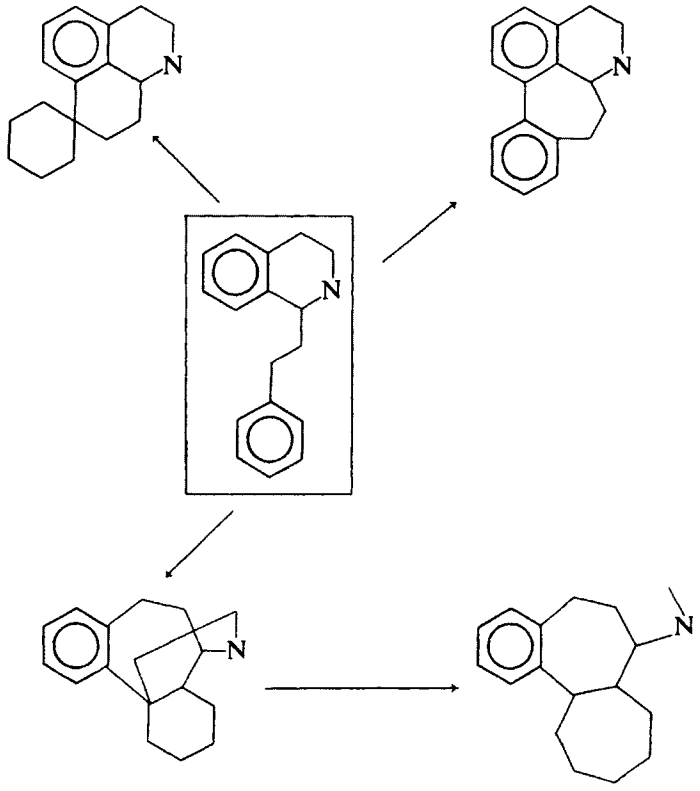
Scheme 42. Biosynthetic origin of parent tetrahydroisoquinolines.



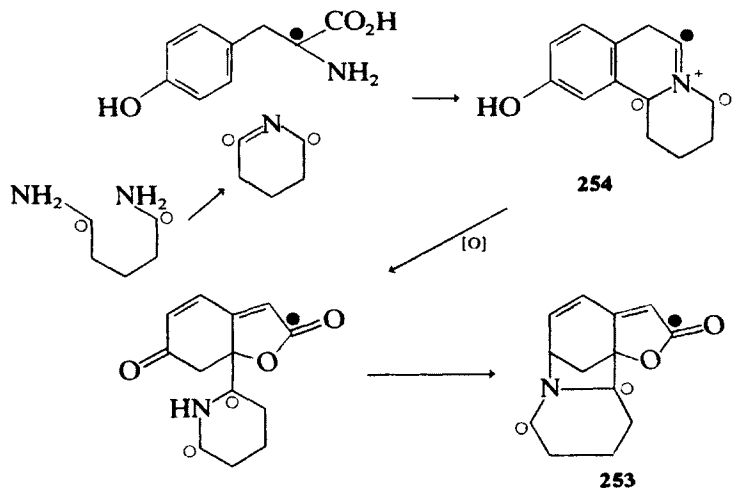
Scheme 43. 1-Benzylisoquinoline alkaloids having a "berberine bridge."



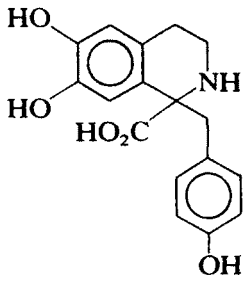
Scheme 44. 1-Benzylisoquinoline alkaloids through oxidative phenol coupling.



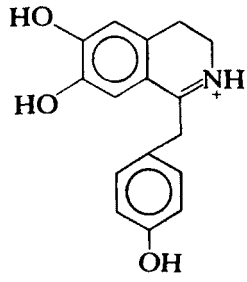
Scheme 45. Modified 1-phenethylisoquinoline alkaloids.



V. Coclaurine (**111**) is biosynthesized[135] by *Anona reticulata* from dopa (isoquinoline portion only) and tyrosine (both aromatic rings) by way of the 1-carboxylic acid (**255**) and the imine (**256**) (cf. biosynthesis of norlaudanosoline, Section V.A).

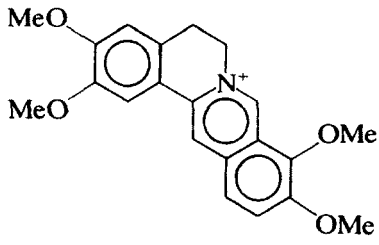


255



256

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257

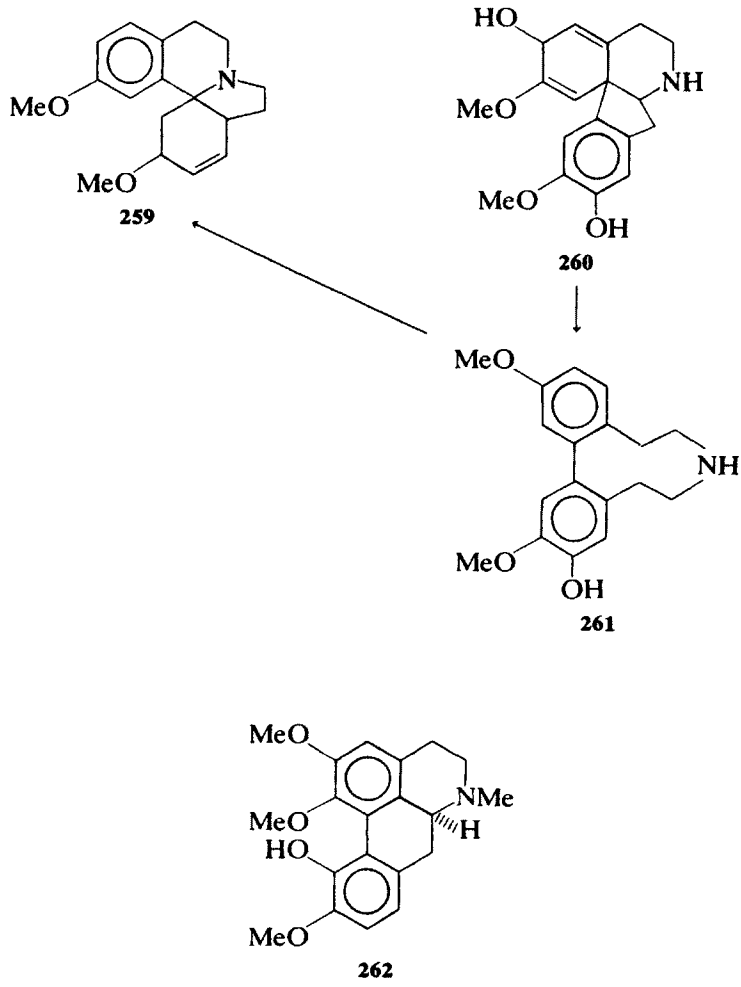
258, tetrahydro derivative

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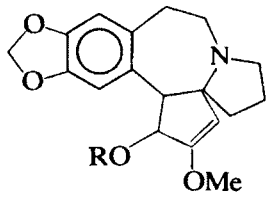
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VII.B(e)(i). The *O*-demethylation step in the conversion of thebaine (**166**) into codeinone (**167**) proceeds by *O*-alkyl cleavage, since ^{18}O from [G-^{14}C,6-^{18}O]thebaine is retained[146] in the final products codeine and morphine. Since a hydrolytic cleavage of the dienolether (**166**) should result in loss of ^{18}O the finding suggests that *O*-demethylation is achieved oxidatively.[146] New results relevant to the role of 1,2-dehydroreticuline (**171**) in morphine biosynthesis have also been reported.[142]

VII.B(f)(ii). The biosynthesis of sebiferine (O-methylflavinantine) has been studied[148] in *Cocculus laurifolius.*

VIII.D. Preliminary work[149] on the biosynthesis of cephalotaxine (**263**) in *Cephalotaxus harringtonia* is consistent with the view that this interesting alkaloid is a modified 1-phenethylisoquinoline.



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XII. REFERENCES AND NOTES

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CHAPTER IV

Quaternary Isoquinolinium Salts

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I. INTRODUCTION TO ISOQUINOLINIUM QUATERNARY COMPOUNDS AND THEIR NATURAL OCCURRENCE

The dedication of an entire chapter of this work to the chemistry of quaternary isoquinolinium compounds could not be justified on the basis of the natural occurrence of such salts, which is rather infrequent, but rather by the interesting chemistry involved in the preparation and reactions of compounds of this type.

A. Introduction

This chapter is limited to the chemistry of quaternary isoquinolinium salts and related betaines and does not include 3,4-dihydro- or other hydrogenated quaternary salts of isoquinoline. An effort has been made to consider any publication indexed in *Chemical Abstracts* under *isoquinolinium* through Volume 82, with an occasional later reference to articles seen in the current literature. Patents and articles in less accessible journals have been examined only by way of abstracts. Access to literature prior to *Chemical Abstracts* has been largely via cross references in later articles, but an excellent account of earlier work, including the chemistry of 3,4-dihydroisoquinolinium salts, will be found in W. J. Gensler's chapter in Elderfield's work on heterocyclic compounds.[1] The review by E. N. Shaw of quaternary pyridinium salts[2] has been useful for comparison between the two heterocyclic systems.

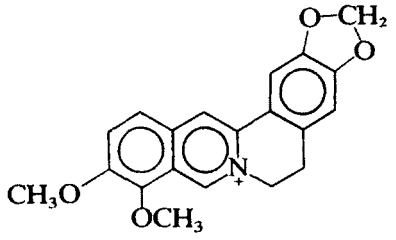
I am indebted to my wife, Dorothy, for carrying out the initial literature search, for proofreading, for drawing the structural formulas, and for some of the editing and typing.

B. Natural Occurrence

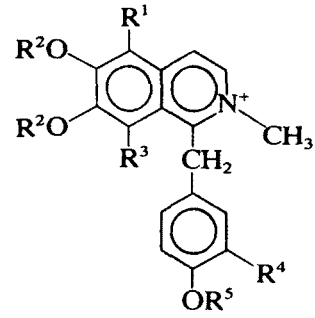
The berberines, as opposed to the tetrahydroberberines, could be classified as isoquinolinium salts. An example of such a salt is **1**, which is still anachronistically referred to as *berberine hydrochloride* despite the fact that it is a quaternary rather than a proton salt. Since the berberines are polycyclic systems, they are outside the scope of the present review and have been adequately reviewed elsewhere.[3]

Several simple isoquinolinium salts that all have a methyl group at position 2 have been found in nature. Most also have a benzyl group at position 1, as is the case with takatonine (**2**),[4,5] *N*-methylpalaudinium (**3**) chloride,[6] and eschalamidine (**4**).[7]

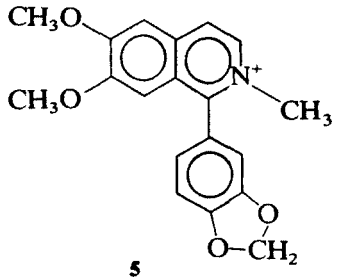
The quaternary salt **5** of the somewhat rarer 1-phenylisoquinolinium series has been isolated from *Cryptostylis erythroglossa*.[8]



1



2, $R^1 = OCH_3$; $R^2 = CH_3$; $R^3 = R^4 = H$; $R^5 = CH_3$
3, $R^1 = R^3 = H$; $R^2 = R^5 = CH_3$; $R^4 = OH$
4, $R^1 = R^3 = R^5 = H$; $R^2—R^2 = CH_2$; $R^4 = OCH_3$

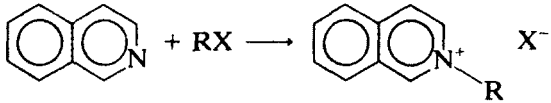


5

It seems likely that a deliberate search for quaternary salts (as opposed to bases) would reveal that their existence is more common than believed.

II. PREPARATION AND FORMATION OF ISOQUINOLINIUM SALTS—ANALYSIS AND PHYSICAL PROPERTIES

Whereas isoquinolinium salts **7** may be made from dihydroisoquinolines, from tetrahydroisoquinolines, and even from compounds not having the isoquinoline skeleton, the great majority are made by alkylation of isoquinoline (**6**) and its fully aromatic derivatives.



(1)

6 7

A. Preparation from Isoquinoline

The most important method for the *N*-alkylation of isoquinolines is by use of simple alkyl halides, although, as is shown later, a large variety of alternative methods have been described.

(a) *By Reaction with Alkyl Halides*

Direct quaternization of heterocyclic bases with alkyl halides (Eq. 1) is sometimes called the *Menschutkin reaction.* Menschutkin[9] investigated the relative rates of reaction of some common heterocyclic bases with methyl bromide at 100°C in benzene and found them to be 578 for pyridine, 96 for quinoline, and 645 for isoquinoline.

More recently,[10] it has been shown that the energy of activation for the formation in nitrobenzene solution of isoquinoline methiodide (13.54 kcal/mole) is significantly lower than that for quinoline (14.79 kcal/mole) and only slightly greater than that for pyridine (13.68 kcal/mole). The difference in energy of activation for the reaction with quinoline and isoquinoline has been explained[10] in terms of the greater steric strain in the activated complex leading to the formation of a quinolinium salt. This strain arises from the presence of a perihydrogen atom adjacent to the nitrogen in quinoline. Thus in quaternization reactions, isoquinoline resembles pyridine in reactivity more than it does quinoline. The most common alkylating agent for isoquinolines is methyl iodide and the methiodide is a standard derivative for comparison and analysis.

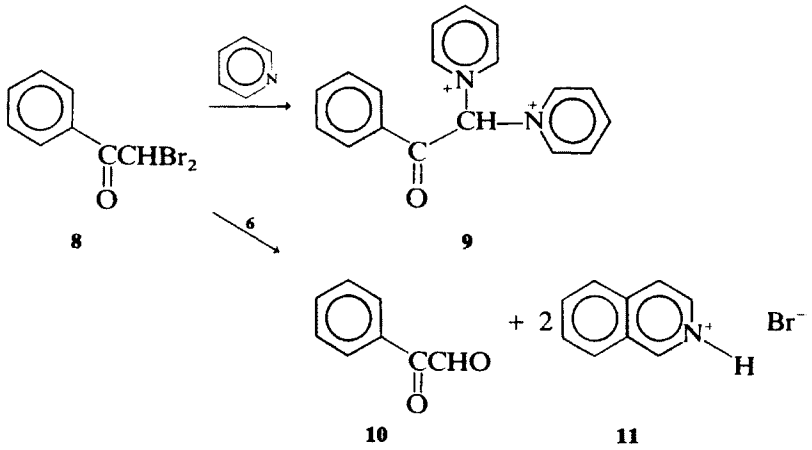
As Duffin[11] has pointed out in his review of quaternization, the relative reactivity of the halides is I > Br > Cl. Although there is little doubt that the secondary halides are less reactive in quaternization than the primary,[11] the reaction of an excess of isopropyl bromide with isoquinoline for 30 min at 100°C is reported[12] to afford a 95% yield of the expected quaternary salt. Secondary butyl iodide reacts almost entirely by elimination, thus affording isoquinolinium hydriodide.

In view of the failure of *tert*-butyl iodide to quaternize other bases,[11] it is not too surprising that no better results have been obtained with isoquinoline,[12,13] with elimination being observed.

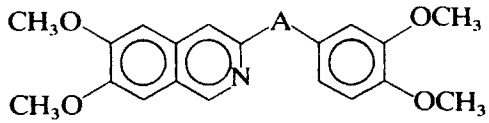
As pointed out by earlier reviewers of the quaternization reaction,[11,14] polar solvents increase the speed of reaction, but there is no direct correlation between reaction rate and the dielectric constant of the solvent.

A difference has been observed between the reaction of ω,ω-dibromoacetophenone (**8**) with pyridine and with isoquinoline. With pyridine, the expected diquaternary salt **9** is formed, whereas with isoquinoline, phenyl glyoxal (**10**) and the hydrobromide **11** are isolated.[15]

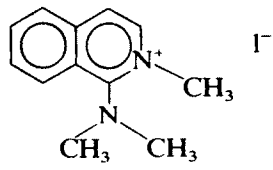
With primary alkyl halides, most isoquinoline derivatives undergo



quarternization, but an exception is 3-(3,4-dimethoxyphenyl)-6,7-dimethoxyisoquinoline (**12**), which was recovered unchanged after being refluxed for 3 hr with ethyl iodide.[16] It seems likely that the dimethoxyphenyl group lowers the reactivity of the system through steric interaction, since the somewhat more electron deficient 3-(3,4-dimethoxybenzoyl)-6,7-dimethoxyisoquinoline (**13**) is reported to react with (the albeit more reactive) methyl iodide to afford a quaternary salt in 78.5% yield.[17]



12, A = —
13, A = CO



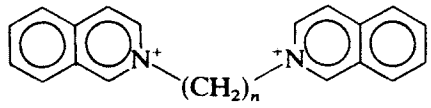
14

Just as 2-aminopyridine reacts with alkyl halides predominantly at the ring nitrogen,[18] 1-dimethylaminoisoquinoline reacts with methyl iodide to afford 1-dimethylamino-2-methylisoquinolinium iodide (**14**).[19]

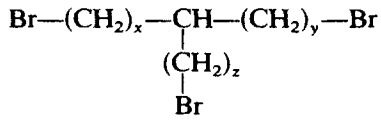
(b) *By Reaction with Alkyl Halides Bearing an Additional Functional Group*

Since chapters in a later volume in this series tabulate the salts of substituted isoquinolines, this section is limited to a brief overview of some selected quaternary salts bearing some type of functionality in the side chain. These are presented not as a complete record, but as an indication of some important types of structure available.

Many bisquaternary salts have been prepared by the reaction of dihalides with isoquinoline and its derivatives. The largest group (**15**) has been prepared[20–26] by use of α,ω-dihalides. With 1,2-bromopropane in which one halogen is primary and the other secondary, a bisquaternary salt was obtained,[24] whereas with 2,5-dibromohexane ($CH_3CHBrCH_2CH_2CHBrCH_3$), a monoquaternary salt was the principal product.[24] Tribromoalkanes of the general formula **16** have been used in the preparation of many trisquaternary salts.[27]

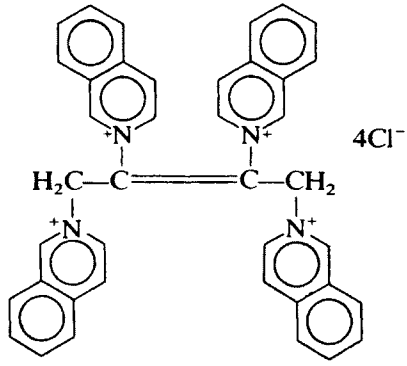


15, n = 1–40

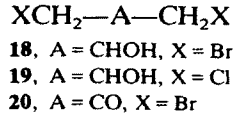


16

Perhaps the most complex polyhalide ever reacted with isoquinoline is 1,2,2,3,3,4-hexachlorobutane. This is reported[28] to undergo elimination as well as substitution affording **17**. 1,3-Dibromo-2-propanol (**18**) and 1,3-dibromopropanone (**20**) were found[24,29,30] to give quaternary salts with isoquinoline, whereas 1,3-dichloro-2-propanol (**19**) was reported[31] to give a monoquaternary salt.



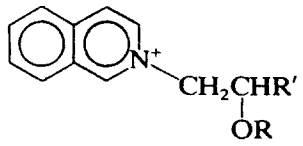
17



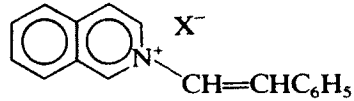
18, A = CHOH, X = Br
19, A = CHOH, X = Cl
20, A = CO, X = Br

Useful intermediates **21** and **22** may be prepared by the reaction of ethylene bromohydrin[32–34] or its esters[33–35] with isoquinoline. The product obtained (**23**)[36–38] when styrene bromohydrin is used as the halide may be dehydrated to 2-styrylisoquinolinium salts **25** by heating with benzoyl chloride[37] (Section VII.F). 3-Chloropropane-1,2-diol reacts with isoquinoline to afford the expected salt **24**.

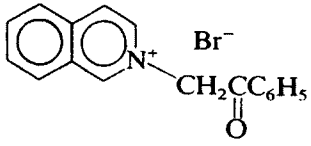
Of the isoquinolinium salts derived from halo ketones, the most important are 2-phenacylisoquinolinium (**26**) and its congeners.[39,40] These can be converted with variable difficulty to the betaines **27** to be discussed later (Section VII.A).



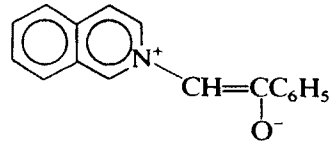
21, R = R′ = H
22, R = COR^2; R′ = H
23, R = H; R′ = C_6H_5
24, R = H; R′ = CH_2OH



25



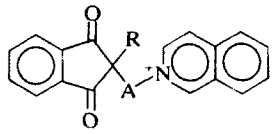
26



27

In the pursuit of biological activity and spectroscopic information many isoquinolinium salts (**28–35**) that have an indan-1,3-dione nucleus attached have been prepared. Table IV.1 lists types of such compounds but ignores substitution patterns.

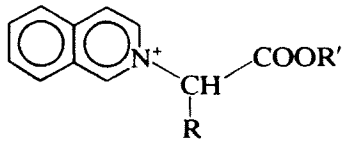
Table IV.1. INDAN-1,3-DIONE ISOQUINOLINIUM SALTS



Compound	R	A	Ref.
28	H	—	24
29	CH_3	—	41
30	C_6H_5	—	42, 43
31	C_6H_5	CH_2	44
32	C_6H_5	$(CH_2)_2$	45, 46
33	C_6H_5	CH_2COCH_2	47
34	C_6H_5	$NH(CH_2)_2$	48
35	C_6H_5	$NH(CH_2)_3$	49

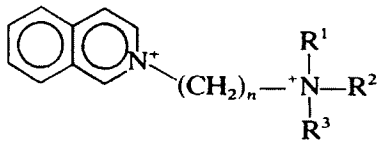
Several isoquinolinium salts bearing ester groups in the side chain are known. Ethyl bromoacetate forms the quaternary salt **36** directly,[50] and the corresponding menthyl and 1-bornyl esters **37** and **38** have been prepared.[51] The use of dimethyl bromomalonate affords an 89% yield of the diester **39**, actually isolated as the ylide.[52,53] With ethyl bromocyanoacetate, the cyanoester **40** was obtained,[54] recovered as the betaine.

Isoquinolinium salts (**41**) with a second quaternary ammonium group in the quaternary side chain have been prepared by reaction of the appropriate

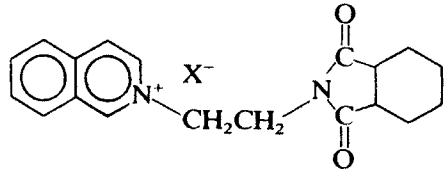


36, R = H; R′ = C_2H_5
37, R = H; R′ = menthyl
38, R = H; R′ = 1-bornyl
39, R = $COOCH_3$; R′ = CH_3
40, R = CN; R′ = C_2H_5

α-bromo-ω-trialkylammonium halide. If a side chain bearing a primary amino group is desired, it can be introduced by alkylation with an ω-phthalimidoalkyl halide followed by hydrolysis of the resulting quaternary salt **42**.[55]

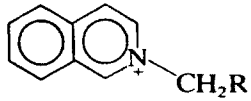


41, n = 3–6

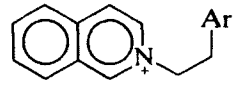


42

A logical extension to the investigation of *N*-benzylisoquinolinium salts **43**[38,56,57] was a study of salts **44** derived from halomethyl heterocycles. These heterocyclic nuclei include pyridine,[58,59] pyrimidine,[57] thiophene,[60] quinoline, and 1,2,4-benzothiadiazine-1,1-oxide.[61]



43, R = C_6H_5
44, R = Het



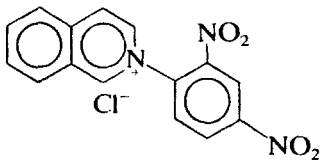
45, Ar = C_6H_5
46, Ar = 3-Indolyl

For certain cyclization reactions, to be discussed later (Sections IV.A and V.A), β-arylethylisoquinolinium salts have been the essential intermediates. Some of the β-phenylethyl derivatives **45**[39,62,63] have provided access to berberine derivatives, whereas the β-3-indolyl quaternary salts **46**[64–66] may be cyclized to structures related to the yohimbine and reserpine alkaloids and to alstoniline, an alkaloid of the alstonine type.

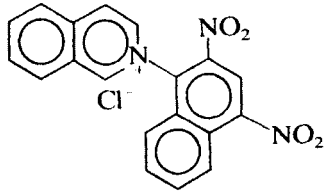
(c) *By Reaction of Aryl Halides*

Reaction with aromatic halides is limited to those that undergo nucleophilic aromatic substitution with ease. As an extension of his study with

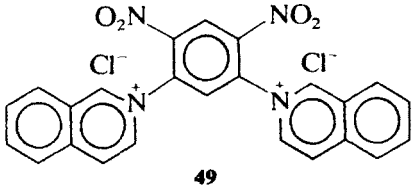
pyridine, Zincke[67] found that 2,4-dinitrochlorobenzene underwent reaction with isoquinoline in ether over a period of 2 to 3 months at room temperature. The reaction conditions selected reflect the observation[67] that the salt **47** is at least partially dissociated into its components in alcohol solution. It is claimed[68] that the reaction time can be shortened to 5 hr if the reactants are heated without solvent at 40°C (93% yield). Zincke and Krollpfeiffer[69] also reported that the structurally related 2,4-dinitro-1-chloronaphthalene forms the quaternary salt **48** with isoquinoline after heating for only 1 hr. The reaction of picryl chloride is similar, affording 2,4,5-trinitrophenylisoquinolinium chloride.[70,71] With isoquinoline, 1,3-dichloro-4,6-dinitrobenzene affords the bisquaternary salt **49**.[72]



47



48



49

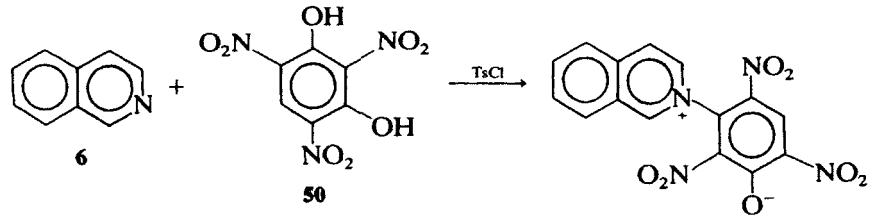
A mixture of isoquinoline, tosyl chloride, and 2,4,6-trinitroresorcinol (**50**) affords the betaine **51**. The function of the tosyl chloride is removal of a hydroxyl group from the trinitroresorcinol, but it is not clear whether there is an intermediate formation of a trinitrochlorophenol.

The apparent absence in the literature of *N*-aryl derivatives of the readily available 3-methylisoquinoline suggests that the presence of a group ortho to the nitrogen atom may prevent reaction as it does in the pyridine series.[73]

(d) *By Reaction of Other Halides*

On the basis of observations made in the pyridine[2] and quinoline[74,75] series, there seems little doubt that an acid chloride reacts with isoquinoline to form an acylium salt **52**. Such a salt (usually $R = C_6H_5$ or analog) is believed to be formed in the first step of the Reissert reaction[76] of isoquinoline. Typically, such salts are noncrystalline and hygroscopic, as well as quite reactive, which explains why there is sparse information about such salts in the isoquinolinium series.

Spectral evidence for the existence of the *N*-acetylisoquinolinium salt **52**



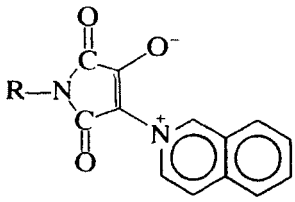
6 50 51



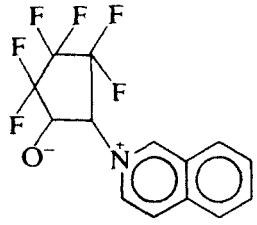
52 53

(R = CH_3, X = Br) has been published,[77] and by measuring the conductivity of isoquinoline in acetyl bromide solution, the existence of partly ionized complexes of the general formula **52** has been indicated.[77] As is discussed later (Section V.G), it has been demonstrated that acylium isoquinolinium salts formed *in situ* undergo nucleophilic attack by indoles.[78] Cyanogen bromide affords *N*-cyanoisoquinolinium bromide (**53**),[79] which is very reactive toward nucleophiles.

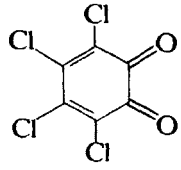
Quaternary salts have been prepared by the reaction of isoquinolines with activated vinyl chlorides. Usually these vinyl chlorides are reactive because they are vinylogous acid chlorides. *N*-Benzhydryl-1,2-dichloromaleimide affords a betaine (**54**) in 95% yield.[80] A similar betaine (**55**) was reported[81] from *N*-allyl-1,2-dichloromaleimide. As would be expected from reports concerning the lack of reactivity of alkyl fluorides in quaternization reaction,[82] 1-methoxy-2-chloro-3,3,4,4,5,5-hexafluorocyclopentane reacts only by replacement of chloride, thus affording **56** in 94% yield.[83] It has been reported[84] that the tetrachloro-*o*-benzoquinone (**57**) reacts with isoquinoline to produce a salt of unknown structure.



54, R = $(C_6H_5)_2CH$
55, R = $CH_2CH{=}CH_2$



56

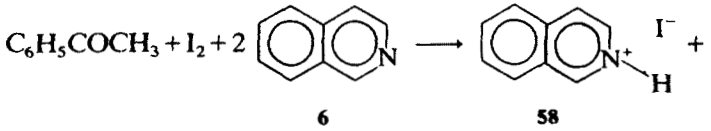


57

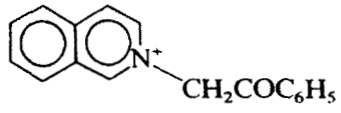
(e) *By King Reaction*

In illustrating the use of his new procedure, King[85] showed that acetophenone, in the presence of iodine and an excess of isoquinoline (**6**),

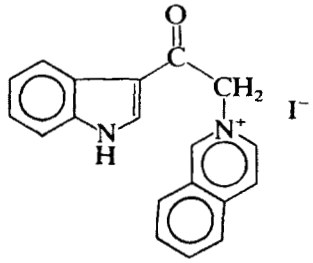
gave a 95% yield of 2-phenacylisoquinolinium iodide (**59**) (Eq. 2). Only half of the base is converted to a quaternary salt, but the part of the base that forms the hydriodide **58** can be recovered. Liljegren and Potts[86,87] have made use of this method to prepare the isoquinolinium **60** from 3-acetoindole in 94% yield.



6 **58**

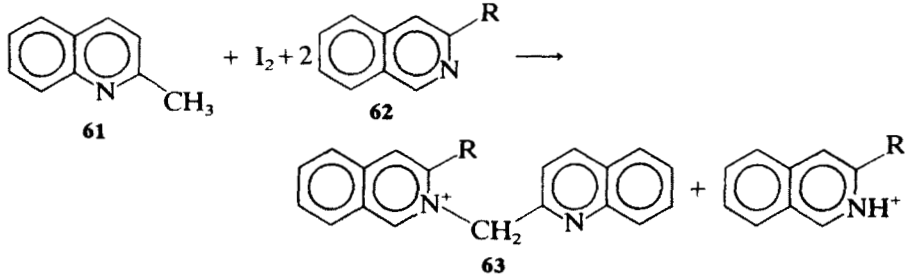


59 (2)



60

King and Abramo[88] showed that the methyl group participating in the iodination and quaternization sequence could be activated by positioning ortho or para to a heterocyclic nitrogen. For example, quinaldine (**61**) reacted with isoquinoline (**62**, R = H) in 39% yield, whereas with 3-methylisoquinoline (**62**, R = CH_3), it reacted in 81% yield, thus affording the salt **63** (R = CH_3).

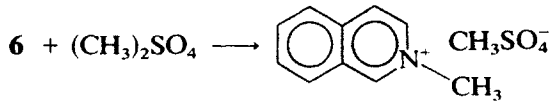


61 **62** **63**

(f) *By Reaction with Sulfur Derivatives*

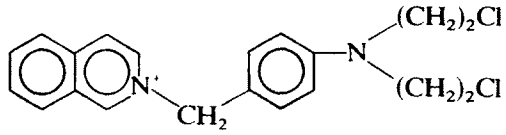
A cheaper methylating agent than methyl iodide, and one that can be used at moderately high temperatures without recourse to sealed tubes or

autoclaves, is dimethyl sulfate (eq. 3).[89] The use of other alkyl sulfates appears to be unimportant.

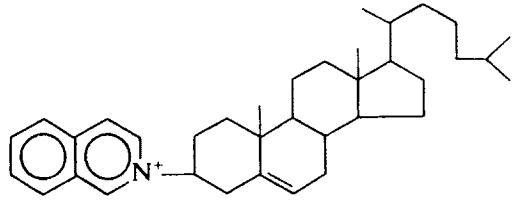


(3)

Tosylates are useful alkylating agents that need not be isolated. A mixture of the alcohol, tosyl chloride, and isoquinoline is allowed to react, producing the *N*-alkylated compound as the *p*-toluenesulfonate salt. In this way, 4-(*N*,*N*-bis-2-chloroethyl)benzyl alcohol was converted to **64**[90] and cholesterol converted to a *N*-3β-cholesteryl salt **65**.[91]

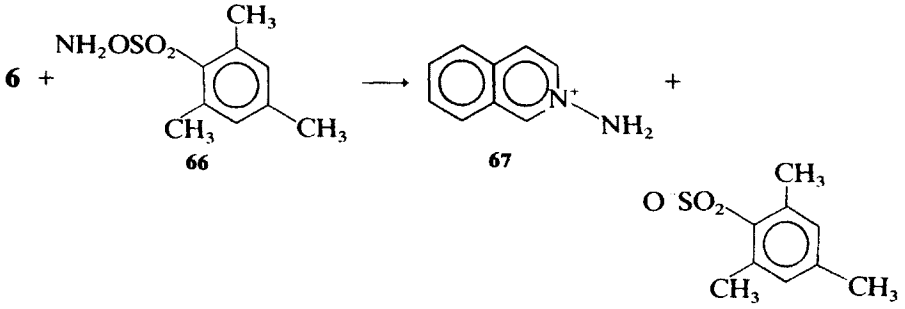


64



65

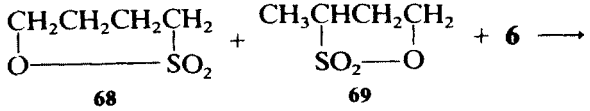
Tamura and co-workers[92] have shown that a 2-aminoisoquinolinium salt (**67**) can be made directly from the base by the action of *O*-(mesitylsulfonyl)hydroxylamine (**66**).



Sultones, which are internal esters of hydroxysulfonic acids, can also alkylate isoquinoline. Unfortunately, the example presented here[93] (Eq. 4) involved a mixture of sultones (**68** and **69**), and the product was probably a mixture of **70** and **71**.

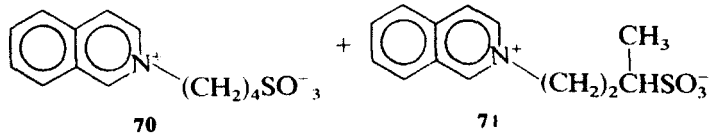
Nucleophilic displacement of an isothiocyanate ion from 2,4,6-

trinitrophenylisothiocyanate (**72**) by isoquinoline (**6**) has been reported (Eq. 5).[94]

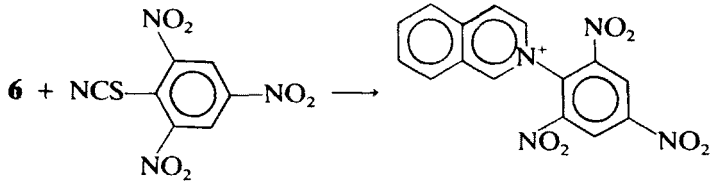


68 **69**

(4)



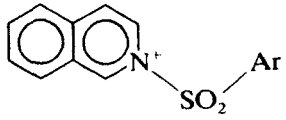
70 **71**



72

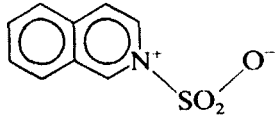
(5)

Although some would not wish to classify *N*-arylsulfonylisoquinolinium salts **73** as quaternary salts since all four linkages of nitrogen are not connected to carbon, they are as a class easily prepared in high yield, and they are more reactive than classical *N*-alkyl quaternary salts. They may be recrystallized, and their behavior can be interpreted in a manner analogous to that of typical quaternary isoquinolinium salts.[95–97]



73

The betaine **74** produced by the addition of sulfur trioxide to isoquinoline undergoes ring-opening reactions that exactly parallel those of the more conventional quaternary salts.[98] This is discussed further in Section V.A.

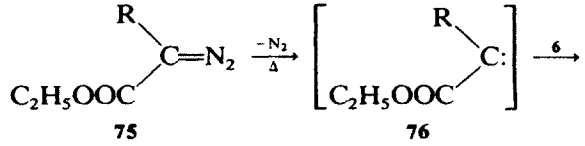


74

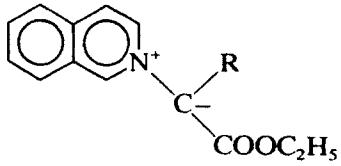
(g) *By Reaction with Diazo Compounds*

The reaction of isoquinoline (**6**) with aliphatic diazo compounds through the free base or through the hydriodide leads to similar products by

pathways that may be quite different. With the free base, the betaine is obtained through an intermediate carbene **76** (Eq. 6). When the ester was ethyl diazoacetate (**75**, R = H), the yields of the betaine were better than when the more thermally stable diazomalonate (**75**, R = $COOC_2H_5$) was used.[99]

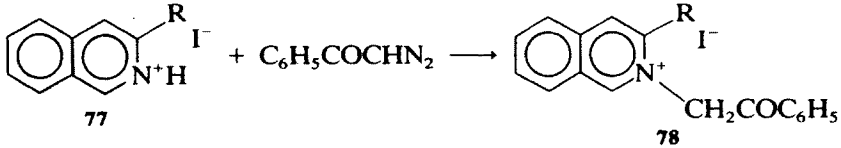


75 **76**



(6)

When the hydriodide of isoquinoline (**77**, R = H) or of 3-methylisoquinoline (**77**, R = CH_3) was allowed to react with diazoacetophenone (Eq. 7), the yields of the *N*-phenacylisoquinolinium salt **78** were 68% or 60%, respectively.[100] The possibility that phenacyl iodide was an intermediate was eliminated by the demonstration that the yield in such reactions did not decline when anions of low nucleophilicity such as perchlorate were used. It has also been shown[101] that isoquinolinium fluoroborate reacts with diazomethane to produce a 74% yield of the 2-methylisoquinolinium salt.



77 **78**

(7)

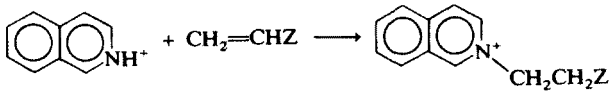
(h) *By Addition to an Alkene*

An important and interesting way to produce isoquinolinium quaternary satls that have an electron-withdrawing group at the β position of the *N*-alkyl side chain is by addition of the protonated base to a suitable alkene (Table IV.2).

The need for electron deficiency in the alkene suggests that the base, rather than the protonated base, actually reacts with the alkene, and the role of the protonated base may be to protonate the betaine first formed.

One of the earliest examples of this type of reaction in the isoquinolinium series was with maleic and fumaric acids that were found to yield the betaine

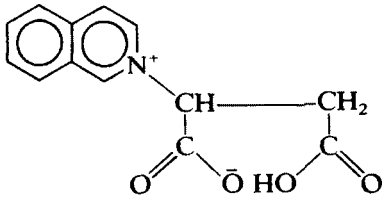
TABLE IV.2. ADDITION OF ISOQUINOLINIUM ION TO POLAR ALKENES



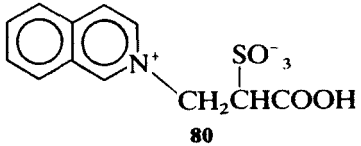
$Z^{a,b}$	Yield (%)	Ref.
COOH	79	102
$CONH_2$	85	103, 104
SO_2Cl	78	105
SO_2OR	51–67	104, 106
$4\text{-}C_2H_5\text{-}2\text{-pyridyl}$	[c]	107

[a] In this reaction the base is protonated by the organic acid.
[b] The product was recovered as a betaine.
[c] Not stated.

79.[108] With sulfomaleic anhydride, the addition reaction is accompanied by decarboxylation, thus affording the betaine **80**.[109]

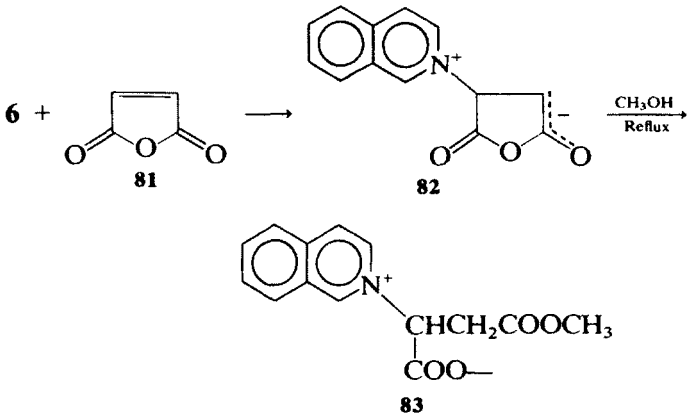


79



80

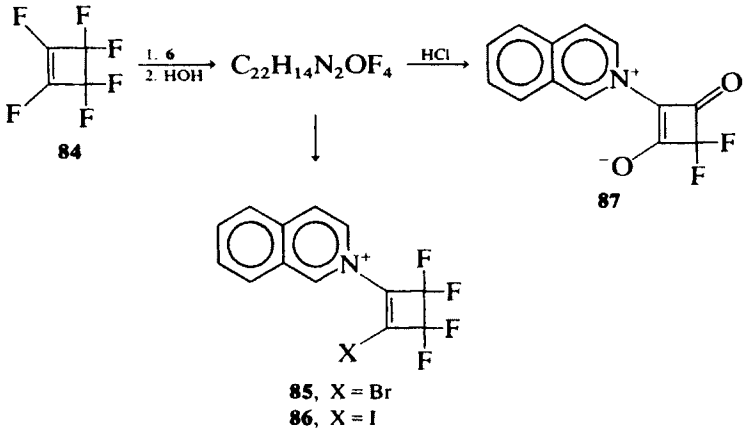
The reaction between maleic anhydride (**81**) and isoquinoline was carried out[110] without protonation of the base. In dry benzene, a brick-red betaine **82** formed which, on refluxing with methanol, afforded the betaine ester **83** through opening of the anhydride ring (Eq. 8).



81 **82** **83**

(8)

The electron deficiency of the double bond may be induced by the presence of fluorine as in perfluorocyclobutene (**84**) which, on reaction with isoquinoline and hydrolysis, affords in 59% yield a compound of unknown structure that can be converted to quaternary salts **85** and **86** by a brief treatment with concentrated hydrobromic or hydriodic acid.[111] Hydrolysis by heating with hydrochloric acid leads to betaine **87** in 45% yield (Scheme 1).



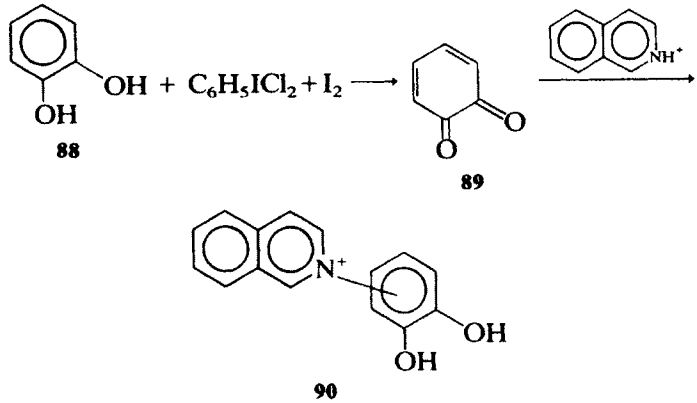
84

87

85, X = Br
86, X = I

Scheme 1

A complex quaternization procedure, but one that could presumably involve addition to an electron-deficient double bond, involved the use of a mixture of phenyl iododichloride, catechol (**88**), and iodine. It is believed[112] that the catechol is first oxidized to orthobenzoquinone (**89**) and that this reacts with isoquinoline (**6**) to afford a 2-(dihydroxyphenyl)isoquinoline (**90**) in which the location of the hydroxyl groups has not been established (Eq. 9).



88

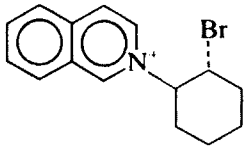
89

90

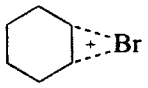
(9)

(i) *By Reaction of Alkenes in Presence of Halogen*

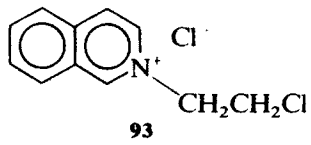
It has been shown[113] that the bromination of cyclohexene in the presence of isoquinoline affords a 14% yield of *trans*-2-(2-bromocyclohexyl)-isoquinolinium bromide (**91**) and that 1,2-dibromocyclohexane cannot be an intermediate in such a reaction, thus suggesting that the alkylating agent is the cyclohexenyl bromonium ion (**92**). A process for producing 2-(2-chloroethyl)-isoquinolinium chloride (**93**) by the reaction of chlorine with ethylene in the presence of isoquinoline in methylene chloride has been patented.[114]



91



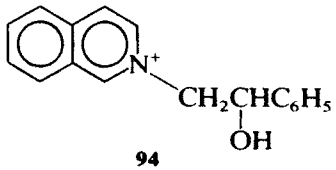
92



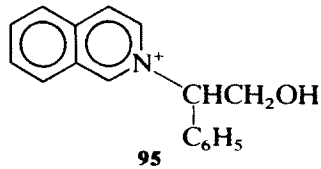
93

(j) *By Reaction with Epoxides, Ethers, Esters, Lactones, and Related Compounds*

Styrene oxide undergoes ring opening with isoquinolinium bromide to yield a mixture of **94** and **95**.[115] More useful synthetically is the reaction

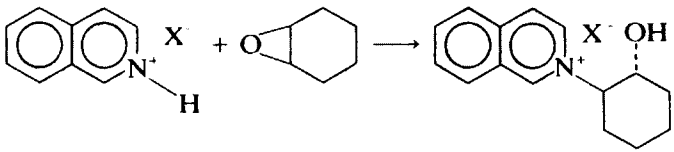


94



95

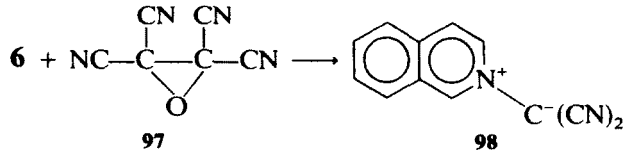
with cyclohexene oxide[116] in which the product is the trans hydroxyl derivative **96** (Eq. 10). Where the anion was tosylate, the yield was 91%.



(10)

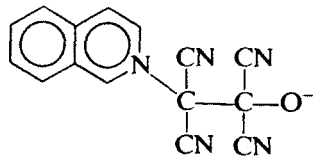
96

Tetracyanoethylene oxide (**97**) reacts directly with the base, thus affording a 56% yield of the betaine **98** of the 2-dicyanomethyl isoquinolinium cation (eq. 11).[117] The products are easily understood if it is assumed that the first step is addition with ring opening to afford the betaine **99**, followed by a retroaldol reaction. 2,4,6-Trinitroanisole (**100**) methylates isoquinoline, thus yielding 2-methylisoquinolinium picrate (**101**, Eq. 12).[118]

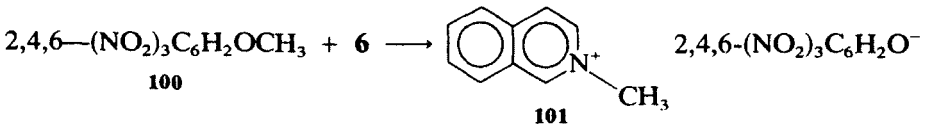


97 **98**

(11)



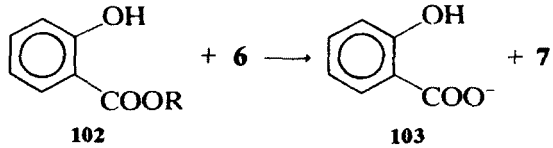
99



100 **101**

(12)

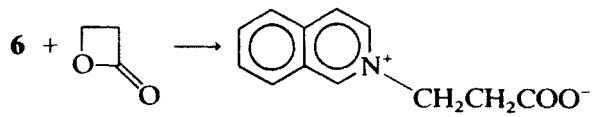
At 165 to 170°C alkyl esters of salicyclic acid (**102**) can act as alkylating agents (Eq. 13), but in the series methyl to butyl, the yields fell from 68% to 5% and reaction time increased.[119] The products could be isolated as the salicylate **103** picrate or iodide.[120]



102 **103**

(13)

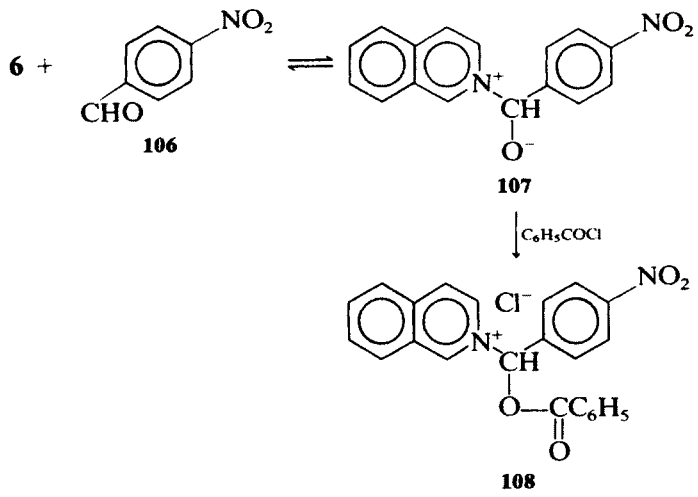
β-Propiolactone (**104**) can react with tertiary amines to produce betaines of quaternary salts.[121] With isoquinoline, the expected betaine **105** was obtained in a yield of 94% (Eq. 14).



104 **105**

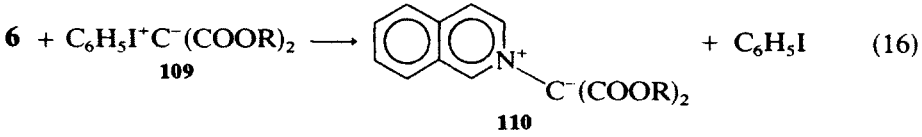
(14)

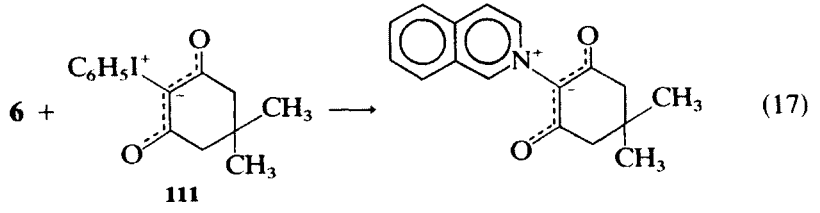
Another quaternization reaction[122] involves the use of a combination of *p*-nitrobenzaldehyde (**106**) and benzoyl chloride, giving, in the case of isoquinoline, an 83% yield of 2-(α-benzoyloxy-4-nitrobenzyl)isoquinolinium salt (**108**, Eq. 15). The success of the reaction must depend on trapping, by acylation, the betaine **107** formed when the aldehyde and the base interact.



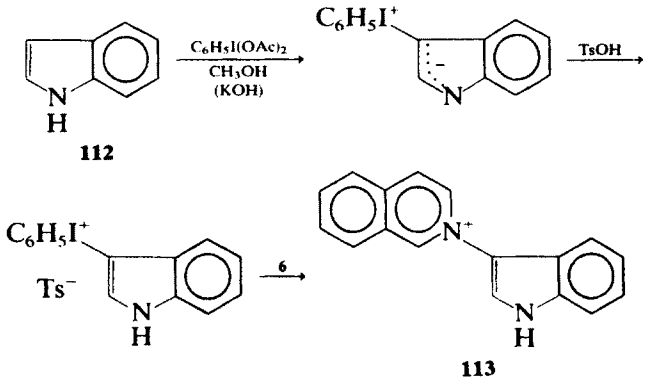
(k) *By Transalkylation and Transylidation*

Quaternization of a base may be accomplished by transfer of a group from a salt or betaine. The iodonium betaine **109** in Eq. 16 reacts with isoquinoline in the presence of copper acetylacetonate to afford the betaine **110** in 88% yield ($R = CH_3$) or 79% yield ($R = C_2H_5$).[123] In the same way, isoquinoline may be quaternized by the iodonium betaine **111** derived from dimedone (Eq. 17), by using cuprous chloride or copper acetonylacetonate catalysts (45% yield).[124]



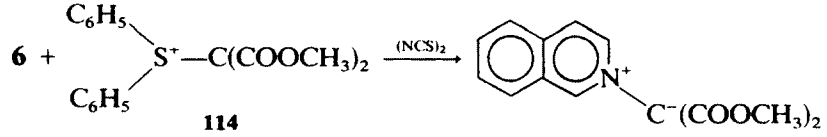


Transalkylation is involved in a potentially useful synthesis[125] of 2-(3-indolyl)isoquinolinium (**113**) tosylate, starting with indole (**112**, Eq. 18). A more familiar example of an alkylating agent of this class is triethyloxonium tetrafluoroborate (Eq. 160, Section VIII.B).



(18)

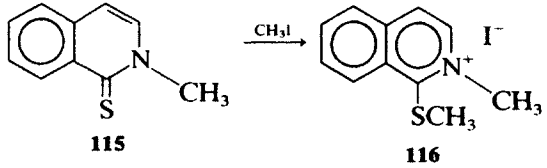
Transylidation of isoquinoline (**6**) by a solfonium betaine **114** in the presence of thiocyanogen as a catalyst has been observed (Eq. 19).[126] For reasons that are not yet clear, the yields obtained with isoquinoline are quite inferior to those found when pyridine is quaternized in the same type of reaction.



+ $C_6H_5SCH_3$ (19)

(l) *By Alkylation at a Position Other Than* 2

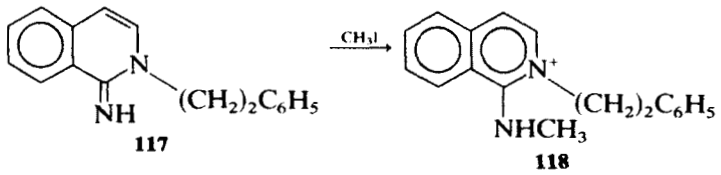
It is well known that the quaternization of 1-alkyl-2- or 4-thiopyridines can occur at sulfur rather than at nitrogen.[127] In an exactly parallel reaction, 2-methylisoquinoline-1-thione (**115**) is methylated[128] on sulfur, thus affording a 97% yield of 1-thiomethyl-2-methylisoquinolinium iodide (**116**, Eq. 20).



(20)

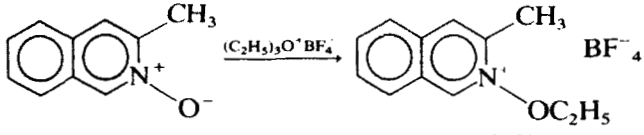
Analogous to this is the selective alkylation of 2-(2-phenylethyl)isocarbostyryl imine (**117**)[129] at the imino nitrogen (Eq. 21) to afford 1-methylamino-2-(2-phenylethyl)isoquinolinium iodide (**118**).

The alkylation (Eq. 22)[130,131] acylation[132] or sulfonylation[133] (Eq. 23) of

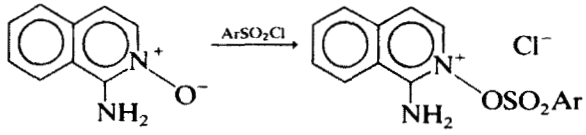


117 118 (21)

isoquinoline *N*-oxide derivatives afford cations (e.g., **119** and **120**) that closely resemble those of quaternary salts in both structure and reactivity.



119 66% (22)



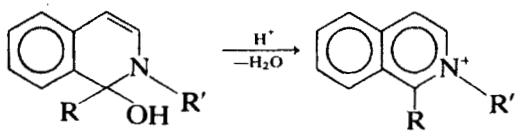
120 (23)

B. Preparation from Dihydroisoquinolines

Quaternary isoquinolinium salts may be prepared from suitable *N*-alkyl-1,2-dihydroisoquinolines by elimination, dehydrogenation, or disproportionation.

(a) *By Elimination*

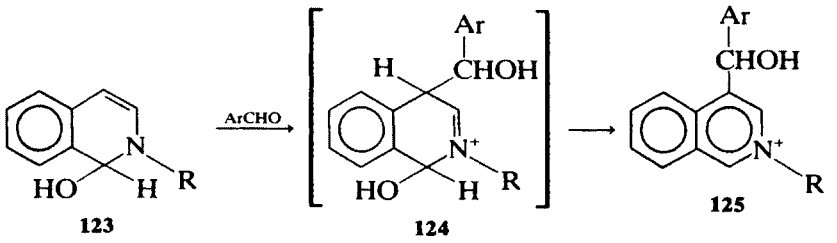
The most familiar example of the formation of the isoquinolinium quaternary salt **122** by elimination is the reaction of the carbinolamine **121** (pseudobase) with acid (Eq. 24; R = H). Exactly parallel to this is the dehydration of the carbinolamine **121** (R = alkyl or aryl) obtained by reaction of an *N*-alkyl- or arylisocarbostyryl with the Grignard reagent.[134,135]



121 **122** (24)

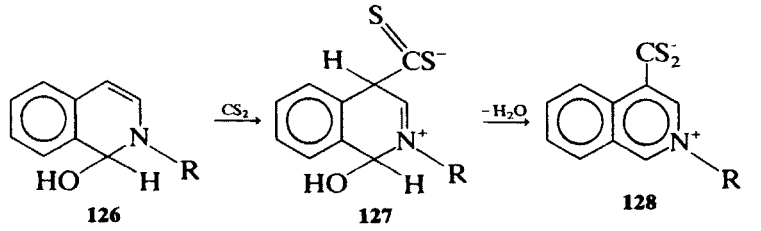
In the reaction in which a carbinolamine, an aromatic aldehyde, and an alkali are brought together,[136] it is almost certain that the carbinolamine[123] reacts as an enamine that adds to the aldehyde through the intermediate

124, thus affording the 4-(α-hydroxy-α-arylmethyl)isoquinolinium quaternary salt **125** on dehydration (Eq. 25) [see Section VII.B(a)].



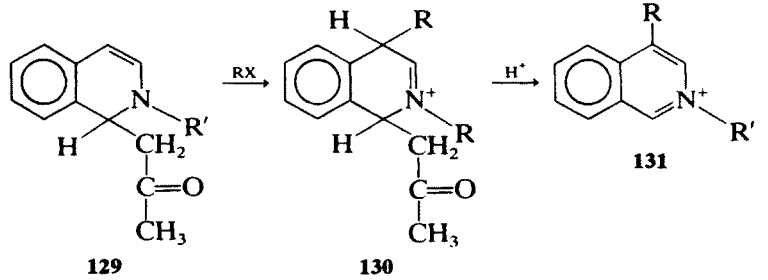
123 **124** **125** (25)

The reaction of a carbinolamine **126** with carbon disulfide to form the betaine **128** (Eq. 26)[137] must also involve loss of water from the dihydro intermediate **127**.



126 **127** **128** (26)

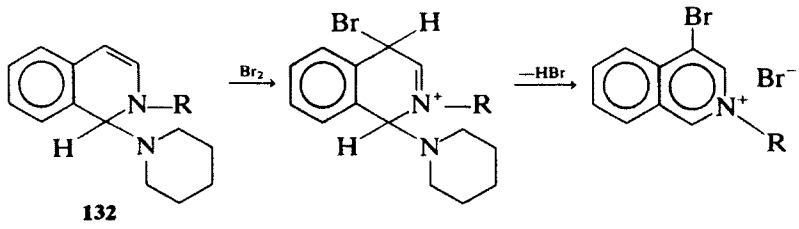
The recent demonstration[138] that 4-substituted isoquinolinium quaternary salts **131** can be prepared through alkylation or acylation of 1-acetonyl-1,2-dihydroisoquinoline **129** involved the transannular elimination of acetone in the final step (Eq. 27). Kröhnke and Vogt[139] have shown that *N*-alkyl-1-



129 **130** **131** (27)

acetonyl-1,2-dihydroisoquinolines **130** undergo loss of acetone when treated with strong mineral acids. A similar elimination reaction must be involved in the bromination of 2-alkyl-1-(1-piperidyl)isoquinolines **132** (Eq. 28).[139]

The acid-catalyzed rearrangement of the benzyl group of 1-benzyl-2-alkyl-1,2-dihydroisoquinoline **133** to position 3[140-142] is usually accompanied by a side reaction in which the benzyl group is eliminated to yield **134** (Eq. 29). Another side reaction is disproportionation, which is discussed in Section II.B(c). Since 1*N* acetic acid produces nearly twice as much elimination as does 1*N* hydrochloric acid, Knabe et al.[140] concluded that it is



132 (28)

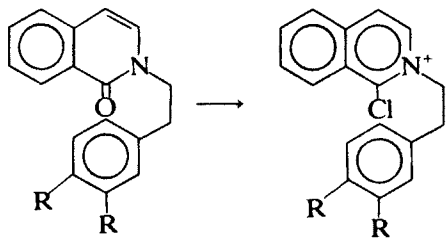
probably the unprotonated enamine **133** that participates in the elimination reaction.



133 + Disproportionation Product (29)

134

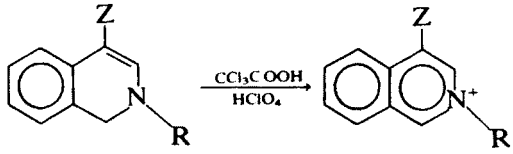
Another elimination reaction that involves the action of phosphorus oxychloride on isocarbostyryl derivative **135** to afford the 1-chloro-2-aralkylisoquinolinium salts **136** (Eq. 30)[129] is of particular interest in that an earlier worker[143] had claimed that cyclodehydration to a dihydrodibenzo [*a*, *h*]-quinolizinium derivative occurred under those conditions.



135 136 (30)

(b) *By Dehydrogenation*

Since 2-alkyl-1,2-dihydroisoquinolines are usually made by reduction of 2-alkylisoquinolinium salts (Section IV.A), there appears to have been little occasion to dehydrogenate the 1,2-dihydroisoquinolines **137** back to the quaternary salt. Thiullier et al.[144] have shown that dihydroisoquinolines that have a nitrile or an amide group at position 4 are dehydrogenated by heating in a mixture of perchloric and acetic acids (Eq. 31). Sainesbury and co-workers,[145,146] followed the alkylation or acylation of 1,2-dihydroisoquinoline **138** by dehydrogenation with iodine in the presence of

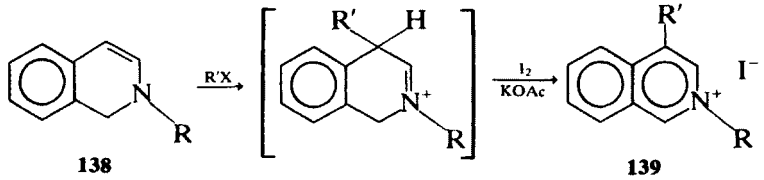


(31)

137

Z = CN or $CONH_2$

potassium acetate (Eq. 32), thus affording 2,4-disubstituted isoquinolinium salts **139**.

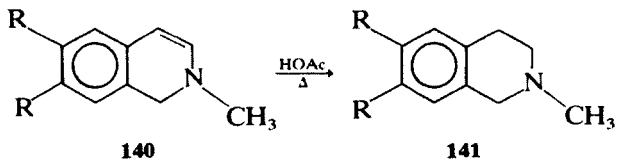


(32)

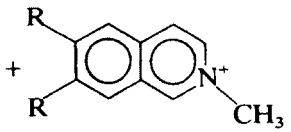
138 **139**

(c) *By Disproportionation*

Kirk[147] has demonstrated that in warm dilute acetic acid, 2-methyl-1,2-dihydroisoquinolines **140** (R = H or OCH_3) disproportionated to yield the tetrahydro derivatives **141** plus the fully aromatic isoquinolinium salts **142** (Eq. 33).



140 **141**



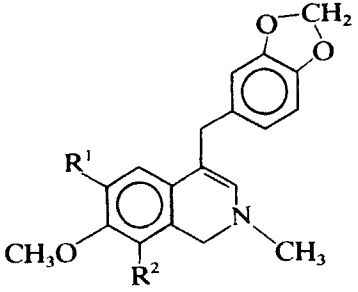
(33)

142

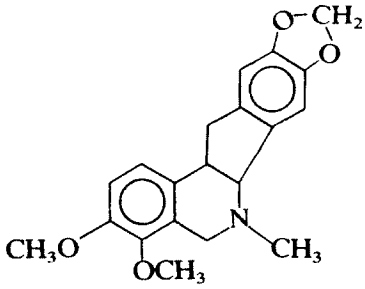
A similar disproportionation was found[142] to accompany efforts to rearrange the benzyl group of 1-benzyl-2-alkyl-1,2-dihydroisoquinoline or the styryl group of 1-(β-styryl)-2-methyl-1,2-dihydroisoquinoline[148] or of the cyclopropyl group of 1-cyclopropyl-2-methyl-6,7-dimethoxy-1,2-dihydroisoquinoline.[149]

Gensler et al.[150] concluded that the action of mineral acid on a substituted 4-benzyl-1,2-dihydroisoquinoline (**143**) had afforded a tetrahydroindenoisoquinoline (**145**). Dyke et al.[151] using the same conditions, found that disproportionation was the major reaction observed, leading to a mixture of **146** and **148** in almost equal quantities. That disproportion did indeed occur

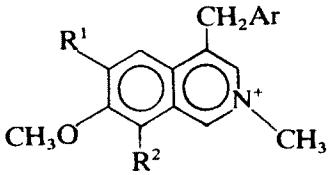
was confirmed by Gensler.[152] Dyke,[151] also observed that disproportionation (**144** → **147** + **149**) also occurred when the methoxyl groups were at positions 6 and 7 instead of 7 and 8.



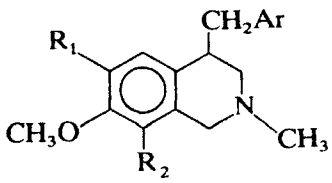
143, $R^1 = H$; $R^2 = OCH_3$
144, $R^1 = OCH_3$; $R^2 = H$



145



146, $R^1 = H$; $R^2 = OCH_3$,
147, $R^1 = OCH_3$; $R^2 = H$,
$Ar = 3,4\text{-}OCH_2OC_6H_3$



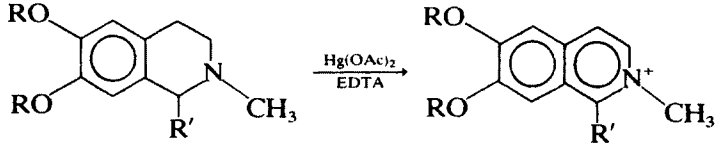
148, $R^1 = H$; $R^2 = OCH_3$
149, $R^1 = OCH_3$; $R^2 = H$

C. Preparation from 1,2,3,4-Tetrahydroisoquinolines

Depending on the substituents present in the unsaturated ring, *N*-substituted 1,2,3,4-tetrahydroisoquinolines may be converted to quaternary isoquinolinium salts by way of dehydrogenation, by a combination of dehydrogenation and elimination, or by elimination only.

(a) *By Dehydrogenation*

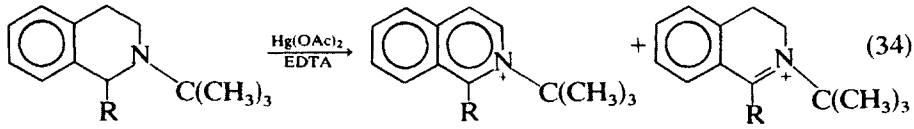
A combination of mercury(II)acetate and ethylenediamine tetraacetic acid has been used in the dehydrogenation of a variety of 1-alkyl- or 1-aralkyl-2-methyl-1,2,3,4-tetrahydroisoquinolines **150**, although it fails in the case of the 1-methyl derivative **150** ($R' = CH_3$). It was assumed that there might be conformational grounds for the behavior of the methyl compound.[153] Mercury(II)acetate is also reported to dehydrogenate a 1-phenyl-1,2,3,4-tetrahydroisoquinoline.[154] The fact that dehydrogenation can be accomplished when there is no substituent at position 1 is illustrated by the synthesis of 2-*tert*-butylisoquinolinium ion (**153**, R = H; Eq. 34), which



150 **151**

$R' = C_2H_5$, C_4H_9, $C_6H_5CH_2CH_2$, t-C_4H_9

cannot be made by direct alkylation of isoquinoline.[13] The 1-benzyl analogue has been prepared similarly.[155]

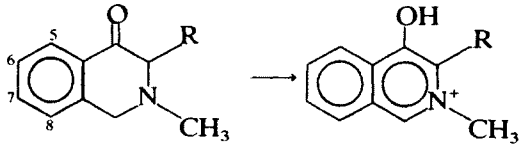


(34)

152 **153**

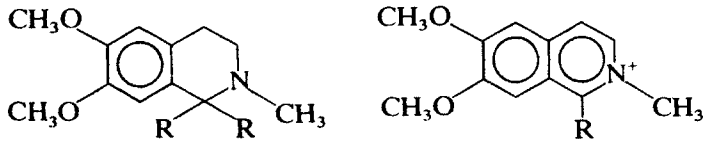
$R = H, C_6H_5CH_2$

The task of dehydrogenating *N*-alkyl-dihydro-4-isoquinolones **154** to 4-isoquinolinols **155** is relatively easy. It has been carried out (where R = H) by the use of either copper(II)chloride, bromine,[156] or mercury(II)acetate.[157] In analogous systems with an ethoxycarbonyl group at position 3 (**154**, $R = COOC_2H_5$) dehydrogenation was accomplished by using either copper acetylacetonate[156] or mercury(II)acetate.[157] Observations[157] made with the ethoxycarbonyl series appear to indicate that dehydrogenation is facilitated by the presence of methoxyl groups at positions 6 or 8.



154 **155**

Attempts to dehydrogenate tetrahydroisoquinoline derivatives that have two alkyl groups at position 1 (**156** and **157**) have had mixed success.[158] Where the substituent groups were benzyl (**156**), mercury(II)acetate caused cleavage of a carbon–carbon bond, thus affording a 1-benzyl-2-methyl-6,7-dimethoxyisoquinolinium ion (**158**). Where the substituent groups were methyl (**157**), there was no evidence of the formation of an isoquinolinium salt.

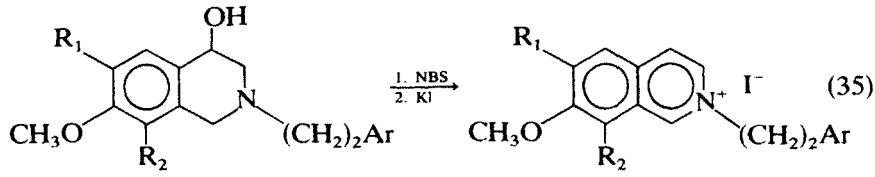


156, $R = C_6H_5CH_2$
157, $R = CH_3$

158, $R = C_6H_5CH_2$

(b) *By Dehydrogenation and Elimination*

If there is present in the ring to be dehydrogenated a group that can undergo β-elimination, the aromatization process is greatly facilitated.[159] In Eq. 35, using *N*-bromosuccinimide (NBS) as the dehydrogenating agent, the yield of **159** was 67% where $R^1 = OCH_3$, and $R^2 = H$ and 72% where $R^1 = H$ and $R^2 = OCH_3$.

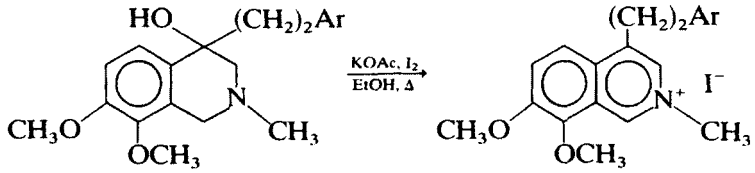


(35)

159

Ar = 3,4-$(OCH_3)_2C_6H_3$

An example of dehydrogenation plus elimination by the action of iodine and potassium acetate is seen in Eq. 36, which takes place with a yield of 85%.[152]



(36)

Ar = 3,4-$OCH_2OC_6H_3$

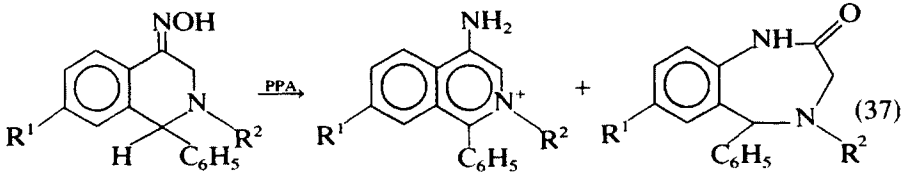
(c) *By Elimination Only*

2-Oximino-1,2,3,4-tetrahydroisoquinoline derivatives **160** can simply undergo dehydration in polyphosphoric acid to afford 4-aminoisoquinolinium quaternary salts **161** (Eq. 37),[160] but at least part of the oxime undergoes a Beckmann rearrangement to afford a benzodiazepin-2-one **162**. Where $R^1 = Cl$ and $R^2 = C_6H_5CH_2$, the yield of the aminoisoquinolinium salt **161** was 74%.

D. Preparation from Isomers

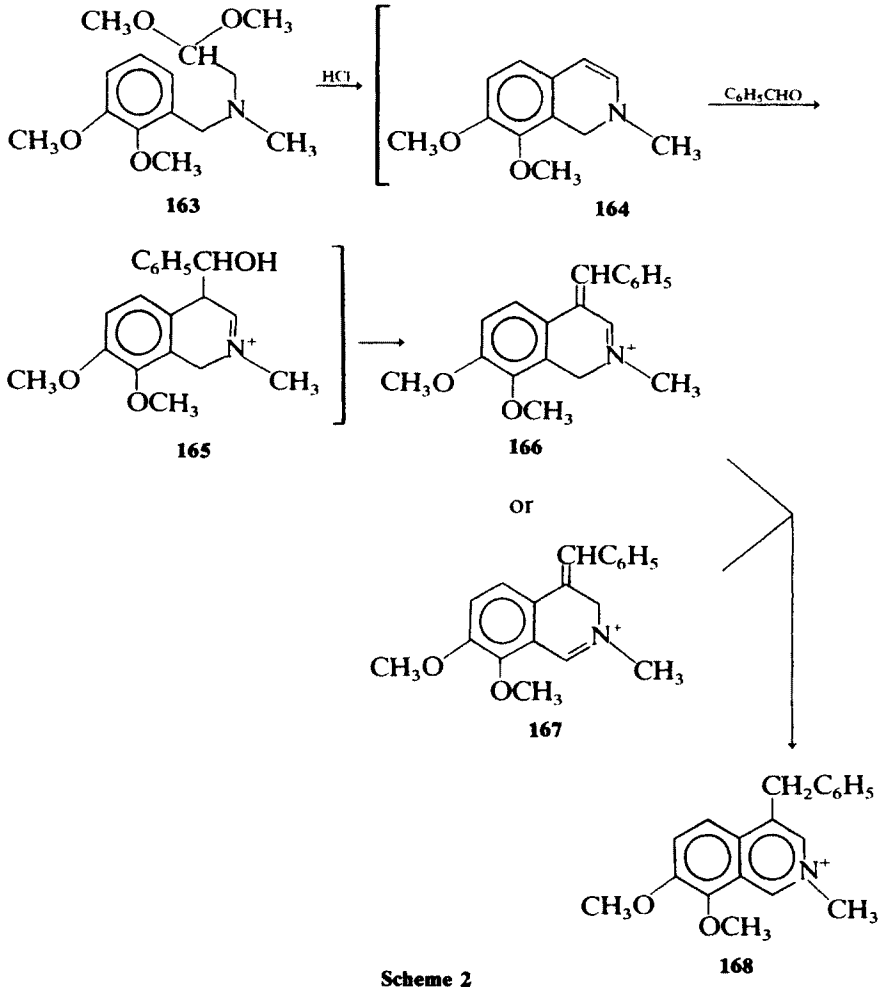
(a) *Without Skeletal Rearrangement*

On the basis of an earlier investigation,[161] the enamine **164**, produced by the cyclization of acetal **163**, was allowed to react with benzaldehyde.[162] It



160 161 162

was believed that the enamine **164** added to the aldehyde to form the carbinol **165**, which lost water, under the conditions of the reaction, to afford the salt **166** or possibly **167**. Attempts to crystallize the salt resulted in isomerization to the 4-benzylisoquinoline derivative **168** (Scheme 2). Brown et al.[163] later prepared several 1,4-dihydro-4-benzylideneisoquinolines

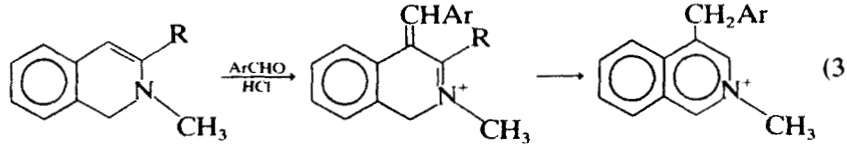


163 164 165 166 167 168

Scheme 2

similar to **166** and showed that these could be isomerized to 1-benzylisoquinolinium salts by heating for 20 hr in methanol.

The reaction of arylaldehydes with 1,2-dihydroisoquinoline **169** (Eq. 38) to afford 4-arylmethylisoquinolinium salts **173** is quite general and presumably occurs by way of isomerization of a 1,4-dihydro-4-benzylideneisoquinoline intermediate **171**. If an attempt is made to carry out a similar reaction using 3-methyl-1,2-dihydroisoquinoline **170**, no isomerization occurs, and the 1,4-dihydrobenzylidene isomer **172** is obtained instead of 3-methylisoquinolinium salts.[162]



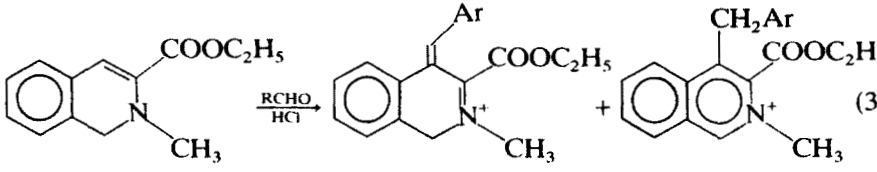
(38)

169, R = H
170, R = CH_3

171, R = H
172, R = CH_3

173

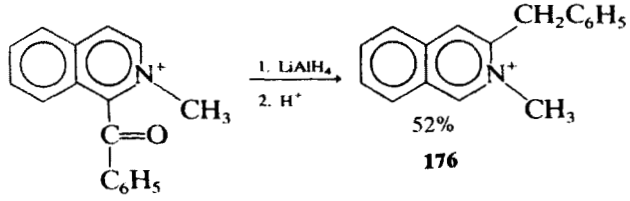
The observation[164] that the presence of an ethoxycarbonyl group at position 3 in the 1,2-dihydroisoquinoline **174** is sufficient to at least partially restrain the final isomerization (Eq. 39) suggests that the influence of the group at position 3 may be steric, thus reflecting the strain involved in



(39)

174

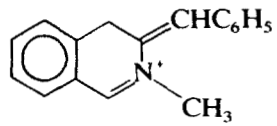
achievement of the planar arrangement of the substituents. The transformation of 1-benzoyl-2-methylisoquinolinium ion (**175**) to 2-methyl-3-benzylisoquinolinium ion (**176**) is believed[165] to occur through an intermediate **177** having an exocyclic double bond.



52%

175

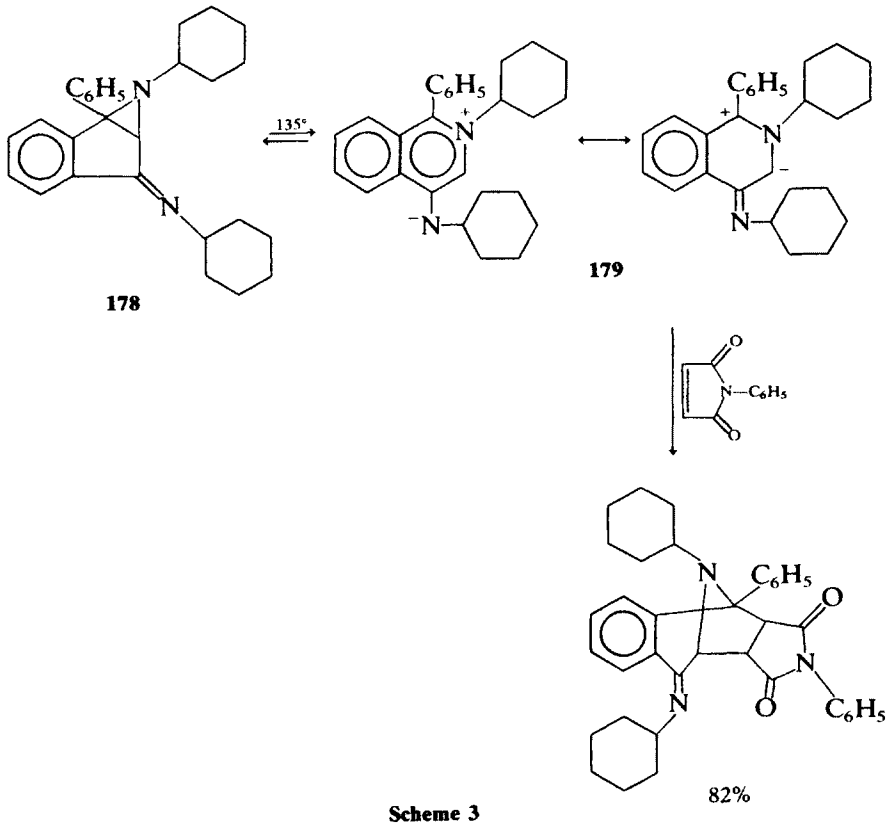
176



177

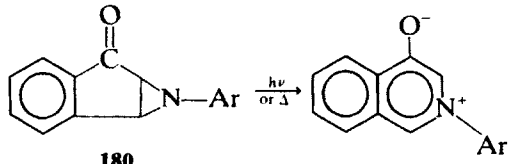
(b) *With Skeletal Rearrangement*

If 1-cyclohexyl-6-(cyclohexylimino)-1a-phenylindano[1,2-*b*]aziridine (**178**) is heated to 135°C in toluene, it is transformed to a colored isoquinolinium imine betaine **179** (Scheme 3) that may be trapped by the dipolar addition of *N*-phenylmaleimide.[166]



Scheme 3

Hansen and Undheim[167] have shown that certain *N*-arylaziridines **180** may be ring opened photochemically, or less effectively, thermally, to betaines of 2-aryl-4-hydroxy isoquinolinium ion **181** (Eq. 40).



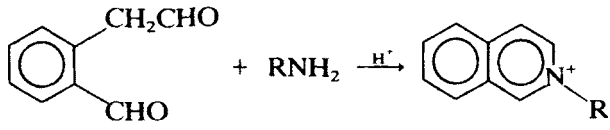
180 **181** (40)

Ar = C_6H_5, *p*-$CH_3OC_6H_4$, *p*-$NO_2C_6H_4$

E. Preparation from Homophthaldehyde and Its Derivatives

(a) *From Homophthaldehyde*

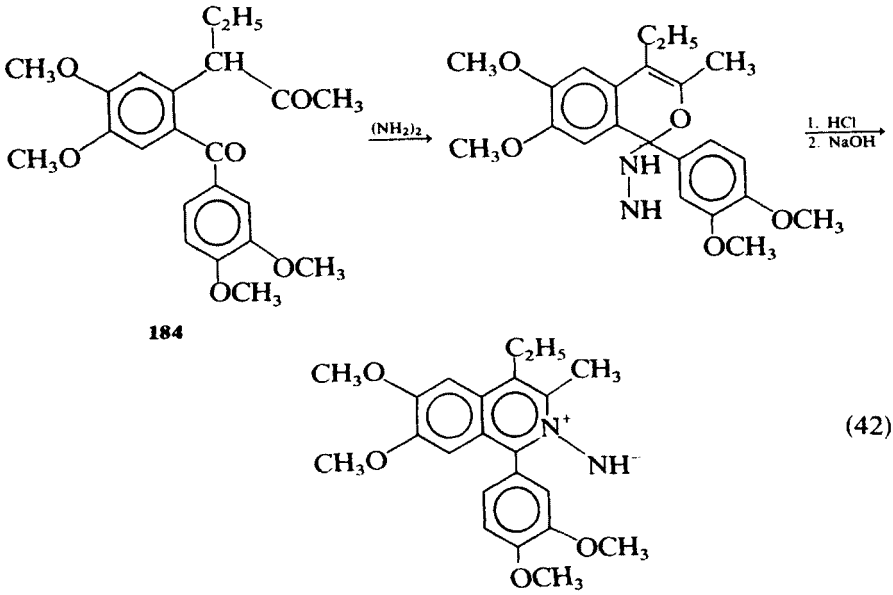
Homophthaldehyde (**182**), which is available by ozonization of indene,[168] reacts with primary amines to produce isoquinolinium quaternary salts **183**,[169,170] some of which are not obtainable by direct alkylation (Eq. 41).



182 **183** (41)

R = C_6H_5, $C_6H_5CH_2CH_2$, 2-(3-indolylethyl), 2,4-$(NO_2)_2C_6H_3NH$

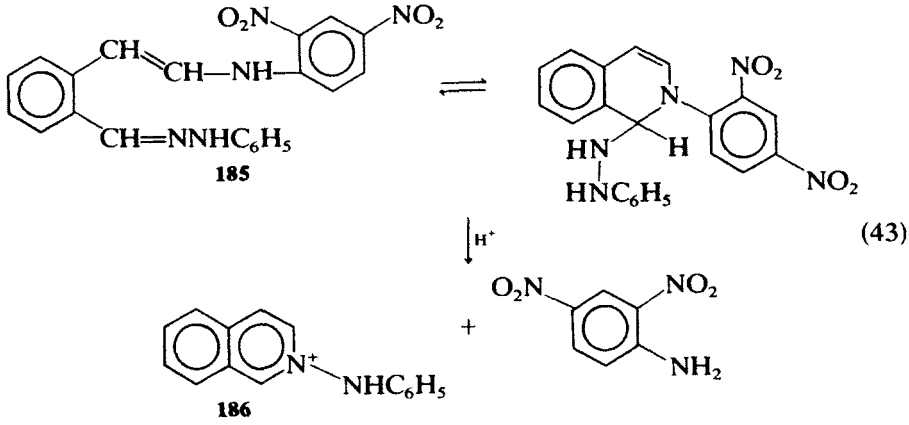
The cyclization of a related diketone **184** by reaction with hydrazine (Eq. 42) has been shown[171] to occur in two steps.



184 (42)

(b) *From 2-Formyl-β-Aminostyrene Derivatives*

Zincke and Weisspfenning[67] showed that the phenylhydrazone **185** of 2-formyl-β-(2,4-dinitrophenylamino)styrene, represented here as a ring-chain tautomeric equilibrium mixture,[172] undergoes cyclization when it is heated with acid eliminating 2,4-dinitroaniline, thus affording *N*-anilinoisoquinolinium salt **186,** (Eq. 43).

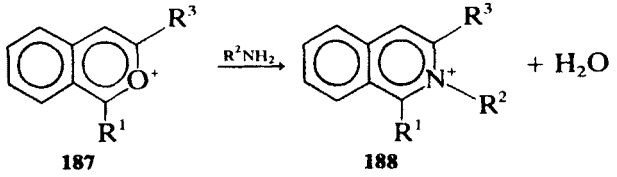


(43)

Since the required starting hydrazone or its congeners[172] may be prepared conveniently from 2-(2,4-dinitrophenyl)isoquinolinium salts (see Section V.C) and since it is not even necessary to isolate the hydrazone or related intermediates, this reaction forms a convenient route to 2-aminoisoquinolinium salts and their derivatives. If aniline or *p*-toluidine is used instead of phenylhydrazine in the original ring-opening reaction, the overall reaction sequence yields *N*-arylisoquinolinium salts.

F. Preparation from Benzopyrylium Salts

Pyrylium salts react with primary amines to afford quaternary pyridinium salts;[173] similarly, aliphatic and aromatic amines react with 2-benzopyrylium salts **187** to afford isoquinolinium salts **188** (eq. 44).

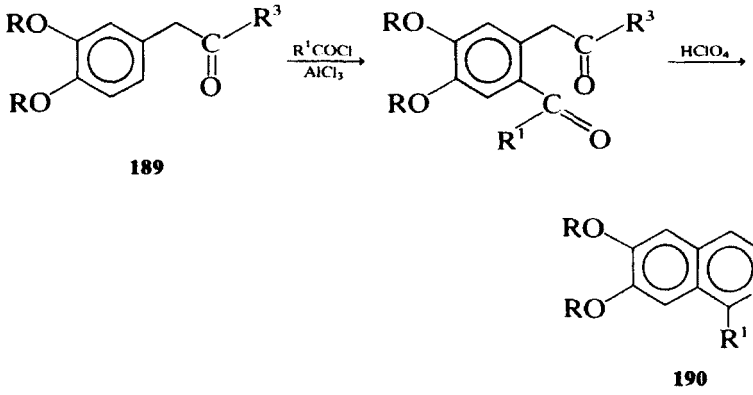


(44)

Poorest yields appear to have been obtained where R^1 and $R^3 = C_6H_5$ (30 to 52%),[174] whereas the best yields (93% and 96%) were obtained where $R^1 = 3,4\text{-}(CH_3O)_2C_6H_3CH_2$ and $R^2 = CH_3$.[175] For two series, both having methyl at position 1, yields were reported[176] to be good (60 to 90%) when R^3 was methyl and almost as good (50 to 65%) when R^3 was methoxycarbonyl.[177]

For the synthesis of 6,7-dialkoxyisoquinolinium salts that have a substituent at position 3, the overall reaction is sufficiently simple and versatile to merit wider use than it has received. The necessary benzopyrylium salts

190 are usually prepared by a Friedel–Crafts acylation of 3,4-dialkoxybenzyl ketone **189** (Eq. 45).[175]

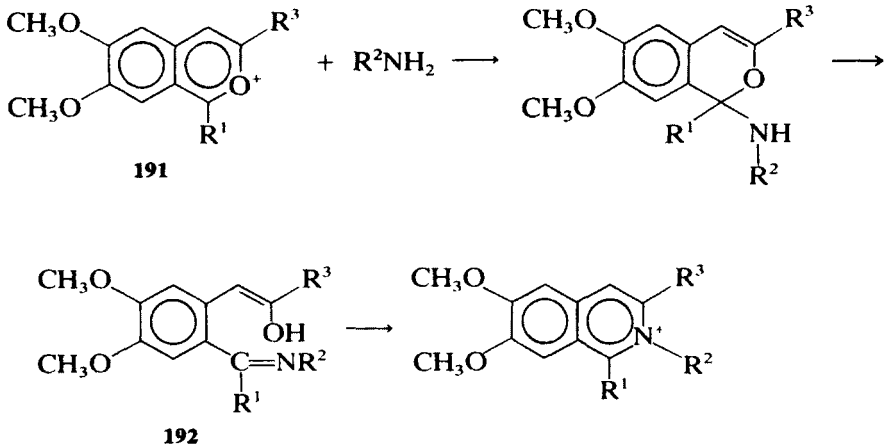


189

(45)

190

The ring-opening and -reclosing reaction is believed[174] to involve initial attack of the amine at position 1 of the benzopyrylium salt **191** (Eq. 46). This is followed by a cyclodehydration reaction involving the ketone and imine side chains of **192**.



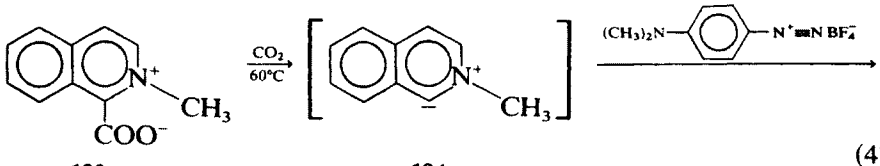
191

(46)

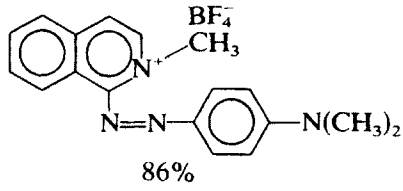
192

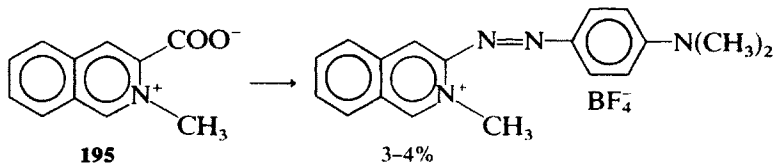
G. Preparation by Decarboxylation

The decarboxylation of the betaine **193**, 2-methylisoquinolinium-1-carboxylate, occurs readily at 60°C in aprotic solvents,[178] and the reactive betaine **194** formed can be trapped by electrophiles such as 4-dimethylaminobenzenediazonium fluoborate (Eq. 47). The analogous transformation of the 3-isomer **195** requires a higher temperature to produce even a small yield of product (Eq. 48).



(47)





(48)

H. Analytical and Spectroscopic Studies

As in other areas of organic chemistry, modern synthetic work involving isoquinolinium salts is monitored by use of physical methods, in particular by nmr, electronic spectroscopy, and mass spectrometry. The physical data selected for inclusion in this section have been chosen for their fundamental relevance to isoquinolinium salts in general.

(a) *Electronic Spectroscopy*

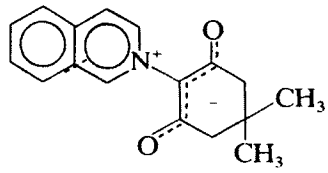
As part of a larger study, Spinner[179] compared the spectrum of isoquinolinium methochloride with that of an isoquinolinium ion. As in the case of other bases not affected by steric complications, a bathochromic shift of the π–π^* bands was observed (Table IV.3), thus confirming an earlier

TABLE IV.3 COMPARISON OF ABSORPTION SPECTRA OF ISOQUINOLINIUM AND 2-METHOISOQUINOLINIUM IONS IN WATER

		Wavelength of absorption (log ϵ)	
Ion	β-Band	p-Band	α-Band
Isoquinolinium	226.5 (4.57)	266 (3.29), 274 (3.30), 285 sh (3.01)	325 sh (3.61) 332 (3.64)
Methoisoquinolinium	231 (4.70)	269 (3.41), 276 (3.42), 289 sh (3.10)	327 sh (3.60), 335 (3.63)

observation by Osborne et al.[180] The *N*-methyl isoquinolinium spectrum has been rationalized[181] by using a Nishimoto model and applying the Pariser–Parr–Pople method. Electronic spectra have been useful in solving structural problems that have arisen in the study of isoquinolinium betaines,[182–184] and certain of these betaines have been proposed as acid–base indicators.[185]

The infrared spectrum of the betaines **196** was used to demonstrate that the O–C–C–C–O system had a symmetrical distribution of electronic charge.[186]



196

(b) *Nuclear Magnetic Resonance Spectroscopy*

The proton magnetic resonance spectrum of isoquinolinium salts that have no substituent at position 1 is usually characterized by an easily identifiable singlet in the 10.1δ region. The shift or disappearance of the one-proton signal is frequently a convenient measure of the progress of a reaction involving isoquinolinium salts as exemplified by the work of Zoltewicz et al.[187] on the reaction of 1-methylisoquinolinium iodide with liquid ammonia (Section V.C).

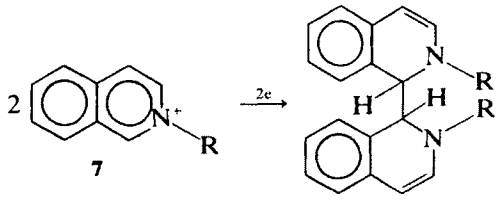
To provide a model for a study of cinnoline protonation, Palmer and Semple[188] compared the change in chemical shift of isoquinolinium protons $\Delta\nu_n$, where n represents the position of the carbon to which the proton is attached, when the nitrogen atom of isoquinoline is methylated by methyl iodide. The observed shifts were $\Delta\nu_1+0.71$, $\Delta\nu_3+0.21$, and $\Delta\nu_4+0.81$. Other examples of the use of nmr in the study of the chemistry of isoquinolinium salts are mentioned later (e.g., Sections V.C, V.E, and VII.B).

(c) *Polarography and Electron Spectroscopy for Chemical Analysis*

Polarography has given considerable insight into the mode of reduction of isoquinolinium salts. As part of a larger study, Kato et al.[189] have investigated 2-methylisoquinolinium iodide and found that reduction occurs stepwise: $1e$, $1e+H^+$. But in aqueous solutions, in contrast to aprotic solvents, reduction was complicated by the adsorption of reduced products on the surface of the mercury.

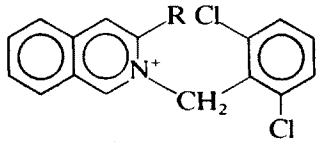
Other papers have described the polarographic reduction of isoquinolinium salts.[190,191] It has been shown[192] that electrolytic reduction of

isoquinolinium salts **7** at the potential of the first polarographic waves produces the 1,1-dimer **197** (Eq. 49), except in the case in which there was a phenyl substituent at position 1. Electron spin resonance failed to show the presence of a neutral radical intermediate in the reduction.



7 **197** (49)

2-(2,6-Dichlorobenzyl)isoquinolinium bromide (**198**) and its 3-methyl homolog **199** were used in a study of the polarographic transfer reaction of cations to the anion of nitromethane (Section V).

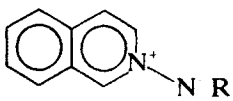


198, R = H
199, R = CH_3

Jack and Hercules[193] have used electron spectroscopy for chemical analysis (ESCA) to measure the nitrogen (1s) binding energy of aromatic quaternary systems. In this study 2-*n*-butylisoquinolinium ion was found to have a binding energy of 399.9 eV. This result placed isoquinolinium below the pyridinium ion but above quinolinium in binding energy.

(d) *Mass Spectrometry*

The mass spectrum of isoquinolinium methiodide reflects the ease of thermal dissociation of the salt into isoquinoline and methyl iodide, but the parent peak can be seen. The same pattern appears with the methoperchlorate, but there is another peak at M+15 due to oxidation to the isocarbostyryl.[194] The mass spectrum of the betaines derived from 2-aminoisoquinolinium ion show much the same cleavage pattern. Fragmentation of the N–N bond appears to be most prominent for the betaine **200** from *N*-anilinoisoquinolinium derivates.[195] The same pattern emerges from the mass spectrum of the betaine **201** derived from the 2-benzoylaminoisoquinolinium ion.[196]



200, R = aryl
201, R = COC_6H_5

(e) *Other Analytical Methods*

Mixtures including isoquinolinium quaternary salts have been separated by use of paper chromatography with various solvent system.[197] Detection may be accomplished by the use of Dragendorff reagent or potassium iodoplatinate. Not surprisingly, the R_f values for fully aromatic isoquinolinium salts appear to be lower than those for 1,2,3,4-tetrahydro analogs.[198]

Cross[199] has recommended the use of sodium tetraphenylborate as a reagent capable of the determination of laurylisoquinolinium ion (among others) in a mixture of surfactants. The method is complex and involves titration at pH values of 3.0, 10.0, and 13.0 on the same sample.

III. MOLECULAR COMPLEXES

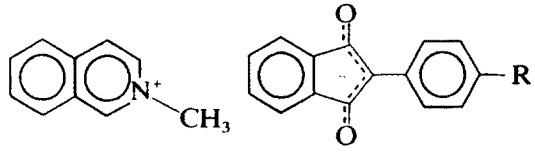
Like the 1-methylpyridinium ion,[200–203] the 2-methylisoquinolinium ion with many substrates forms molecular complexes, most of which have the character of a charge-transfer complex. The division of this section into subsections has been somewhat arbitrary.

A. Charge-Transfer Complexes

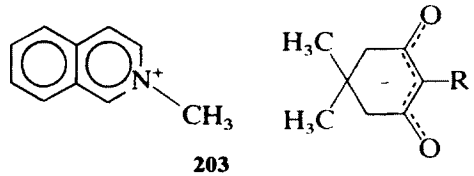
Mason[204] included the 2-methylisoquinolinium ion in the series of polycyclic cations studied, thus demonstrating the existence of iodide ion charge-transfer complexes through comparison of the ultraviolet absorption spectra of the iodides and perchlorates of a given cation. Mason also demonstrated the existence of a charge-transfer complex between the *N*-methylisoquinolinium ion and dimethylaniline.[205] Nasielski and Van der Donckt[206] showed that polycyclic aromatic hydrocarbons likewise formed spectroscopically detectable charge-transfer complexes with the *N*-methylisoquinolinium ion. Similar complexes of isoquinoline methochloride and isoquinoline were demonstrated, and the association constant in 30% methanol was shown to be 4 ± 1 liter/mole.[207]

Kampars and Neilands[208,209] have made an interesting spectroscopic study of 2-methylisoquinolinium–2-aryl-1,3-indanedione anion salts (**202**) measuring the change in charge-transfer energy as R was varied. These changes correlated very well with the Brown–Okamoto substituent constant, σ^+,[210] reflecting the conjugation between R and the anionic center. The formation of charge-transfer bands was likewise demonstrated[211] using anions derived from dimedone (**203**).

The charge-transfer-induced bathochromic shift may be readily seen if *N*-alkylisoquinolinium salts are formed with anions that normally have visible (though light) color. This phenomenon has been designated by



202

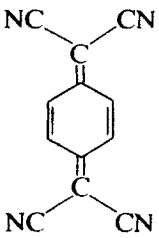


203

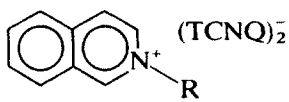
Kröhnke[212] as "interionic mesomerism." Among the anions used are ferrocyanide,[21,30,212,213] which is reported to give a blue–violet color, and the octocyanotungstenate ion,[214] which is gray–blue.

B. Organic Semiconductors

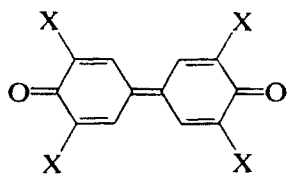
In the search for new organic semiconductors, some new ion–radical salts have been prepared. These include **205**, which is reported[215] to show high electrical conductivity and is obtained by allowing 7,7,8,8-tetracyanoquinonedimethane (TCNQ) (**204**) to react with an isoquinolinium iodide salt in acetonitrile. Similar ion–radical salts have been obtained from tetrachloro-*p*-diphenoquinone (TCDQ, **206**) and the tetrabromo analogue **207**. The salts from the bromoquinone **207** showed lower resistivity than did their chloro analogs **206**.



204



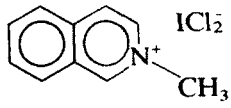
205



206, X = Cl
207, X = Br

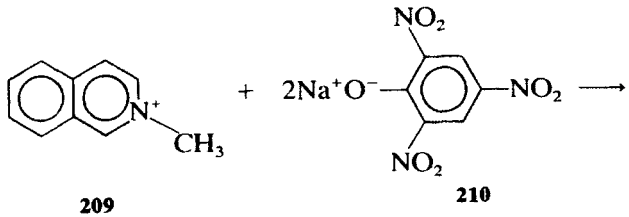
C. Complexes with Inorganic Salts

Isoquinoline quaternary salts share with those of many other aromatic cations the ability to form trihalide salts. These salts are frequently encountered when quaternary bromides or iodides are subjected to the action of halogen or halogenating agents. The Cl_2I^- salt **208** of 2-methylisoquinolinium was formed by the action of thionyl chloride on the corresponding methiodide.[216]



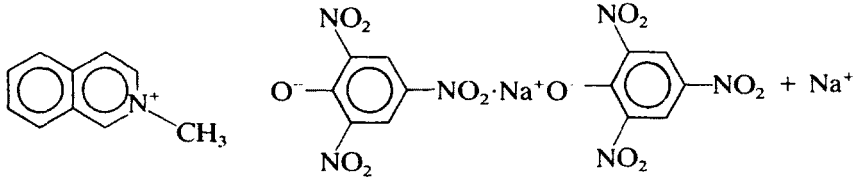
208

The addition of a solution of 2-methylisoquinolinium salt (**209**) to a solution of sodium picrate (**210**) can lead to the formation of the double salt **211** containing 1 mole of sodium picrate (Eq. 50).[217] The stability of such salts varies widely, and it has been found[218] that the 2-ethylisoquinolinium ion does not form such a double salt.



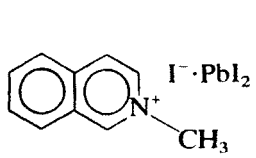
209 **210**

(50)

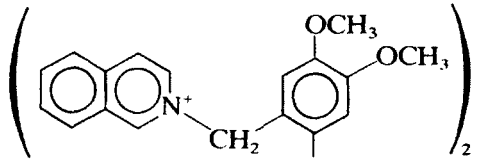


211

Like the isoquinolinium ion itself,[219] the *N*-alkylisoquinolinium ions have been found[220] to form double salts with the salts of heavy metals. Addition of lead acetate to a solution of isoquinolinium methiodide produced a lead iodide double salt (**212**). The bisquaternary salt **213** is reported[221] to form a blue-green complex with cobalt chloride.



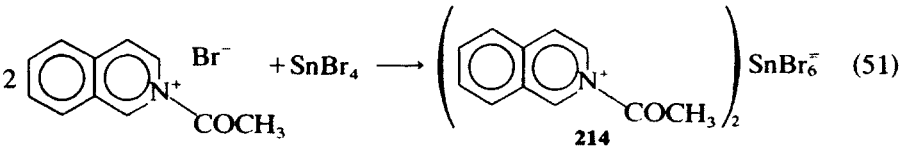
212



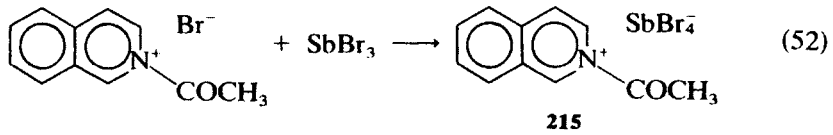
213

Paul et al.[222] have studied complex formation through measurement of the change in conductivity as tin or antimony bromides were added to an aromatic base dissolved in an excess of acetyl bromide. With isoquinoline, as with most bases studied, there was a minimum of conductivity (complex formation) when the $SnBr_4$:base ratio was 1:2, thus indicating formation of a $SnBr_6^=$ salt (**214**, Eq. 51). When a solution of isoquinoline in acetyl bromide was titrated with antimony tribomide, a precipitate (**215**) formed

when the reagents were at the 1 : 1 molar ratio (Eq. 52). The precipitate was not dissolved or the conductivity appreciably changed by further addition of antimony tribromide.



(51)



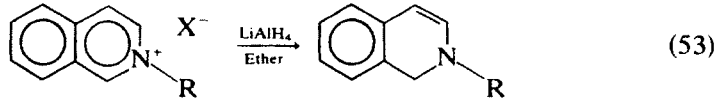
(52)

IV. REDUCTION AND OXIDATION OF ISOQUINOLINIUM SALTS

Means are available for the reduction of quaternary isoquinolinium salts to 1,2-dihydro-, 1,2,3,4-tetrahydro-, and decahydroisoquinolines. The oxidation of isoquinolinium quaternary salts appears to have been carried out only rarely and has negligible synthetic utility.

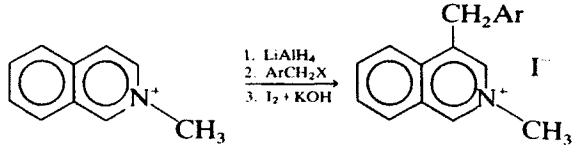
A. Reduction to 1,2-Dihydroisoquinolines

Although it seems likely that 1,2-dihydroisoquinolines are formed as intermediates in nearly every reduction of the nucleus of quaternary isoquinolinium salts **7**, the first isolation of the 1,2-dihydro derivatives **216** came as the result of the use of lithium aluminium hydride as the reducing

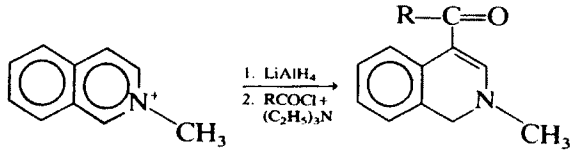


(53)

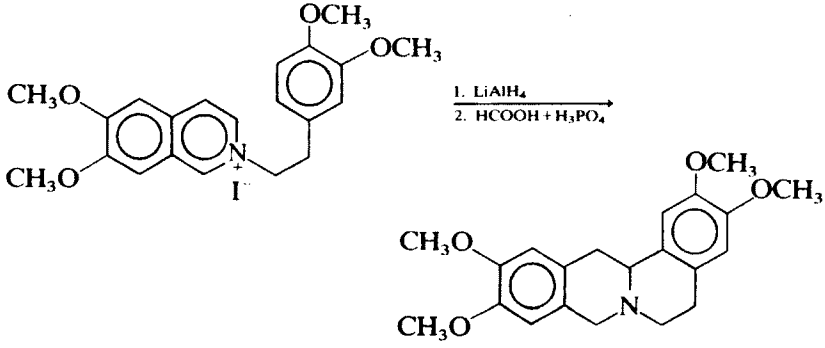
agent by Schmid and Karrer[223] (Eq. 53). 1,2-Dihydroisoquinolines are enamines, and the array of alkylations (Eq. 54),[136,145,150,224–226] acylations (Eq. 55),[136,146,227] cyclizations (Eqs. 56 and 57),[62,64–66,86,87,159,170,228–240] disproportionations (Eq. 58),[140,141,148,151,241,242] and rearrangements (Eq. 59)[140–142,148,241–249] that these compounds undergo has provided some of the most interesting chemistry to be found in the isoquinoline field[250] (see also Chapter I) but can only be illustrated by a few examples (Eqs. 54–59). For the investigation and synthetic application of some of these new reactions, many *N*-substituted dihydroisoquinolines have been prepared, chiefly by the



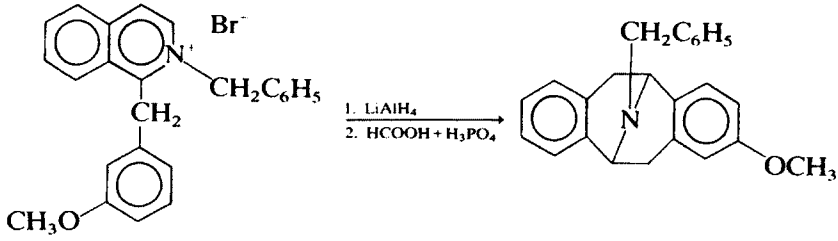
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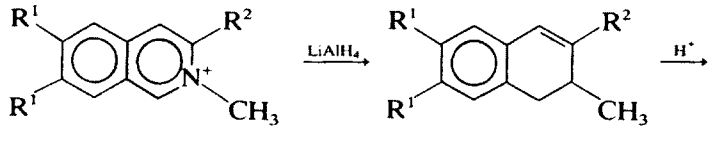
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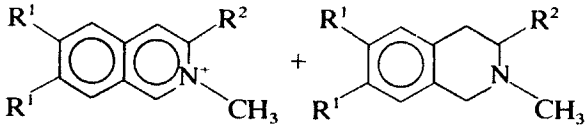


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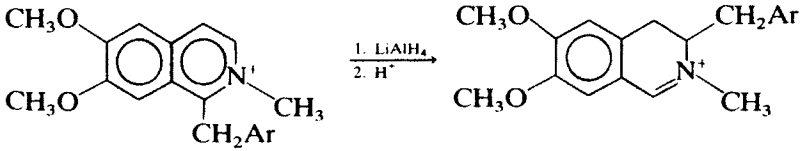


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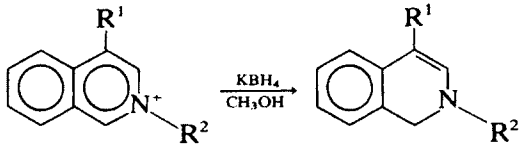
(58)



(59)

use of lithium aluminum hydride[62,64,86,87,140,141,145,146,148,151,159,165,170,228–232,234,238–249,251–254] as the reducing agent, although there is evidence[254] that some of the tetrahydroisoquinoline may be formed as a side product. More recently, instances of the use of sodium borohydride in pyridine as recommended by Barton et al.[255] have been encountered. When borohydride is used in the presence of protic solvents, the usual reaction is reduction to the 1,2,3,4-tetrahydro stage (Section IV.B) but in anhydrous pyridine or dimethylformamide,[256] reduction can be halted at the 1,2-dihydro stage.[257,258] Another modified sodium borohydride reaction has been used, a sodium borohydride–sodium cyanide combination.[65,66]

Even in protic solvents, potassium borohydride reductions have been found[144] to stop at the dihydro stage if there is a suitable substituent at position 4 of the isoquinolinium salt **217** (Eq. 60). Similar results with sodium borohydride have been reported.[259,260] The stability of the dihydroisoquinoline **218** is affected by the nature of the group on nitrogen, and the dihydro product **218** is more stable where R^2 was benzyl instead of methyl. It is significant that each of the position-4 substituents shown in equation 60 is electron withdrawing. When the position 4-substituent was $NHCOCH_3$, reduction to the tetrahydro stage occurred.[144]



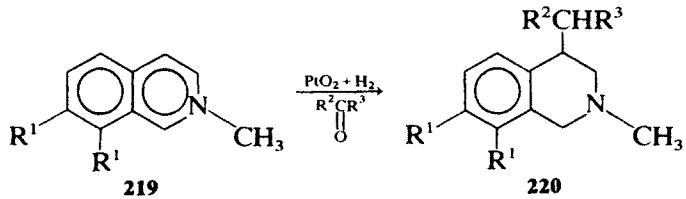
(60)

217 **218**

$R^1 = CONR_2$, COOR, COOH, CN

Since 1,2-dihydroisoquinolines are enamines and usually are both reactive and unstable, many procedures avoid the isolation of pure 1,2-dihydro compounds and belong to the category of "one-pot" reactions in which an isoquinolinium salt is the starting material.

An alternate approach is to use a procedure that would normally be expected to reduce the isoquinolinium salt to the 1,2,3,4-tetrahydroisoquinoline, except that the reduction is carried out in the presence of a reagent capable of intercepting a 1,2-dihydroisoquinoline, and is itself reduced more slowly than is the isoquinolinium ion. For instance, the catalytic reduction of 2-methylisoquinolinium salts **219** in the presence of aldehydes[150,224] or cyclohexanone[224] gave gratifying yields of a 4-alkylated 1,2,3,4-tetrahydroisoquinoline **220** (Eq. 61).

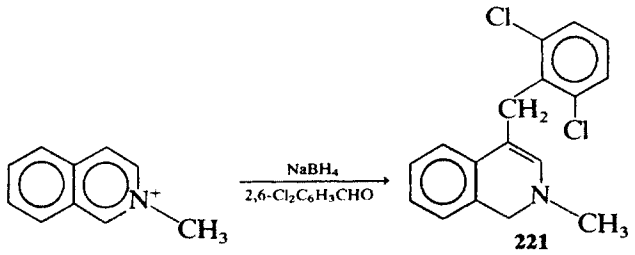


(61)

219 **220**

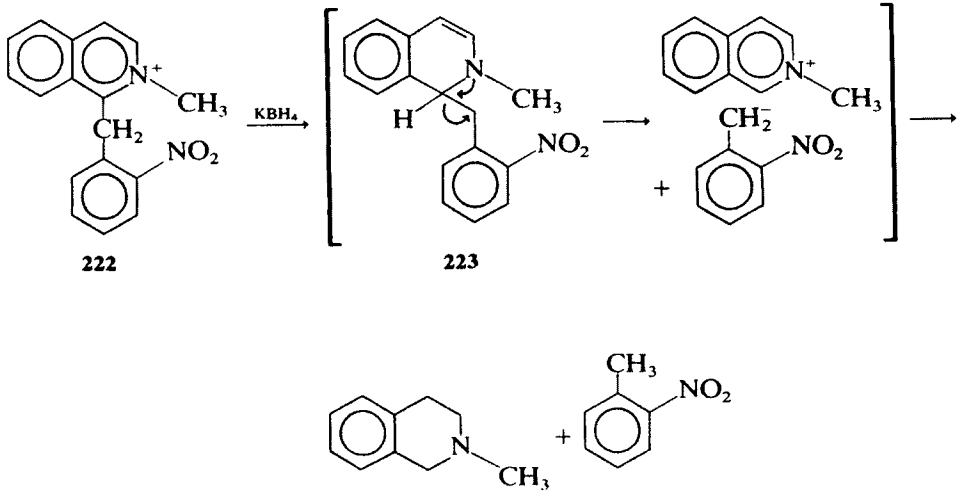
$R^1 = H, OCH_3$

A somewhat similar alkylation has been carried out in the presence of sodium borohydride (Eq. 62), except that the final product is a 1,2-dihydroisoquinoline **221**.[226] It is believed that the bulky 2,6-disubstituted benzyl substituent prevents further reduction.



221 (62)

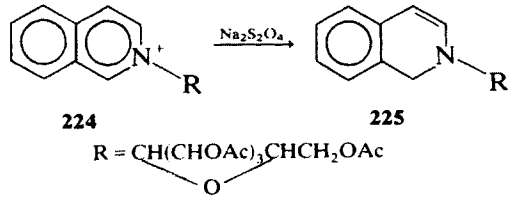
Carbon–carbon bond cleavage which has been observed[261] when 1-(2-nitrobenzyl)-2-methylisoquinolinium salts (**222**) are reduced by the action of potassium borohydride has been attributed to a retro reaction that occurs after reduction has reached the dihydro stage **223** (Scheme 4).



222 **223**

Scheme 4

Commercial exploitation of 1,2-dihydroisoquinoline chemistry may be restrained by the cost of hydride-reducing agents unless some alternative type of reducing agent can be found. Thus it is of interest that 1-(tetraacetylglucosido)isoquinolinium bromide (**224**) can be reduced to the 1,2-dihydro derivative **225** by sodium hydrosulfite (Eq. 63).[262] The *N*-methyl and *N*-octyl analogue (**224**, R = CH_3,*n*-octyl) were also believed to give 1,2-dihydroisoquinolines, **225** but an analysis of the products obtained by sodium hydrosulfite reduction of *N*-tetradecyl and *N*-cetylisoquinolinium salts revealed them to contain 3.5 to 4% sulfur.[262]



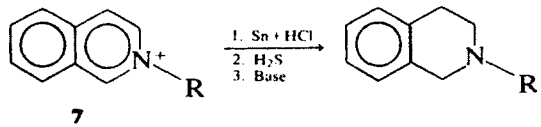
(63)

B. Reduction to 1,2,3,4-Tetrahydroisoquinolines

This reduction has long been useful as the first step in degrading the pyridine ring of isoquinolinium salts via the Hofmann reaction in the search for compounds of enhanced physiological activity, or, more commonly, in an effort to establish structural relationships.

(a) *By Use of Dissolving Metals*

One of the first reduction methods involved dissolving a metal, usually tin, in hydrochloric acid in the presence of the quaternary salt.[263–267] An effective way of removing the tin ion was by subsequent addition of hydrogen sulfide (Eq. 64). Very similar results have been obtained with zinc and acetic acid.[268]



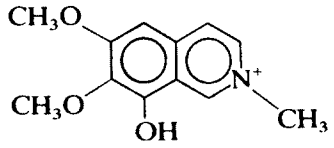
(64)

(b) *By Catalytic Reduction*

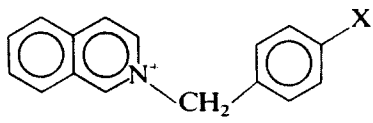
Until sodium borohydride became readily available, catalytic hydrogenation was the favorite method for the reduction of the pyridine ring of isoquinolinium salts. The most frequently used catalyst was platinum (usually from platinum oxide),[17,34,35,50,150,160,224,260,267,269–286] but palladium[157,287–289] and Raney nickel[290–295] have been used to a significant extent.

It was reported[267] that a 2-methyl-6,7-dimethoxy-8-hydroxyisoquinolinium ion (**226**) did not reduce over a platinum catalyst but gave satisfactory reduction with tin and hydrochloric acid. The selective reduction[287] of the nitro group of **227** over palladium catalyst affording the amine **228** in which the isoquinolinium ring is unchanged may be useful in planning syntheses.

The selective hydrogenolysis of a quaternary benzyl group from 4-hydroxy-2-benzylisoquinolinium derivatives is discussed in Section XVI.



226

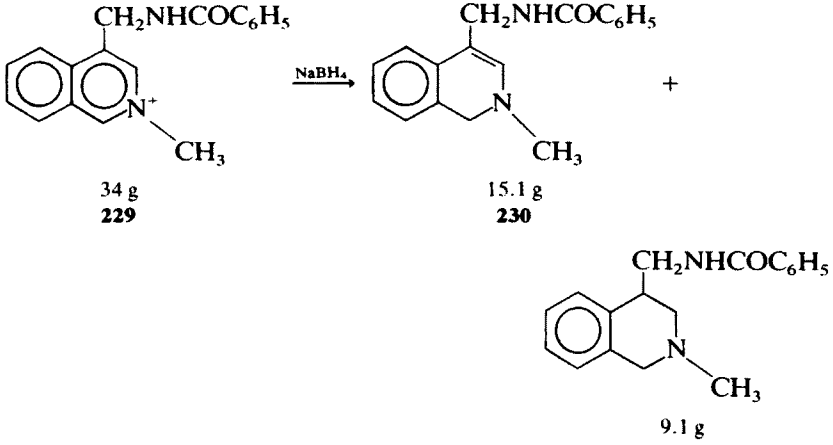


227, X = NO_2
228, X = NH_2

(c) *By Reduction with Borohydrides*

When a source of protons is available, sodium borohydride[17,62,64,129,136,140,148,158,225,230,232,236,251,260,279,284,285,296–310] and potassium borohydride[61,311–314] provided convenient and very general reagents for the conversion of isoquinolinium salts to 1,2,3,4-tetrahydroisoquinolines.

Some of the limitations of the borohydride reductions are obvious: aldehyde and ketone groups will be reduced and occasionally ester groups as well.[230] The problem of reduction being halted at the 1,2-dihydro stage when electron-withdrawing groups are present at position 4 was illustrated in Equation 60. Kröhnke and Zecher observed that even a benzamidomethyl group at position 4 can make the dihydro reduction product **230** the major one (Eq. 65), thus suggesting that the presence of any group except the strongly electron-releasing one[144] at that position may prevent complete reduction of the ring with borohydride. Catalytic reduction of the benzamidomethylisoquinolinium salt **229** took place in good yield.



34 g
229

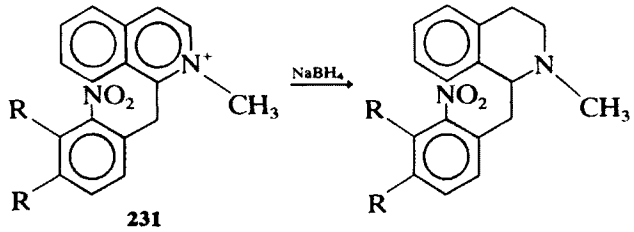
15.1 g
230

9.1 g

(65)

In Scheme 4 it was shown that 1-(2-nitrobenzyl)-2-alkylisoquinolinium salts undergo cleavage as well as reduction when potassium borohydride is used. It has now been shown[261,313] that introduction of a pair of methoxyl groups flanking the nitro group permits "normal" reduction of **231** in 80% yield (Eq. 66). A very plausible explanation for this striking difference in

behavior of two such closely related compounds is that when the flanking methoxyl groups are present, they force the nitro group out of plane and prevent the resonance that would normally stabilize the *o*-nitrotoluene carbanion (Scheme 4).

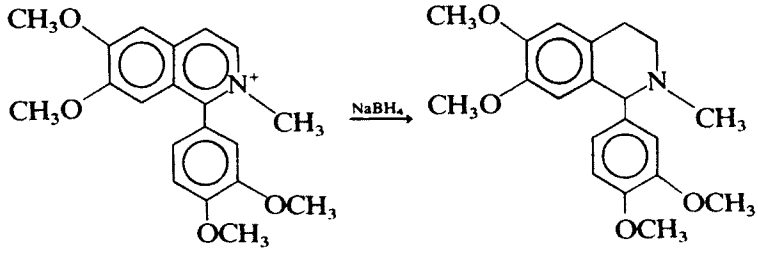


(66)

231

R = H; yield 0%
R = OCH_3; yield 80%

An example of how the catalytic and the borohydride methods complement each other is seen in the easy borohydride reduction of 1-(3,4-dimethoxyphenyl)-2-methyl-6,7-dimethoxyisoquinolinium iodide (**232**) to the tetrahydro derivative **233** (Eq. 67).[304] The same salt **232** could not be reduced by hydrogen over palladium catalyst.

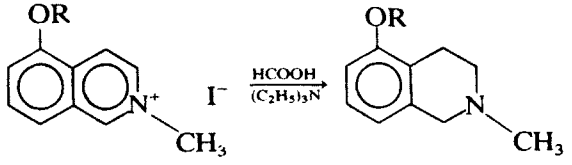


(67)

232 **233**

(d) *By Other Reducing Agents*

The tendency of lithium aluminum hydride to yield only 1,2-dihydroisoquinoline on reduction of isoquinoline salts may be modified[277] by the addition of aluminum chloride. The resulting complex affords tetrahydroisoquinoline in moderate yield.



(68)

234 **235**

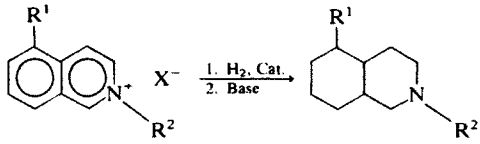
R = H; yield 89%
R = CH_3; yield 77%

A cheap and potentially very useful reducing agent has been used by Durand et al.[284] The quaternary salt **234** is heated with formic acid and triethylamine to afford the 1,2,3,4-tetrahydroisoquinoline **235** in good yields (Eq. 68). This method of reduction is attributed to Yudin et al.[316]

C. Reduction to Decahydroisoquinolines

By choice of suitable conditions, isoquinolinium quaternary salts may be reduced to decahydroisoquinoline without isolation of the 1,2,3,4-tetrahydroisoquinoline intermediate. Mathison and co-workers[282,317] have studied the reduction of some 5-substituted isoquinolinium salts (Table IV.4).

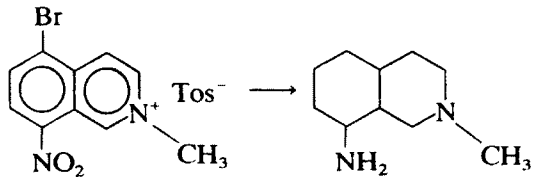
TABLE IV.4 THE REDUCTION OF ISOQUINOLINIUM SALTS TO DECAHYDROISOQUINOLINES



R^1	R^2	X	R^1	Yield (%)
OH	C_2H_5	Br	OH	81
NO_2	CH_3	Tos	NH_2	95

The reduction of the 5-hydroxy salt could be effected in good yield with either platinum oxide[282] or Raney nickel,[318] but when the reduction was carried out in acetic acid containing a trace of sulfuric acid,[319] the bis(2-ethyldecahydroisoquinoline) ether instead of the alcohol was obtained.

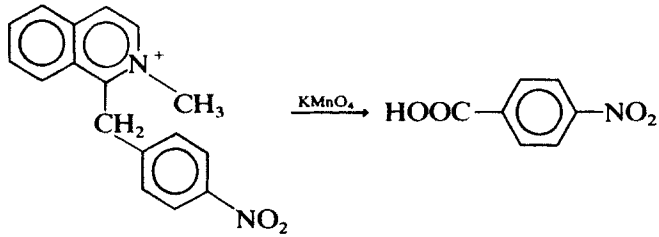
The reduction of the nitro group of 5-nitro-2-methylisoquinolinium tosylate and the saturation of the isoquinolinium nucleus can be carried out in a single step,[317,320] and at 160°C the cis:trans ratio is highest at 1500 psi.[321] Convenient access to the isomeric 8-aminodecahydroisoquinoline **237** is afforded by the reduction–hydrogenolysis of 5-bromo-8-nitro-2-methylisoquinolinium tosylate **236** (Eq. 69).[322]



236 **237** (69)

D. Oxidation

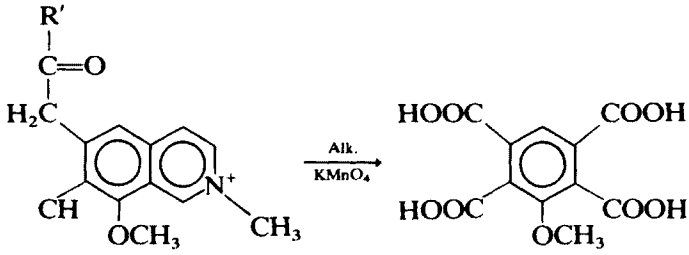
The oxidation of isoquinolinium salts has little synthetic interest. Even the use of oxidation in carrying out degradations for the purpose of structure determination appears to have been limited, perhaps because of the advantages offered by a reduction to the 1,2,3,4-tetrahydro derivatives, followed by a degradation by the Hofmann method. When permanganate oxidation is used, it is not unlikely that the initial step in the reaction is formation of the carbinol amine (Section V) by attack of the hydroxide ion present. In any case, the primary attack appears to be on the pyridinoid ring of the isoquinolinium salts. It was demonstrated[323] by permanganate oxidation (Eq. 70) that the product of the nitration of 1-benzyl-2-methylisoquinolinium ion was the 1-(4-nitrobenzyl) derivative **238**.



(70)

238

In the oxidation of the methiodide of aporubropunctamine-*O*-methyl ether (**239**) with alkaline permanganate, the benzenoid ring remains intact, thus affording some 2,3,5,6-tetracarboxyanisole (**240**, Eq. 71).[4]



(71)

239 **240**

V. ATTACK OF NUCLEOPHILES ON NUCLEUS

Position 1 of the isoquinolinium nucleus is the most electron deficient and is the usual locus for attack by nucleophiles. The rate of this attack[324–326] and, to a considerable extent, the nature of the products isolated, is affected by the degree of electron withdrawal of the substituents, particularly at position 2. Where the substituent at position 2 is methoxyl, Katritzky and

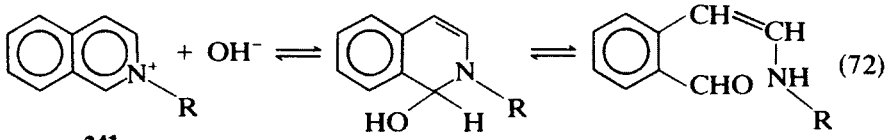
Lunt[327] have shown that the course of the reaction may be influenced by the hardness or softness[328,329] of the nucleophile.

A. Water and Hydroxide Ion

Before the advent of the Brönstedt–Lowry concept of acids and bases, quaternary ammonium salts were assumed to be derived from the quaternary hydroxide or "base." When it was found that the addition of hydroxide ion to certain aromatic quaternary salts, including the isoquinolinium salts, led to the formation of a carbinol amine, Hantzsch[330,331] designated these carbinol amines as "pseudobases."

(a) *Carbinolamine–Aldehyde Equilibrium*

To account for certain ring-opened products, Gadamer[332,333] proposed a threefold tautomerism involving the ammonium salts **241**, the carbinol amine **242**, and the open chain aldehyde **243**. A somewhat modernized representation of the proposal is shown in Eq. 72. Beke,[334] in a review

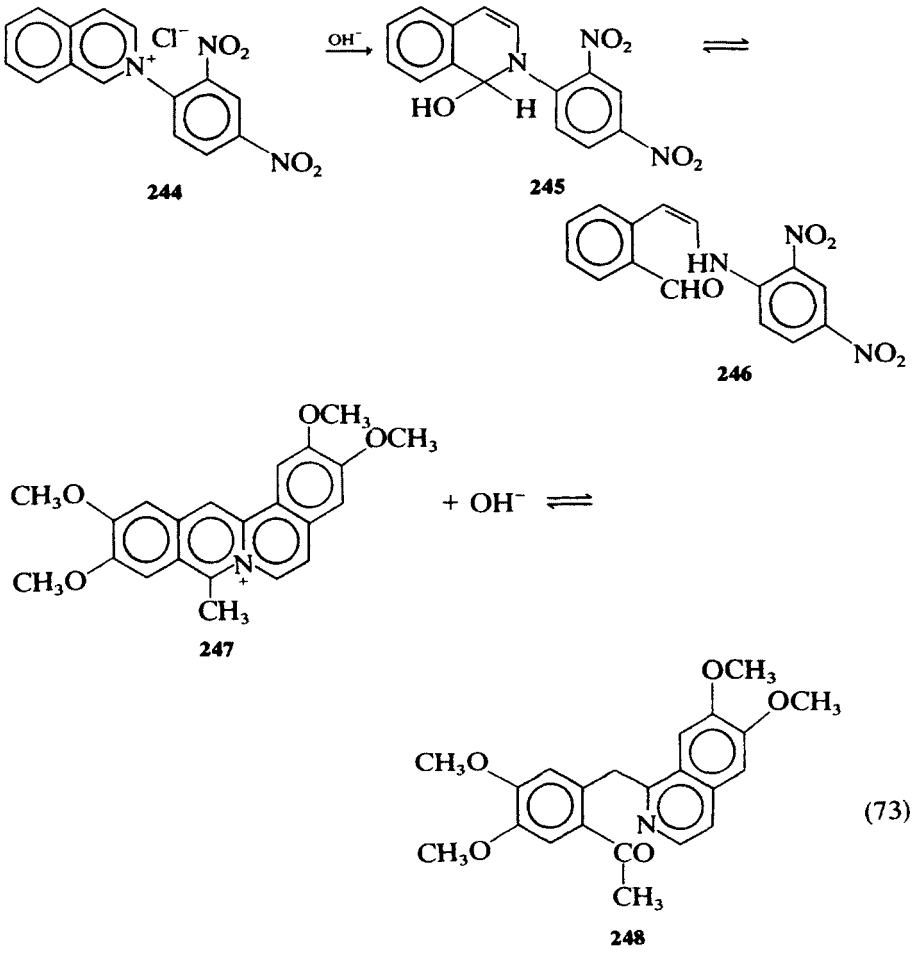


(72)

241 **242** **243**

dealing with heterocyclic pseudobases, has questioned the existence of any equilibrium mixture containing all three species, whereas other authors[335] feel that the accuracy of the physical methods applied in analysis does not exclude the existence of a small quantity of the aldehyde at equilibrium under some conditions. Certainly, the proximity of the aldehyde function to the amine group in the open form would normally favor an equilibrium in which at most only a small quantity of aldehyde was present. This tendency of the carbonyl group and the amine to recombine to yield the cyclic carbinol amine may be reduced by steric and electronic factors. The carbinol amine **245** obtained by the action of sodium carbonate on 2-(2,4-dinitrophenyl)isoquinolinium chloride (**244**) affords, on heating, the aldehyde **246**, which can be isolated.[336] At least one other instance of the isolation of the aldehyde form is known.[337] In this case it is probable that the low basicity of the amine group of the amino aldehyde, as well as the size of the dinitrophenyl group, combine to make recyclization relatively unfavorable.

Coralyne (**247**) has long been recognized[338] as having an isolable open form **248** which is a ketone rather than an aldehyde (Eq. 73).

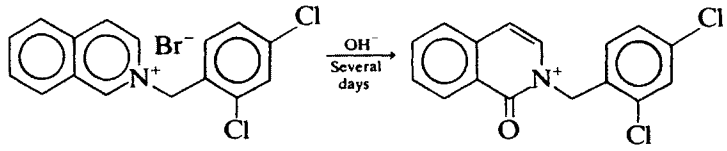


(73)

(b) *Irreversible Changes*

In addition to the reversible hydration of isoquinolinium salts (with or without ring opening), there are irreversible changes that occur when isoquinolinium salts are allowed to stand in alkaline solution. An example is the observation[139] that 2-(2,4-dichlorobenzyl)isoquinolinium bromide (**249**) on standing for several days in sodium hydroxide at room temperature afforded the isocarbostyryl **250** (Eq. 74). Similar observations[266] have been made when quaternary salts have been heated with alkali.

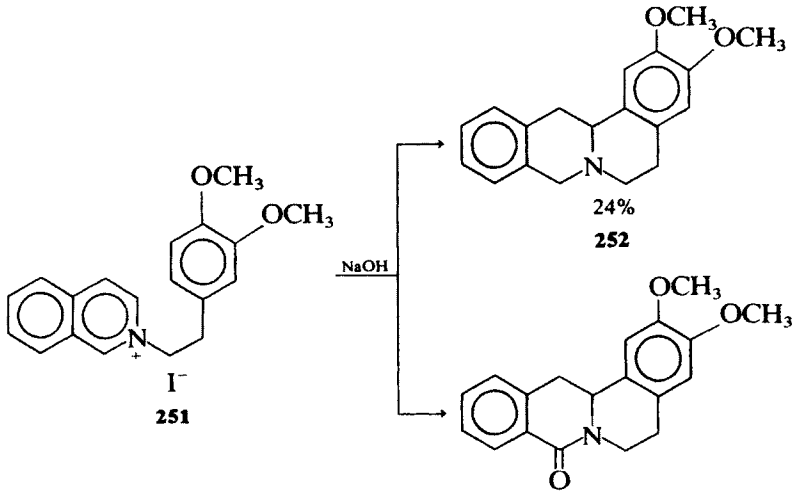
Although this transformation might be attributed to air oxidation of the intermediate carbinolamine, it seems possible that some, if not all, of the isocarbostyryl formation is due to disproportionation, with 1,2-dihydro-2-(2,4-dichlorobenzyl)isoquinoline as the reduced product. Since 1,2-dihydro-



249 250 (74)

isoquinolines are enamines and hence reactive, it would not be too remarkable if no pure product corresponding to the reduction product was usually isolated.

A cyclization has been based on such a disproportionation. Brown and Dyke[339] have found that 2-[2-(3,4-dimethoxyphenyl)ethyl]isoquinolinium iodide (**251**), on treatment with alkali, afforded two cyclization products (**252** and **253**) in almost equal amounts (Eq. 75). The use of this cyclization has been extended by Govindachari et al.[63]

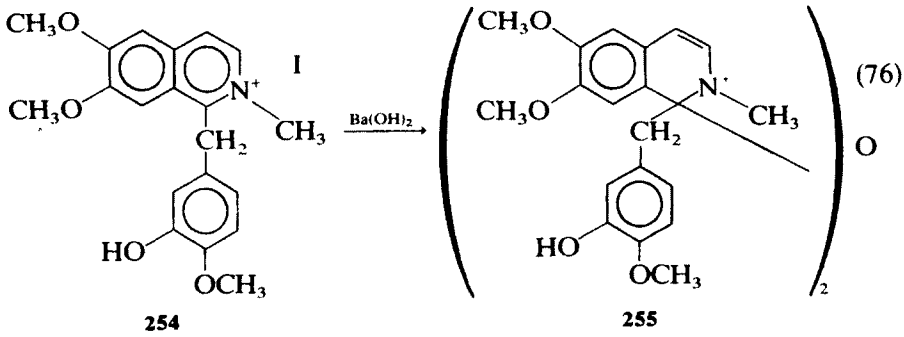


251 252 253 (75)

Another product that may be isolated from the reaction of an isoquinolinium ion and hydroxide ion is the ether **255** (Eq. 76).[269] The ether can be reconverted to the salt **254** by the action of acid.

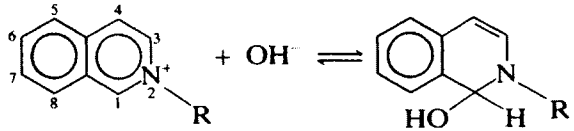
(c) *Physical Studies of Base–Carbinolamine Equilibrium*

A major factor in determining the ease of nucleophilic attack of the hydroxyl ion on the isoquinolinium ion is the degree of electron deficiency at position 1. This electron deficiency may be enhanced by proper substitution on the isoquinolinium nucleus but may be done more effectively by altering the quaternizing group at position 2. An indication of these electron



254 255 (76)

densities is afforded by the work of the Johnson[324,325] and Bunting[326] groups, who determined the acidity at which the carbinol amine **256** and aromatic cation **7** were present in equal amounts, as evidenced by uv spectroscopy (Eq. 77). This acidity was expressed as pK_{ROH}. Where R = CH_3, the introduction of a nitro group at position 5 lowers the pK_{ROH} from about 15.2 to 11.7, a difference in basicity at equilibrium greater than three orders of magnitude. Bromine at position 4 ($pK_{ROH} = 13.5$) or at position 5 ($pK_{ROH} = 13.7$) produces changes that are intermediate in magnitude. Rate coefficients and Arrhenius parameters for reaction of hydroxyl ions with 2-methylisoquinolinium iodide have been reported.[340] The effect of altering the quaternizing group at position 2 from methyl to cyano changes the pK_{ROH} from approximately 15.3 to −2.0, a change of greater than 10^{17} in hydrogen ion concentration at equilibrium. When the 2,4-dinitrophenyl is used as the 2-substituent, the pK_{ROH} is ~8.6, thus nearly 10^{10} less acidic than the 2-cyanoisoquinolinium ion at equilibrium.

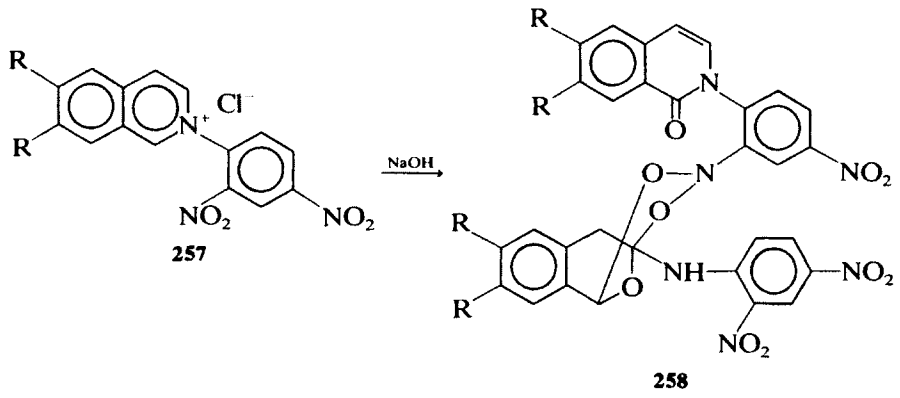


7 256 (77)

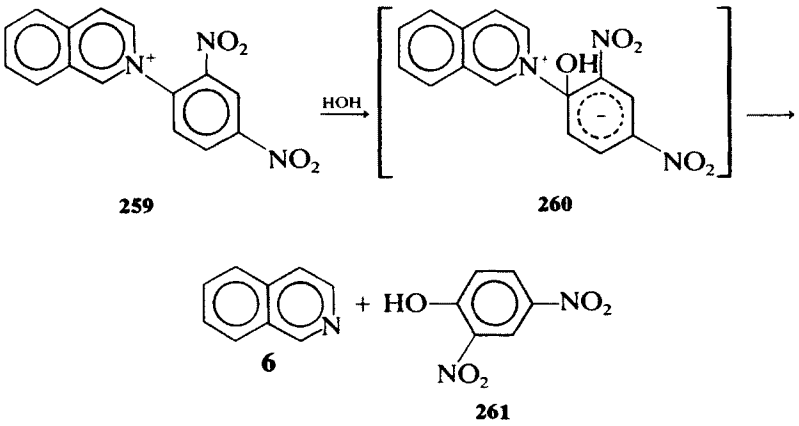
(d) *Reaction of 2-Aryl Salts*

Probably because it affords so many interesting crystalline products, the 2-(2,4-dinitrophenyl)isoquinolinium cation **257** has been a favorite isoquinolinium ion for the study of the reaction of nucleophiles,[67,172,326,341–343] and a number of analogues[69,72,344] have likewise been studied. In all cases the carbinol amine appears to have been one of the derivatives prepared, usually by the addition of aqueous sodium carbonate or ammonia to the cation.

The use of a stronger base such as sodium hydroxide can lead to a mixture of products, some of which (e.g., **258**) are believed to be linked through a



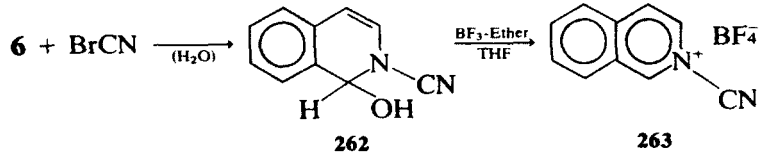
nitrogen atom that was once in a nitro group.[337,341] Azoxy derivatives are also believed to be formed.[341] In keeping with the pK_{ROH} of 8.6, 2-(2,4-dinitrophenyl)isoquinolinium ion (**259**) is not converted to the carbinolamine by water alone. Heating the salt with water brings about a nucleophilic attack on the dinitrophenyl ring, thus yielding isoquinoline (**6**) and 2,4-dinitrophenol (**261**, Eq. 78).[326] A Meisenheimer complex (**260**) was suggested[326] as an intermediate.



(78)

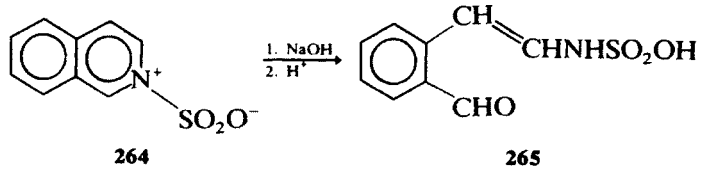
(e) *Reaction of Other 2-Substituted Salts*

An unusually interesting substrate for the study of nucleophilic reaction is the 2-cyanoisoquinolinium ion. It is so susceptible to the attack of even a water molecule that conventional techniques for the preparation of quaternary salts afford the carbinol amine **262** instead (Eq. 79).[79] Conversion of the carbinol amine **262** to the quaternary fluoroborate **263** can be effected by addition of boron trifluoride etherate to a solution of the carbinolamine in tetrahydrofuran.



(79)

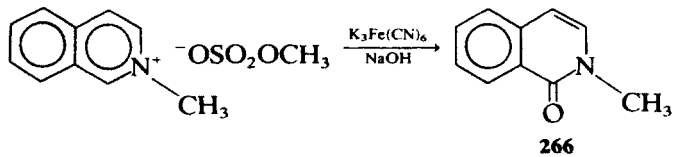
Probably somewhat less electron deficient but still quite reactive is the betaine of 2-sulfoisoquinolinium ion **264** which undergoes ring opening with sodium hydroxide,[98] thus yielding **265** (Eq. 80).



(80)

(f) *Other Reactions*

It was mentioned earlier [Section V.A(b)] that formation of isocarbostyryls may take place if carbinol amines are allowed to stand or are heated with alkali. Yields of the isocarbostyryl **266** can usually be increased by the addition of potassium ferricyanide to the alkaline reaction mixture (Eq. 81),[106] and many such oxidations have been carried out.[32,55,266,345–347]

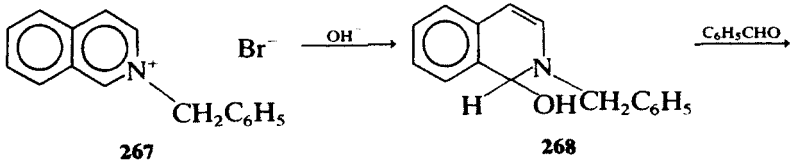


(81)

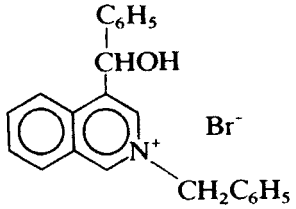
A relatively new development is the utilization of the enamine character of the carbinol amines (e.g., **268**) obtained from isoquinolinium salts. If 2-benzylisoquinolinium bromide (**267**) is treated with alkali in the presence of benzaldehyde, 2-benzyl-4-(α-hydroxybenzyl)isoquinolinium bromide (**269**) is obtained (Eq. 82).[348]

B. Alcohols and Alkoxide Ions

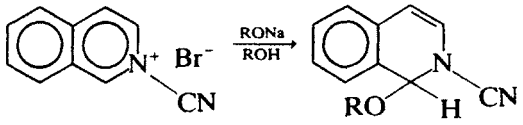
It is not surprising that an alkoxyl ion in solution in the corresponding alcohol converts the 2-cyanoisoquinolinium ion (**270**) to the 1-alkoxy-1,2-dihydro derivative **271** (Eq. 83),[79] since reaction could presumably be carried out without the alkoxide ion. 1-Alkoxy-2-substituted 1,2-dihydroisoquinolines **272** are usually prepared by the reaction of the carbinol amine with the appropriate alcohol (Eq. 84). This may even be done without the isolation of the intermediate carbinol amine.[139]



267 268

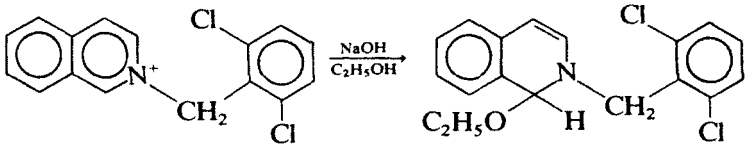


269 (82)



270 271 (83)

R = CH_3, C_2H_5, i-C_3H_7, t-C_4H_9



272 (84)

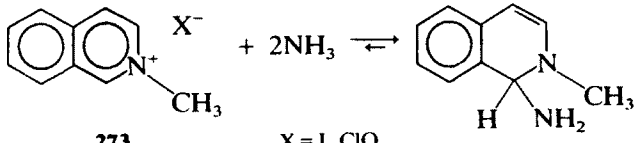
C. Ammonia and Amines

Factors that influence the addition of ammonia and amines to the isoquinolinium nucleus are similar to those seen in the addition of hydroxyl ion (Section V.A). When strongly electron withdrawing substituents are present on the quaternary nitrogen, ring opening can occur.

(a) *Ammonia*

As mentioned in Section V.A, the action of aqueous ammonia on isoquinolinium salts produces the corresponding carbinol amine as a consequence of the presence of hydroxide ion in the equilibrium mixture. Recently, Zoltewicz et al.[187] have examined the behavior of the 2-methylisoquinolinium cation **273** in liquid ammonia (Eq. 85) using, as a

diagnostic means, the characteristically large upfield shift of the nmr signals given by the ring protons of the heterocyclic ring, especially that from the proton of position 1, as the reaction progresses. Even at approximately zero degrees, equilibrium with the 1-amino derivative **274** was reached before the first measurement could be made and all indications showed that conversion was complete. The possibility that a nucleophilic attack by the iodide ion was being observed was virtually eliminated by demonstrating that identical results were obtained when the poorly nucleophilic perchlorate ion was used. The possibility that the attack on the isoquinolinium ion was not by ammonia molecules but by the amide ion ($10^{-13.8}$ *M*) in equilibrium with it (Eq. 86) was disposed of very convincingly by showing that the reaction was 100% complete within the minimum time needed to make an observation, even when the liquid ammonia had been made 1 molar in ammonium bromide.

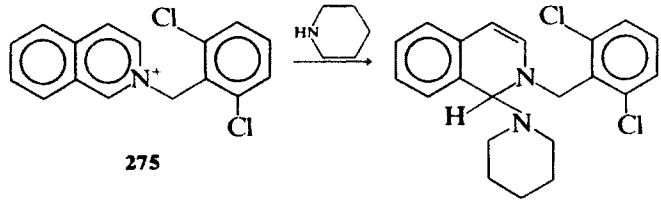


273 X = I, ClO_4 **274** (85)

$$2NH_3 \rightleftharpoons NH_4^+ + NH_2^- \qquad (86)$$

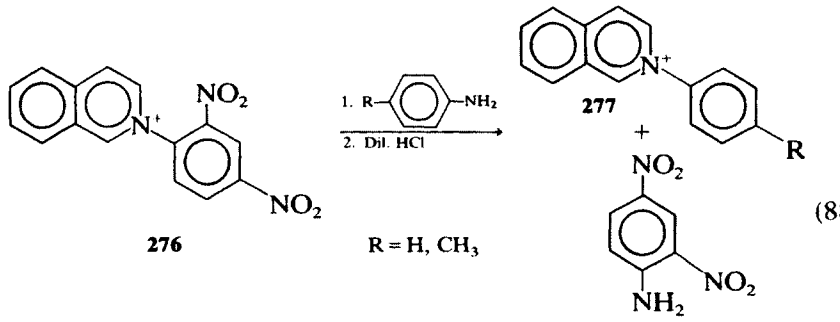
(b) *Simple Amines*

Kröhnke and Vogt[139,349] reported that piperidine, a secondary amine, simply adds to position 1 of 2-(2,6-dichlorobenzyl)isoquinolinium ion (**275**,



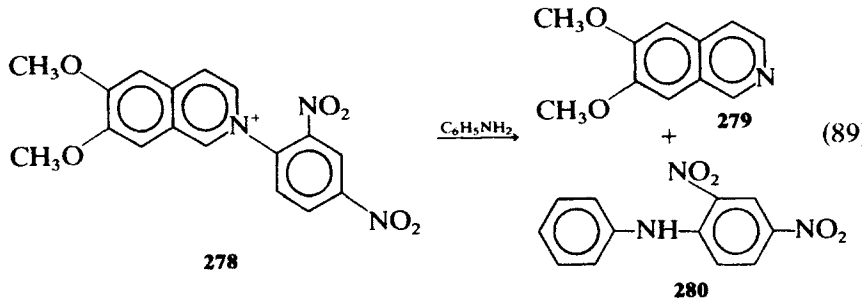
275 (87)

Eq. 87). Zincke and Weisspfennig[67] found that an 2-(2,4-dinitrophenyl)-isoquinolinium cation (**276**) reacted with anilines to produce addition compounds that, when treated with hydrochloric acid, gave 2-phenylisoquinolinium salts (**277**, Eq. 88). Kabachnik and Zitser[344] found that when the reaction was extended to a 2-(2,4-dinitrophenyl)-6,7-dimethoxyisoquinolinium cation (**278**), 2,4-dinitrodiphenylamine (**280**) was produced rather than 2,4-dinitroaniline and the other product was 6,7-dimethoxy isoquinoline (**279**, Eq. 89). This indicates that the dinitrophenyl ring, rather than the isoquinolinium ring, is the more favorable position for nucleophilic attack by aniline, a probable effect of the electron release by



(88)

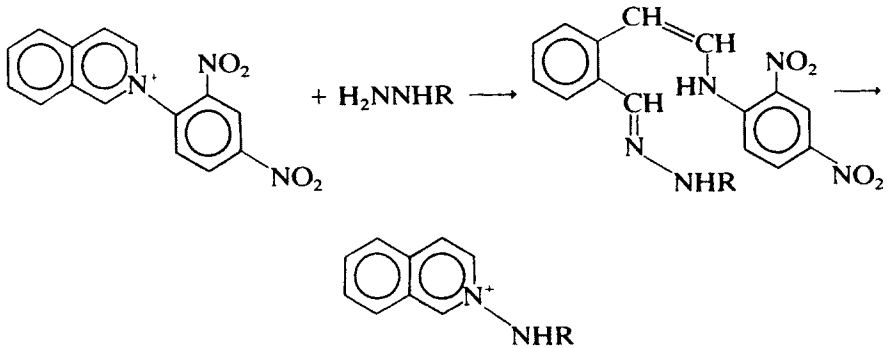
the alkoxyl groups on the electron deficiency at position 1 of the isoquinolinium nucleus.



(89)

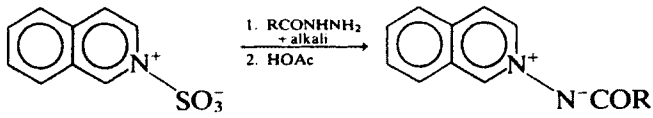
(c) *Hydrazines*

Hydrazine derivatives have been extensively studied as an alternative for aniline in this replacement reaction[172,343,350–353] (Eq. 90). It would seem likely that electron-withdrawing groups other than dinitrophenyl might activate the isoquinolinium ring sufficiently to permit this type of interchange, and one such claim is found in the patent literature (Eq. 91).[354]



(90)

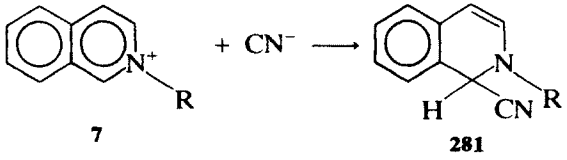
R = H, aryl, acyl, heterocyclic



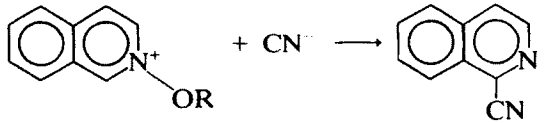
(91)

D. Cyanide Ion

Attack of the cyanide ion on isoquinolinium quaternary salts **7** also occurs at position 1,[79,266,342,355] and the adducts **281** have sometimes been referred to as *pseudocyanides* (Eq. 92).[331] The nature of the substituent on nitrogen may vary from alkyl to cyano without affecting the course of the reaction. Where the substituent on nitrogen is methoxyl (**282**, R = CH_3) addition also occurs, but there is a subsequent elimination of methanol to give 1-cyanoisoquinoline (**283**, Eq. 93).[356] A similar addition–elimination was observed[132] when a cyanide ion was added to the *N*-acetoxyisoquinolinium ion (Eq. 93, R = $COCH_3$).



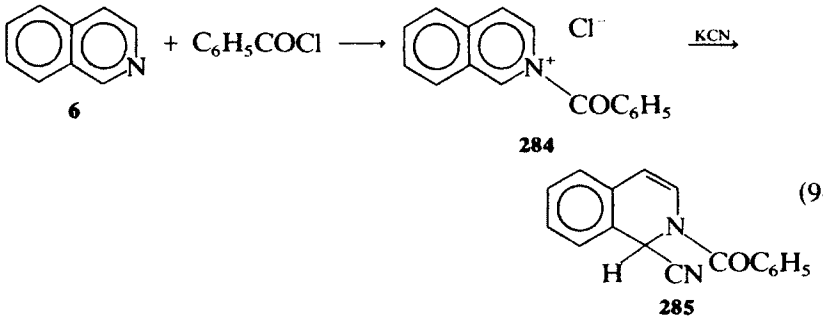
7 **281** (92)



282 **283** (93)

R = CH_3, CH_3CO

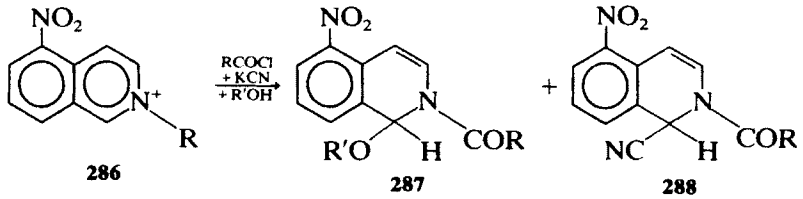
Since the first step in the formation of a Reissert compound **285**[76] is probably the formation of an acylium salt **284**, the second step would be the nucleophilic addition of the cyanide ion at position 1 (Eq. 94). In a recent



6 **284** **285** (94)

study of the behavior of 5-nitroisoquinolinium ion **286** in the Reissert

reaction, Uff et al.[357] have shown that hydroxyl ion, if the solvent is water, or alkoxyl ion, if alcohol is the solvent, attacks preferentially, yielding **287** so that the Reissert compound **288** becomes only the minor product (Eq. 95). Presumably, the 5-nitro group would make the system more electron deficient and hence more reactive toward nucleophiles. Why the system is made so much more preferential toward the attack of hydroxyl and alkoxyl ions is not easy to understand. Uff et al.[357] have suggested that the nitro group makes the intermediate isoquinolinium salt a harder acid on the Pearson–Songstadt scale[329] with a resulting greater preference for attack by hard bases such as hydroxyl and alkoxide instead of cyanide ion, which is classified as soft.



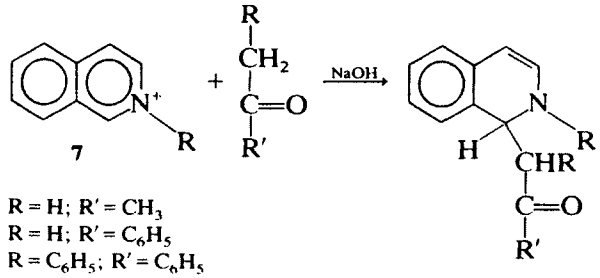
(95)

E. Carbanions

Carbanions are addends of particular interest in that at least some of the products are useful intermediates in synthesis. Of particular interest as intermediates are the products obtained by addition of the anion from *o*-nitrotoluene, although those from enols and nitroalkanes have furnished products of theoretical interest.

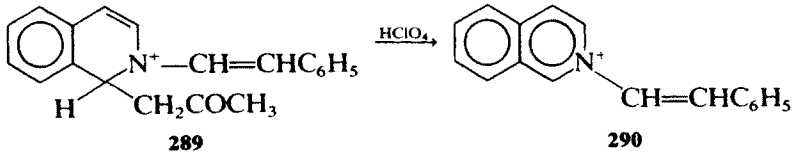
(a) *Enols*

Kröhnke and Voigt[139] showed that isoquinolinium salts **7** in the presence of alkali reacted with acetone, acetophenone, and desoxybenzoin at position 1 (Eq. 96).



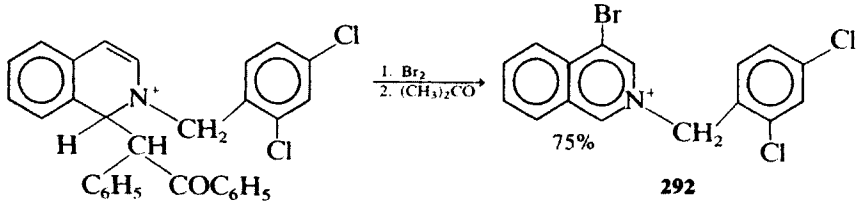
(96)

As a class, the adducts (e.g., **289**) appear to be relatively unstable[139] and revert to the isoquinolinium salt **290** on acidification (Eq. 97).



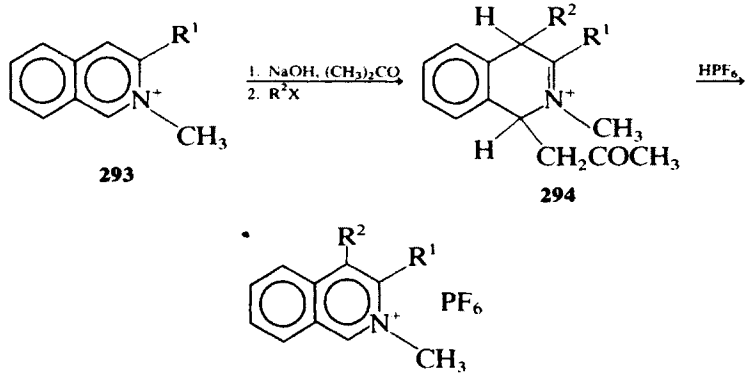
289 290 (97)

There have been some applications based on the enamine character of the products. Kröhnke and Vogt[349] showed that bromination of these adducts (e.g., **291**) provided a convenient route to 3-bromoisoquinolinium salts **292** (Eq. 98).



291 292 (98)

Recently, it has been found[138] that the acetone adduct of isoquinolinium methiodide **293**, not yet isolated in a pure condition, can be alkylated or acylated and the product **294** subsequently cleaved to afford a 4-substituted salt **295** (Eq. 99). This is an extension of a similar alkylation carried out earlier on berberine and its congeners.[358,359]

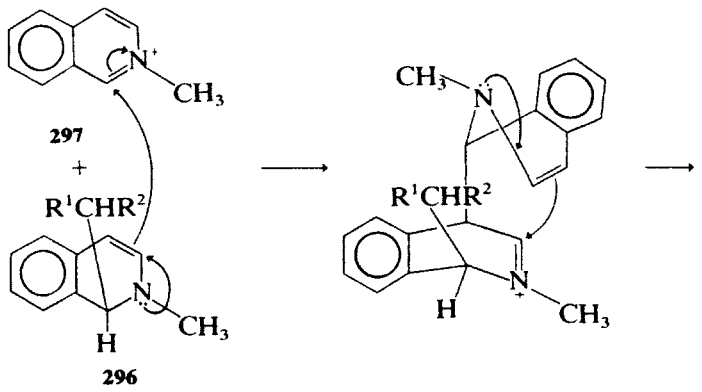


293 294 295 (99)

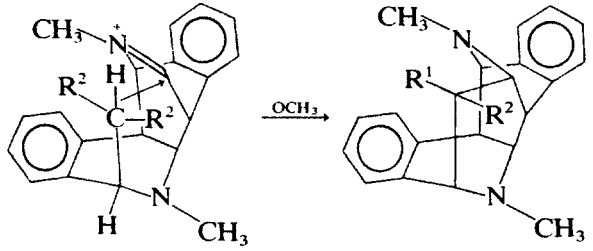
$R^1 = H, CH_3$; R^2 = alkyl or acyl

Schleigh[360] has studied the addition of active methylene compounds with 2-methylisoquinolinium salts under conditions that lead to 2 moles of the salt being added to 1 mole of the active methylene compound. He found that the products **298** were complex bridged systems (Eq. 100).

The reaction is believed to involve an attack by the electrons of the primary addition product (enamine **296**) on position 1 of a second isoquinolinium ion **297**. Two cyclizations follow, both involving additions to



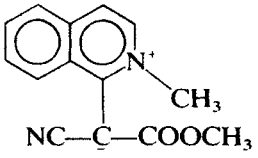
297 + R^1CHR^2 → 296 → (100)



298

$R^1 = CN$; $R^2 = COOCH_3$, $CONH_2$, CN

iminium ions. Some evidence that the initial reaction in the series is the attack of the active methylene compound at position 1 is afforded by the isolation of the betaine **299** or "anhydrobase" in 7% yield when methyl cyanoacetate was used in the addition.

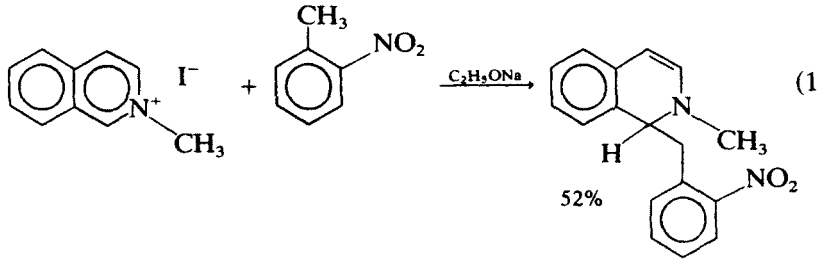


299

(b) *Nitrotoluenes*

Toluenes that have a nitro group ortho[361] or para[244] to the methyl have frequently been condensed with quaternary isoquinolinium salts, usually in the presence of sodium alkoxides. An example[361] may be seen in Eq. 101.

The presence of alkoxyl groups on the toluene[261,305,362,363] or on the isoquinolinium nucleus[363] does not appear to interfere with the success of

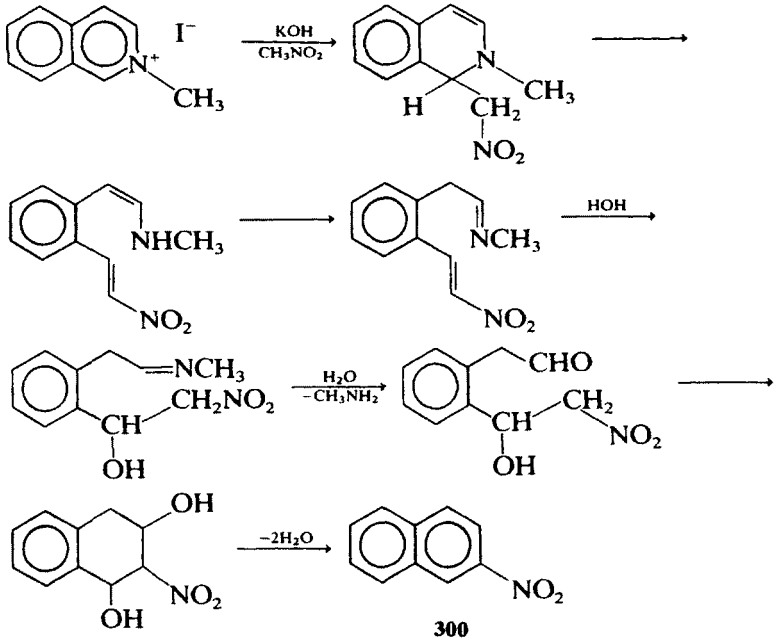


(101)

the reaction. The reaction is probably reversible, for Neumeyer et al.[261] have shown examples of carbon–carbon bond cleavage during the reduction of 1-(2-nitrobenzyl)-2-methylisoquinolinium salts with potassium borohydride (Scheme 4, Section A).

(c) *Nitroalkanes*

The isoquinolinium ion undergoes some base-catalyzed reactions with nitroalkanes, all of which are believed to begin with the attack of the carbanion at the 1-position of the isoquinolinium ring. One such transformation leading to 2-nitronaphthalene (**300**) has been explained by Leonard and Leubner[364] (Scheme 5).



300

Scheme 5

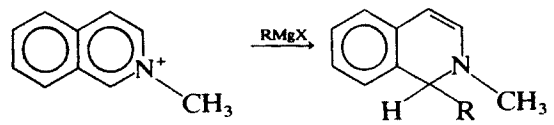
The reaction of 2 moles of the 2-methylisoquinolinium cation with nitroalkanes turned out to be more complex than first[364] believed. Schleigh,[360,365] in an impressive application of pmr techniques, showed that the products are bridged ring compounds (Eq. 100, Section V.E(a); $R^1 = H$, $R^2 = NO_2$; $R^1 = CH_3$, $R^2 = NO_2$). Other authors[366] have determined the relative affinity of the 2-(2,6-dichlorobenzyl)isoquinolinium ion for nucleophilic agents by the polarographic transfer reaction of the cation to the nitromethyl anion.

F. Organometallics

In the reaction with quaternary isoquinolinium salts the Grignard reagent has found more use than has organocadmium and appears to be clearly superior to it. Less is known about the usefulness of the organolithium reagent for such an application.

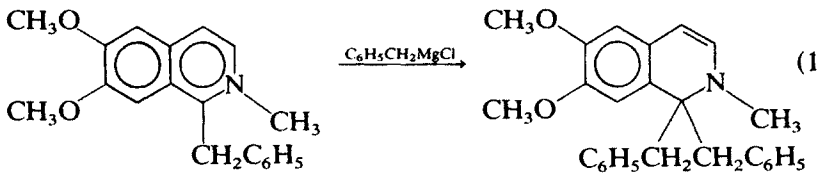
(a) *Grignard Reagent*

Freund and Bode[367] found quite early that the Grignard reagent would add to 2-methylisoquinolinium salts at position 1 (Eq. 102). This



$R = CH_3, C_2H_5, C_6H_5, C_6H_5CH_2$ **301** (102)

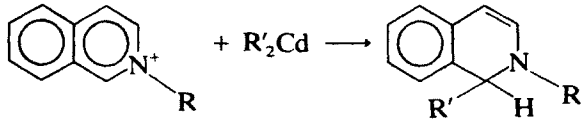
reaction has been used extensively,[12,252,305,368,369] and the yields of the 1,2-disubstituted products **301**, where reported,[12] are usually better than 50%. The reaction seems little affected by the presence of electron-releasing groups in the benzenoid ring[148,252,369,370] or of alkyl substituents at position 1 (Eq. 103).[252,370] A major interest in creating 1-benzyl- (**302**) or 1-allyl-1,2-dihydroisoquinolines was the study of the rearrangement of alkyl groups from position 1 to position 3.[148,252,370]



302 (103)

(b) *Organocadmium Reagents*

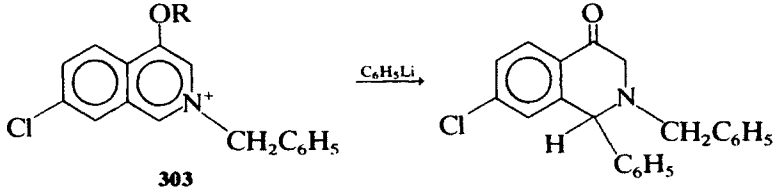
Bradley and Jeffrey[12] have found that, in general, organocadmium reagents add to the isoquinolinium ion more slowly and apparently in poorer yield than do Grignard reagents (Eq. 104).



(104)

(c) *Organolithium Reagents*

Organolithium reagents do not appear to have been used extensively in reactions with isoquinolinium salts. Fryer et al.[160] found that 2-benzyl-4-hydroxy(or methoxy)-7-chloroisoquinolinium salts (**303**) react with phenyllithium to afford 1-phenyl-2-benzyl-7-chloro-2,3-dihydro-4(1*H*)-isoquinolinone (**304**, Eq. 105).



(105)

303 **304**

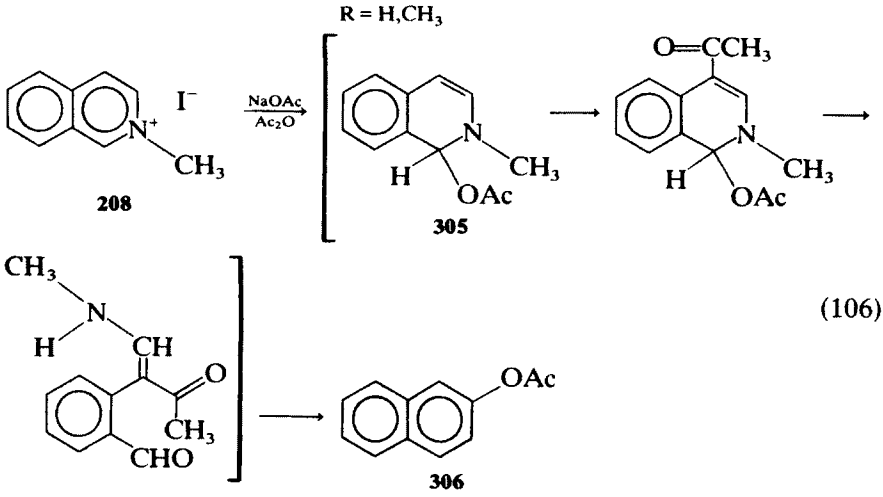
G. Other Nucleophiles

Shamma et al.[371] have proposed that their transformation of 2-methylisoquinolinium ion (**208**) to 2-acetoxynaphthalene (**306**) by the action of sodium acetate and acetic anhydride occurs by way of an initial attack of acetate ion on the isoquinolinium nucleus (Eq. 106). It was also suggested that the resulting acetoxy enamine (**305**) undergoes acylation, ring opening, and recyclization.

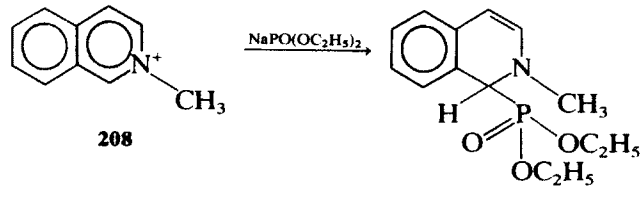
Nucleophilic attack on the isoquinolinium ion **208** by the diethylphosphinate ion has been used to generate a new type of corrosion inhibitor (**307**, Eq. 107).[372,373] The great reactivity of the 2-cyanoisoquinolinium cation (**53**)[79] permits reaction with nucleophiles such as the sodium salt of *tert*-butylhydroperoxide (Eq. 108).

Sheinkman et al.[374] have taken advantage of the reactivity of 2-acylisoquinolinium cations **308** to use them in a hetarylation reaction with compounds such as pyrrole[78] and thiophene and selenophene (Eq. 109).[374]

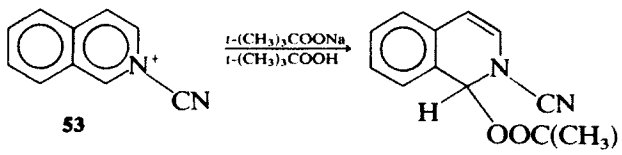
The trichloromethyl carbanion generated by the action of 50% potassium



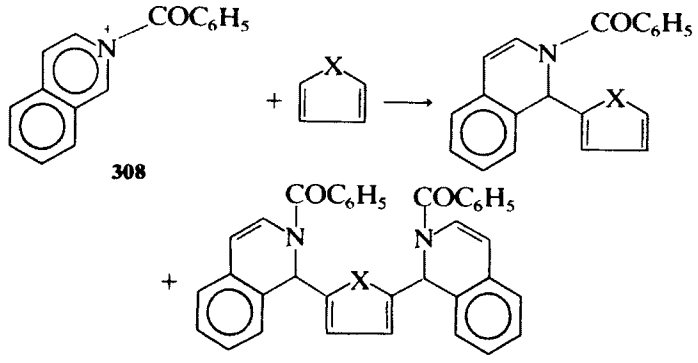
(106)



(107)

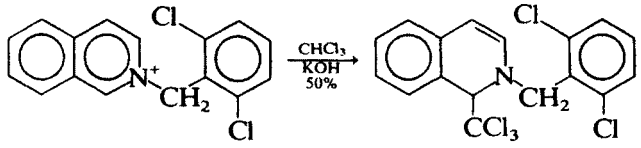


(108)



(109)

hydroxide on chloroform has also been found[375] to function as an effective nucleophile (Eq. 110).



(110)

VI. ELECTROPHILIC SUBSTITUTION

It would be expected that electrophilic substitution of the isoquinolinium quaternary cation would be difficult and no examples were found. It appears to be conceded that electrophilic substitution is better done on the base with quaternization as a subsequent step.

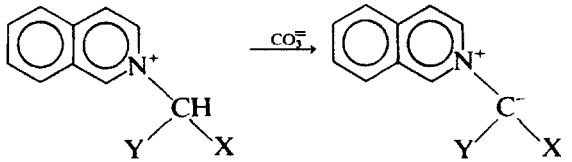
Another alternative is to convert the quaternary salt to an enamine by a nucleophilic reaction. Electrophilic substitution on the enamine can give the substituted aromatic quaternary salt[349] [Eq. 98, Section V.E(a)].

VII. REACTIONS OF QUATERNARY SIDE CHAIN

As discussed earlier [Section II.A(b)], isoquinolinium salts have been prepared with a variety of substituents on the side chain at position 2. The combined effect of these substituents and the charge on quaternary nitrogen lead to betaine formation, condensations, cleavages, rearrangements, addition, and eliminations.

A. Betaine Formation

When the quaternary side chain has one or two electron-withdrawing groups attached to the methylene or methine carbon (e.g., **309**) which is attached to the quaternary nitrogen, the methylene or methine group is usually sufficiently acidic to form the betaine **310** when treated with carbonate ion (eq. 111). Hydroxide ion is less suitable because it induces cleavage (see Section VII.C). The betaines produced[56,376–380] frequently have pronounced color, with the bathochromic effect depending in general on the electron-attracting power of the substituents.[379]



(111)

309 **310**

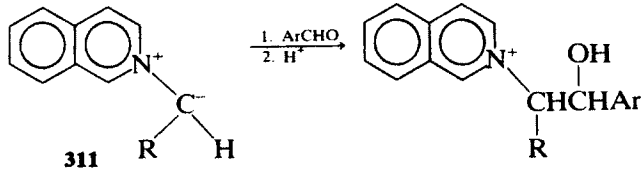
X or Y (or both) are electron-withdrawing substituents

B. Condensation

Isoquinolinium betaines have ylide character and undergo various condensation reactions, including the aldol condensation, alkylation and arylation, acylation, and related transformations.

(a) *Aldol Condensation*

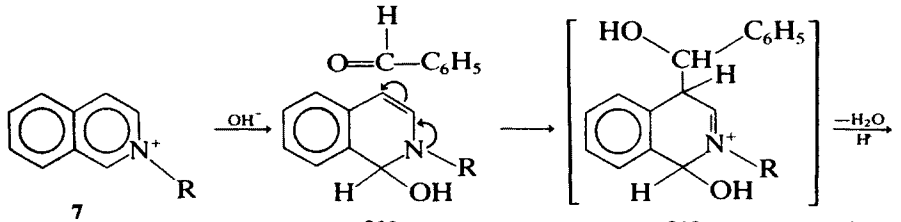
Various instances of aldol condensation between isoquinolinium betaines **311** and aromatic aldehydes have been reported (Eq. 112).[38,381-384]



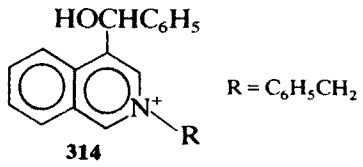
(112)

R = $CH{=}CH_2$, COC_6H_5, $CH_2C_6H_4NO_2$, $CH{=}CHC_6H_5$

Sainsbury et al.[136] have shown that the reaction with aldehydes is more complex than first thought, and in one instance a compound originally described[381] as the simple aldol product actually had the phenylcarbinol group at position 4 (Eq. 113). The explanation[136] for this attack on the isoquinoline nucleus is that the isoquinolinium cation **7** is converted first to the carbinolamine **312**, which functions as an enamine and adds the al-

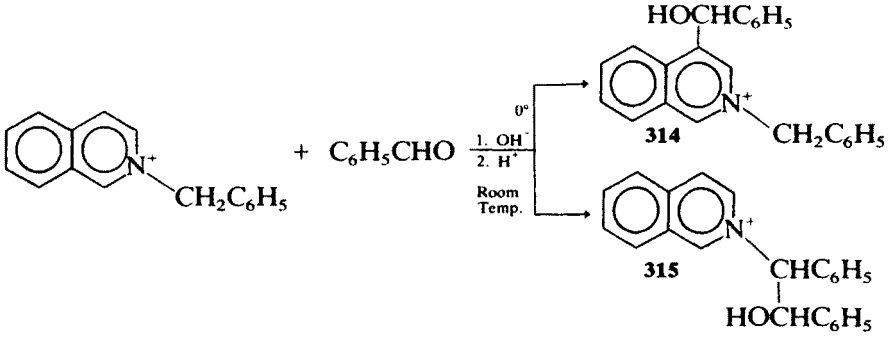


(113)



R = $C_6H_5CH_2$

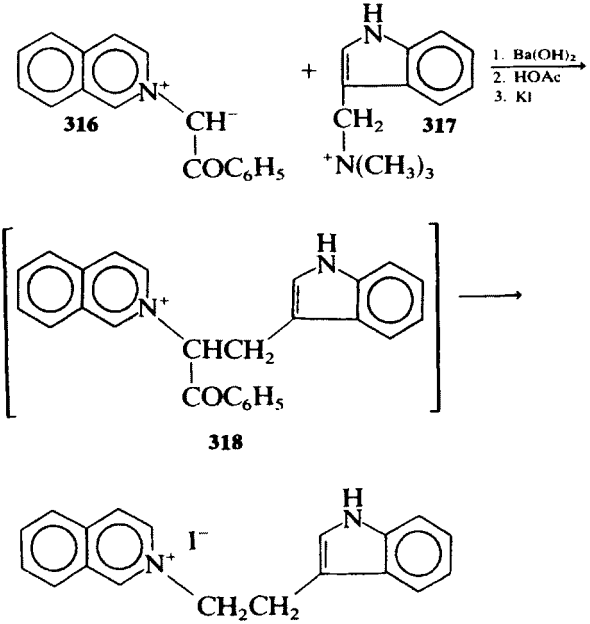
dehyde at position 4 to yield **313** and then loses a molecule of water to produce **314**. Ahlbrecht and Kröhnke[384] found that the temperature at which the reaction was carried out was critical in determining the course of the reaction. When the reaction was carried out as reported previously[381] but allowed to take place at room temperature instead of 0°C, the product was the simple aldol **315** (Scheme 6).



Scheme 6

(b) *Alkylation and Arylation*

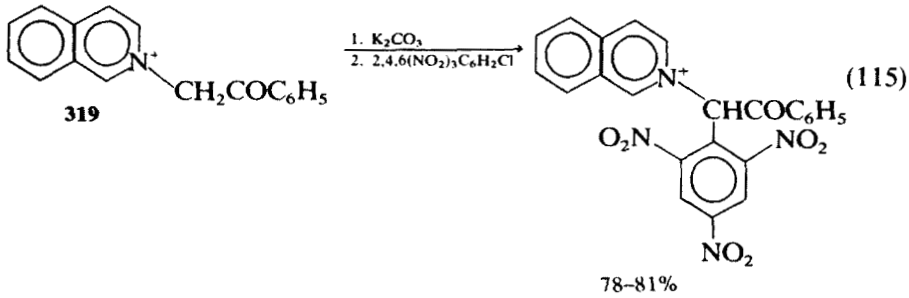
As suggested by analogy to pyridinium salts,[385] the alkylation and arylation of isoquinolinium betaines (e.g. **316**) can be carried out. The alkylating agent was trimethylskatylammonium methyl sulfate (**317**), and, under the alkaline conditions of the condensation reaction, the initial product **318** undergoes cleavage (Eq. 114).[386,387]



(114)

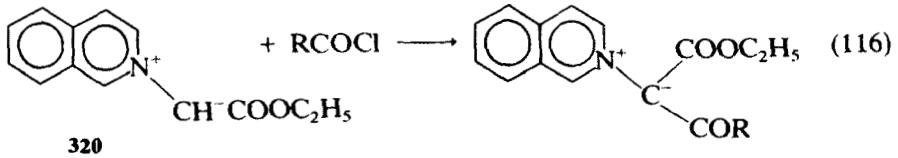
Arylation of the enol betaine of the 2-phenacylisoquinolinium ion **319** has been carried out[378,388] by using picryl chloride (Eq. 115). A parallel reaction

with the use of 2,3-dichloro-1,4-naphthoquinone as the reactive halide has been reported.[378]



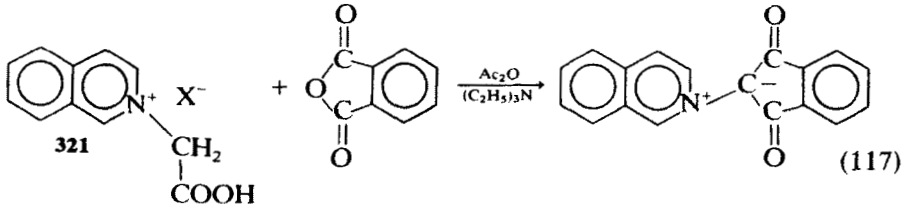
319 78–81% (115)

The betaine **320** derived from 2-ethoxycarbonylmethyl isoquinolinium ion may be acylated with acid chlorides, and the procedure has been offered[389] as a means for the spectrophotometric identification of acid chlorides (Eq. 116).



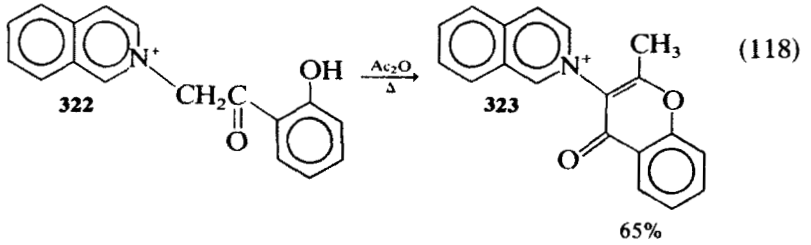
320 (116)

A Russian patent[390] has described a reaction that amounts to an acylation, cyclization, and decarboxylation of a carboxymethylisoquinolinium salt (**321**) (Eq. 117).



321 (117)

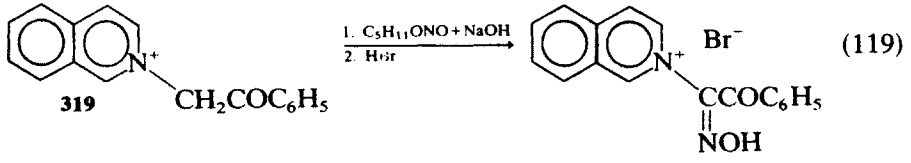
In a reaction that must first involve acylation of the side chain, 2-(2-hydroxyphenacyl)isoquinolinium ion (**322**) is converted efficiently into 2-methyl-3-isoquinolinochromone (**323**) by the action of acetic anhydride (Eq. 118).[391]



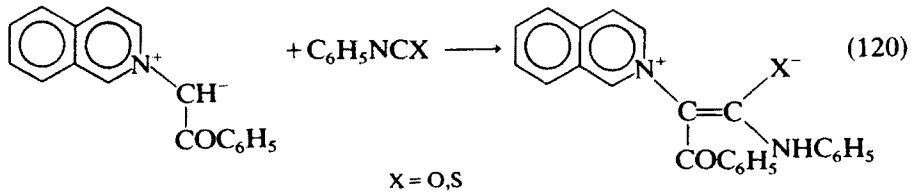
322 **323** 65% (118)

(c) *Reactions of Other Reagents*

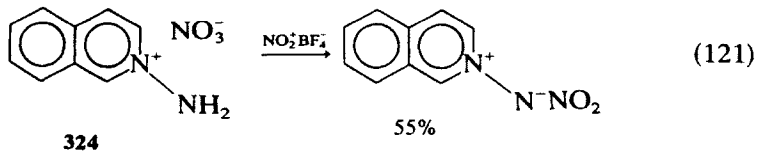
Under the proper conditions, the 2-phenacylisoquinolinium ion **319** undergoes nitrosation of the side chain (Eq. 119).[392] The phenacylisoquinolinium betaine of **319** was first reported to be unreactive toward arylisocyanates,[377] but it was later found that not only phenylisocyanate but also phenylisothiocyanates reacted in dimethylformamide solution (Eq. 120).[393] Nitration of 1-aminoisoquinolinium nitrate **324** occurs on the side chain (Eq. 121).[394]



319 (119)



(120)



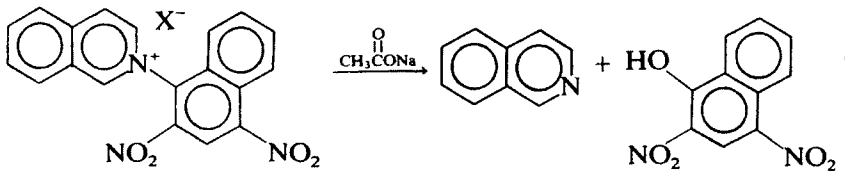
324 (121)

C. Cleavage of Quaternary Side Chain

Cleavage of the quaternary side chain may involve simple loss of all or part of the side chain or exchange with other groups. Sometimes the cleavage is accompanied or preceded by ring opening.

(a) *Simple Cleavage*

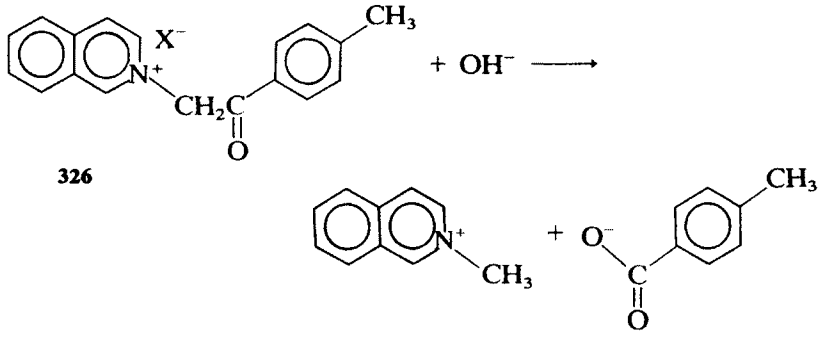
2-Polynitroarylisoquinolinium salts (e.g., **325**) have been observed to undergo relatively easy loss of the side chain when they are heated with relatively mild nucleophilic agents (Eq. 122).[69] The reaction must involve an aromatic nucleophilic substitution of the sort characteristic of aromatic compounds activated by electron-withdrawing groups.[395]



325

(122)

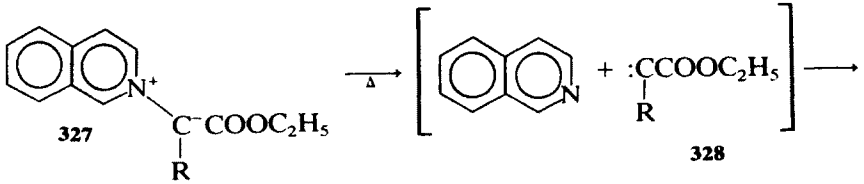
Like the pyridine counterparts,[85,396] *N*-phenacylisoquinoline quaternary salts (e.g., **326**) undergo cleavage in alkali (Eq. 123).[85]



326

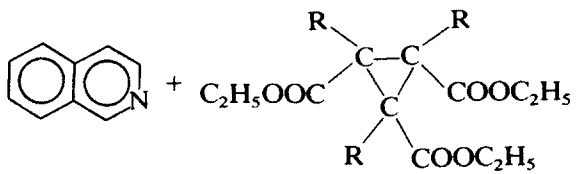
(123)

Cleavage occurs on heating the betaines **327** from 2-[di-(ethoxycarbonyl)-methyl] or 2-ethoxycarbonylmethyl isoquinolinium salts (Eq. 124).[397] It is believed that a carbene **328** is first formed which then trimerizes to yield **329**.



327 328

(124)

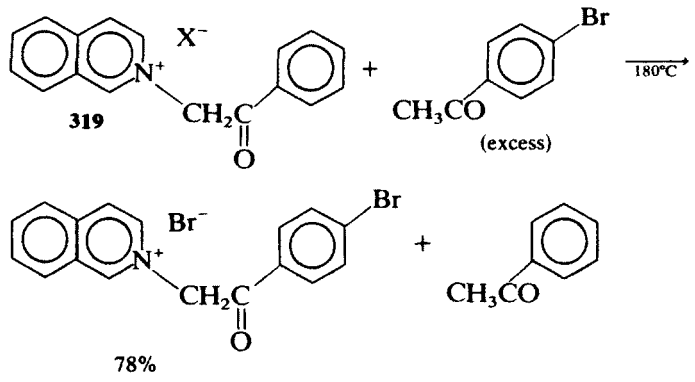


329

R = H,$COOC_2H_5$

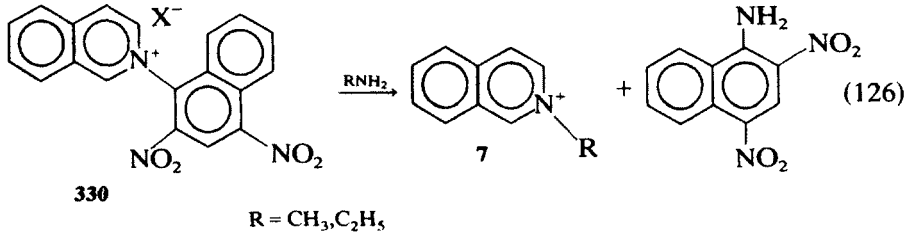
(b) *Cleavages Involving Exchange of Groups*

The simplest such cleavage is a transphenacylation brought about by heating a phenacyl salt (**319**) with an acetophenone (Eq. 125).[398]



(125)

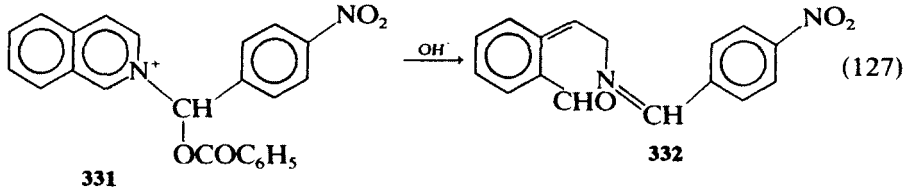
The conversion of 2-(nitroaryl)isoquinolinium salts (e.g., **330**) to the 2-alkylisoquinolinium cation **7** may seem similar to the transphenacylation but is actually a more complex reaction involving ring opening (Eq. 126).[69]



(126)

R = CH_3,C_2H_5

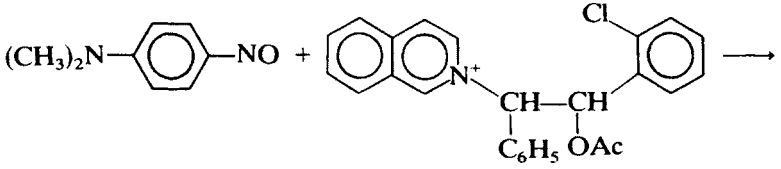
Another ring-opening reaction and one in which the product **332** still has the open chain form is obtained by the action of alkali on the 2-(α-benzoyloxy-4-nitrobenzyl)isoquinolinium cation **331** (Eq. 127).[122]



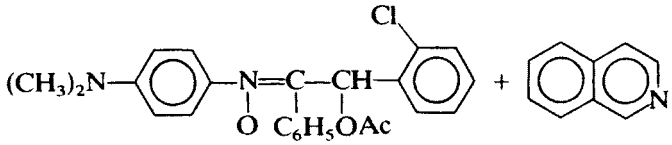
(127)

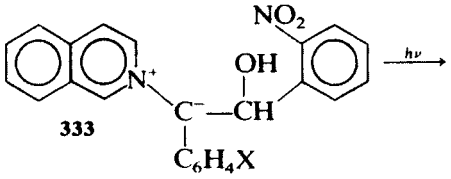
(c) *Other Cleavage Reactions*

Although the formation of nitrones from pyridium salts has been more extensively studied,[399] isoquinolinium salts can likewise yield nitrones.[400] As can be seen in Eq. 128, the reaction involves the cleavage of isoquinoline from the side chain. Another cleavage reaction of less general scope is seen when the betaine **333** from 2-[1-aryl-2-(2-nitrophenyl)-2-hydroxyethyl]-isoquinolinium cation is irradiated (Eq. 129).[38] Isoquinoline is liberated and the side chain cyclizes to afford an isatogen (**334**).

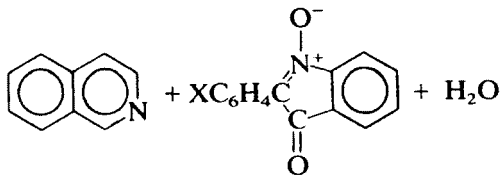


(128)





(129)

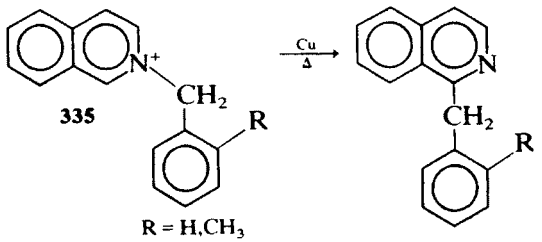


333

334

D. Rearrangements

Examples are known of the transfer of all or part of the quaternary side chain of isoquinolinium salts to the nucleus at position 1. J. von Braun[401] found that heating 2-benzyl or 2-(*o*-tolyl)methylisoquinolinium salts (**335**) in the presence of a small amount of copper led to the formation of the 1-benzyl or 1-(*o*-tolyl)methylisoquinoline (**336**, Eq. 130).



(130)

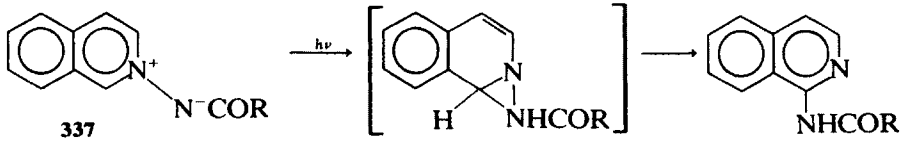
335

R = H,CH_3

336

A photorearrangement has been described by Tamura and co-workers.[172,402–404] The betaines derived from 2-acylaminoisoquinolinium

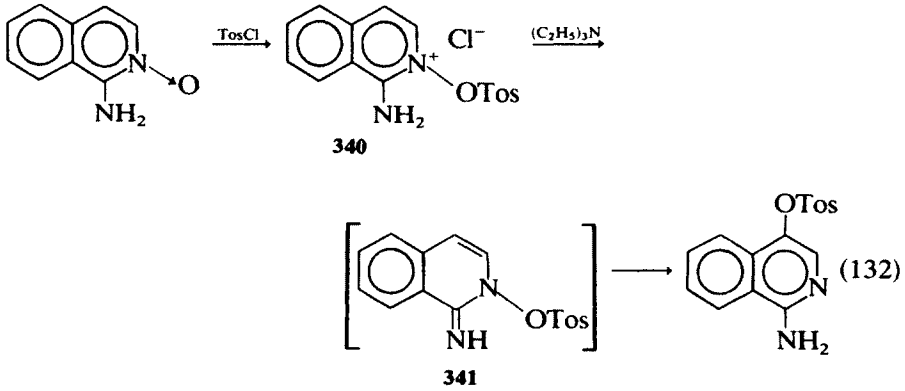
salts **337**, when irradiated with a high-pressure mercury lamp, afforded satisfactory yields of 1-acylaminoisoquinoline **339** (Eq. 131). The intermediate in the rearrangement is believed to be a diazirine **338**, and flash photolysis studies and quantum yield measurements suggest[404] that the reaction cocurs through the excited singlet state. The rearrangement cannot be carried out thermally, for if the betaine is heated to 190 to 200°C, the products are isoquinoline (80%) plus a mixture of products derived from the side chain. A comparison between the photorearrangement and the impact-promoted process (in the mass spectrometer)[405] showed no similarity between the two.



337 **338** **339**

$R = C_6H_5, CH_3, OC_2H_5$ (131)

A rearrangement was observed when 1-amino-2-tosyloxyisoquinolinium chloride (**340**) was treated with triethylamine (Eq. 132).[133] The reaction is believed to proceed by way of the 1-imino "anhydrobase" **341**.



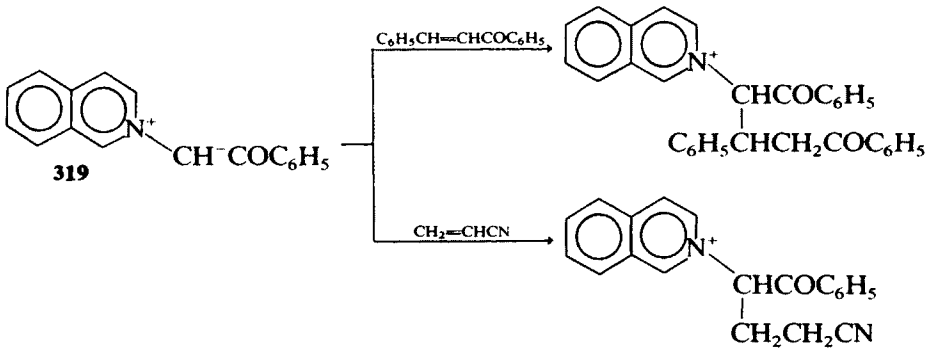
340 **341** (132)

E. Additions

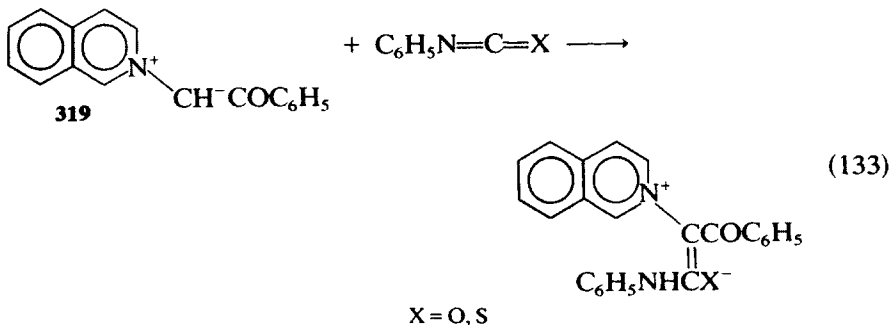
The ylide character of the betaines derived from 2-phenacylisoquinolinium salts **319** may be seen in the tendency of these salts to undergo the Michael reaction with conjugated systems such as benzalacetophenone[406] or acrylonitrile[407] (Scheme 7).

Addition of phenylisocyanates and phenylisothiocyanate may be carried out with the same betaine (**319**) (Eq. 133).[393].

Bromine may be added to the side chain of 2-allylisoquinolinium bromide

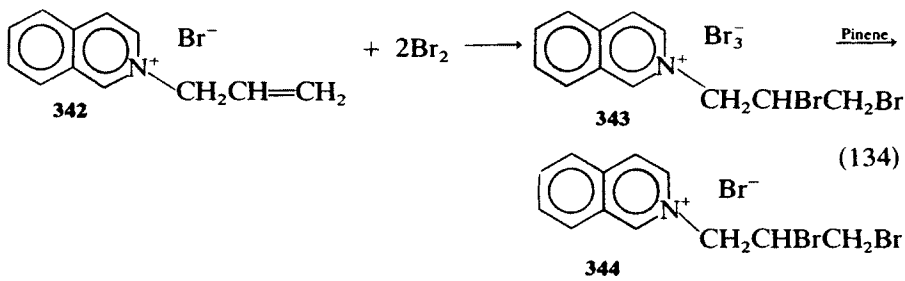


Scheme 7



(133)

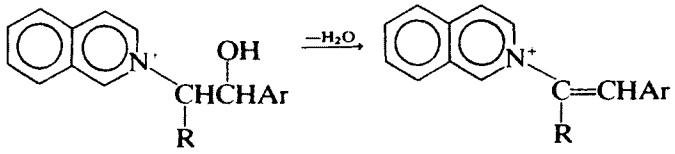
(**342**). The product is first isolated as the tribromide salt **343**, which is converted to the bromide **344** by the action of pinene (Eq. 134).



(134)

F. Eliminations

As an extension of his earlier work with pyridinium salts, Kröhnke[408] showed that 2-(2-hydroxy-2-arylethyl)isoquinolinium salts **345** could be dehydrated by the action of either acetic anhydride[382,383] or benzoyl chloride[37] (Eq. 135).



(135)

345

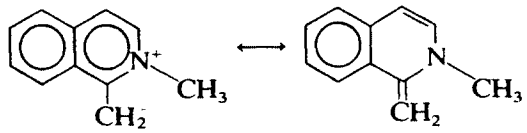
R = aryl, $C_6H_5CH=CH$, H

VIII. CHEMISTRY OF SUBSTITUENTS AT POSITIONS 1 AND 3

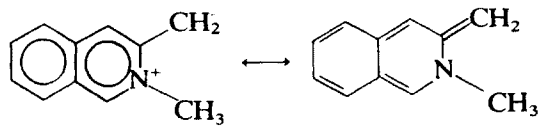
The high localization of positive charge at the quaternary nitrogen of the isoquinolinium ring has an effect on substituents immediately adjacent to it, an effect that is more pronounced at position 1 than at position 3.

A. Alkyl Substituents

Kawasoe et al.[409] have shown that quaternization of the isoquinoline nitrogen atom has a dramatic effect on the rate of deuterium exchange of a methyl group at position 1. They also noted that for the 2-methylisoquinolinium cation the rate of exchange of the protons on a methyl substituent at position 1 was much greater than for a similar substituent at position 3, thus indicating the relative stability of carbanions formed (**346** and **347**). Even a very simplistic approach to resonance theory would lead to



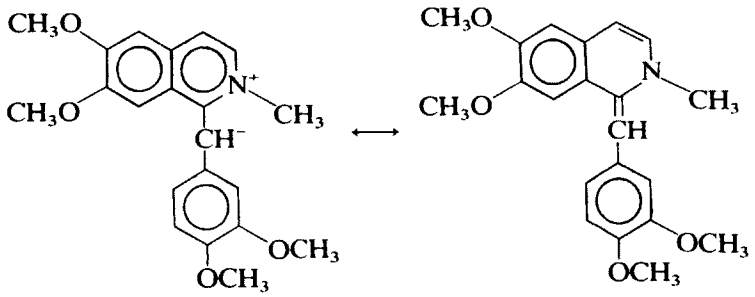
346



347

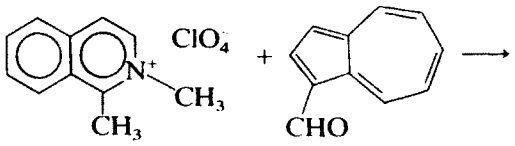
the prediction that the 3-methide ion would be less stable than the 1-methide counterpart. A stable benzene-soluble betaine **348** is obtained[410] by addition of alkali to isopapaverine methiodide. Such betaines have been referred to as *anhydrobases.*

There are several examples of base-catalyzed condensation reactions involving 1-methyl-2-alkylisoquinolinium cations. 1,2-Dimethylisoquinolinium perchlorate (**349**), in the presence of piperidine, condenses with

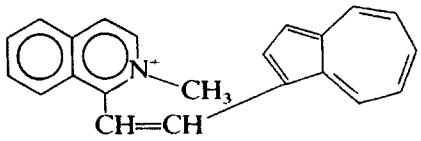


348

1-formylazulene (**350**), thus affording, after 5 min, a 78% yield of product **351** (Eq. 136).[411] Similar condensations have been noted[412] with other aldehydes.



349 350

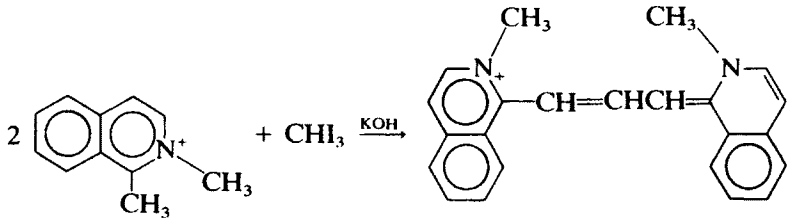


(136)

351

A large part of the study of condensation reactions of 1-methyl-2-alkylisoquinolinium salts has been prompted by the search for useful cyanine dyes, and since these dyes have been adequately reviewed,[413] only a few illustrations are cited.

A pair of 2,3-dimethylisoquinolinium cations **349** may be united by allowing them to react with iodoform and potassium hydroxide (Eq. 137).[414] Alternate approaches to the same product **352** involve the use of ethyl orthoformate[415] or the ethyl acetal of ethyl glyoxylate.[114]

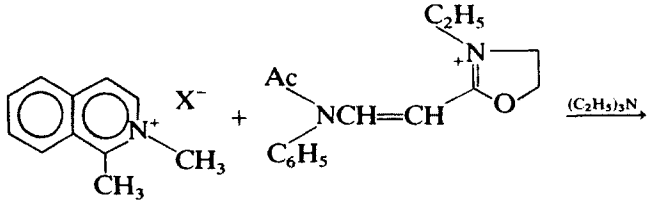


(137)

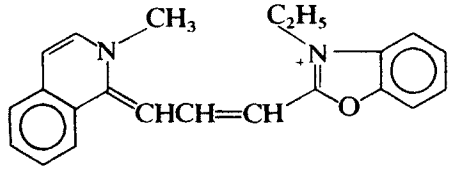
349 352

In addition to base-catalyzed condensation with heterocyclic aldehydes in a manner similar to that shown in Eq. 136, 1-methylisoquinolinium salts **349**

have been used in base-catalyzed displacements on activated vinylamides (e.g., **353**, Eq. 138).[414,415]

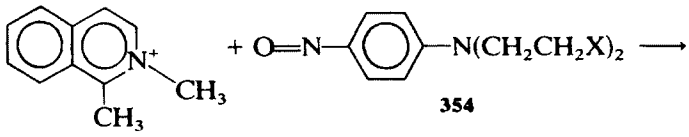


349 **353**

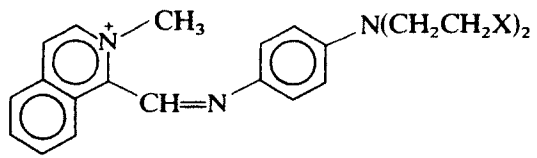


(138)

Schulze and Willitzer[416] have reported conditions for carrying out condensation of β-substituted *p*-diethylaminonitrosobenzene **354** with 1,2-dimethylisoquinolinium ion (**349**) in such a way as to give a Schiff's base **355**



349 **354**

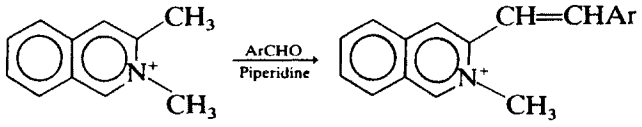


355

X = Cl,OH

(139)

(Eq. 139). Although 3-methyl-2-alkylisoquinolinium salts **356** appear to be less acidic than do the 1-methyl isomers, they do enter into reaction with aromatic aldehydes at fairly high temperatures in the presence of piperidine (Eq. 140).[135]

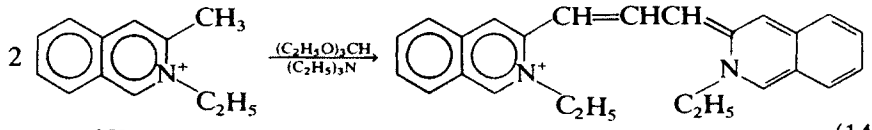


356 **357**

(140)

Some of the condensation products **357** were quickly patented[417,418] as photographic sensitizers. Most of the effort[346,419] that has gone into the synthesis appears to have been prompted by a desire to make photographic sensitizers or to understand[420] the absorption spectra of the products. The reported yields[346] for the condensation of aromatic aldehydes (Eq. 140)

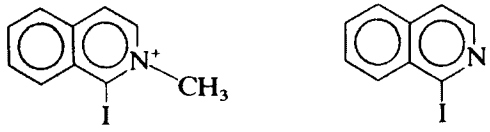
were almost all below 50% of the theoretical, and the formation of a cyanine **359** by reaction of **358** with ethyl formate[346] or orthoformate[417,418] occurs in only minimal yields and under drastic conditions (Eq. 141).



358 **359** (141)

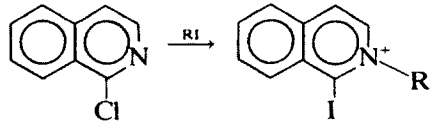
B. Activation of Halogen at Positions 1 and 3

A 1-halo-2-alkylisoquinolinium salt is many times more reactive toward nucleophilic displacement than is its 1-haloisoquinoline counterpart. By comparison of the relative rates of attack of hydroxyl ion, Barlin and Benbow[421] established that 1-iodo-2-methylisoquinolinium iodide (**360**) reacted more than 10^7 times faster than did 1-iodoisoquinoline (**361**).



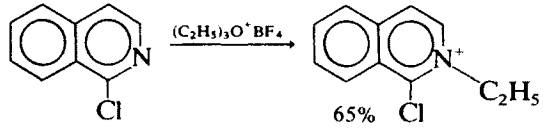
360 **361**

It has been found[422] that during quaternization of 1-chloroisoquinoline (**362**) with alkyl iodides, the chlorine atom is replaced by iodine (Eq. 142).



362 (142)

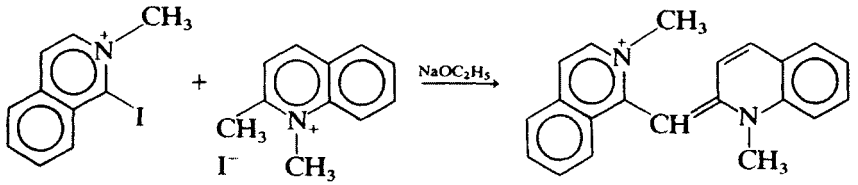
A similar displacement of chlorine by bromine was noted when quaternization with ethyl bromide was carried out in a sealed tube.[422] A simple way to avoid exchange is to carry out the quaternization by use of triethyloxonium tetrafluoroborate (Eq. 143).[423]



362 (143)

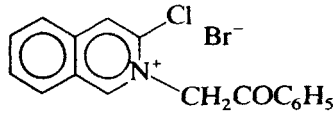
The great reactivity of 1-haloisoquinolinium salts has permitted nucleophilic displacements by ammonia,[422] amines,[238] hydrazines,[368], and the anion from quinaldine methiodide[422] (**363**, Eq. 144). This method of

making cyanine dyes (e.g., **364**)[413] is superior to the addition of the anion of quinoline methiodide to an isoquinolinium quaternary salt that has no halogen at position 1.[422]



360 **363** 79% **364** (144)

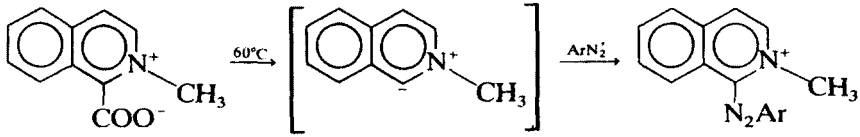
Although 3-haloisoquinolinium salts are not as reactive as the 1-isomer, they are reactive enough to be of use synthetically. 2-Phenacyl-3-chloroisoquinolinium ion (**365**), which undergoes a cyclization reaction when it is heated with aniline,[424] may do so through initial displacement of halogen by aniline.



365

C. Effect on Adjacent Carboxylate Ion

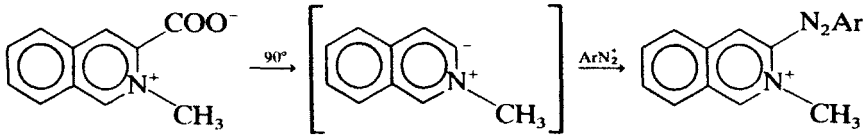
The betaine of the 1-carboxy-2-methylisoquinolinium ion (**366**), when heated in aprotic solvents, decarboxylates readily to form betaine **367**, which can be trapped by a suitable electrophile (Eq. 145).[178] The compara-



366 **367** 86%

Ar = [*p*-$(CH_3)_2$N]C_6H_4 (145)

ble 3-carboxylate isomer **368** undergoes decarboxylation only at a higher temperature, and the betaine **369** is trapped in very poor yield (Eq. 146).



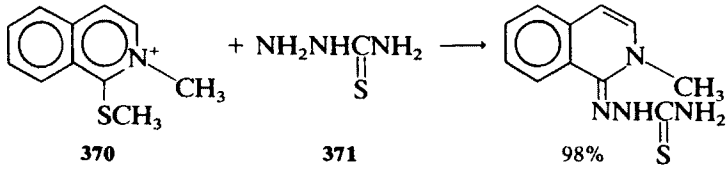
368 **369** 4%

Ar = [*p*-$(CH_3)_2$N]C_6H_4 (146)

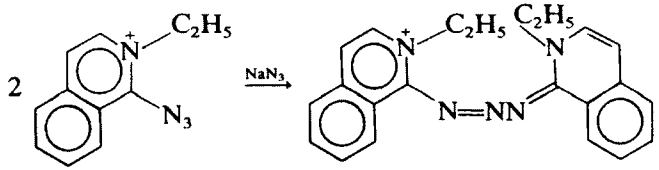
D. Activation of Other Groups at Position 1

The density of charge available at position 1 of isoquinolinium salts renders many groups subject to nucleophilic displacement when they are found at that position.

1-Mercaptomethyl-2-methylisoquinolinium iodide (**370**) reacts readily with thiosemicarbazide[128] (**371**, Eq. 147). Displacement of an azide ion must be involved when 1-azido-2-ethylisoquinolinium fluoroborate (**372**) is heated with sodium azide, thus affording the triazacarbocyanine[425] **373** (Eq. 148).



370 **371** 98% (147)



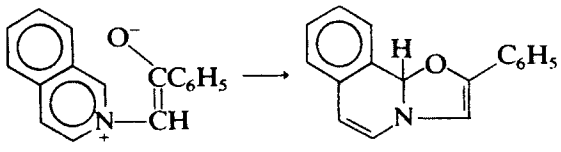
372 **373** (148)

IX. CYCLIZATIONS INVOLVING ATTACK ON NUCLEUS BY A SIDE CHAIN

Isoquinolinium quaternary salts with a great diversity of side chains at position 2 may be prepared with ease, and a suitable choice of a functionalized side chain has been found to make possible cyclization reactions, usually involving position 1.

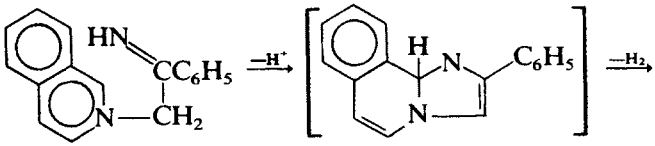
A. Cyclization Involving Attack by Nucleophilic Groups

Kröhnke and Zecher[40] appear to have been the first to appreciate the possibility of a cyclization of an isoquinolinium betaine by nucleophilic attack of the side chain on the nucleus. They pointed out that the inactive form of the betaine **374** derived from phenacylisoquinolinium ion could have an oxazaline structure (**375**) (Eq. 149).

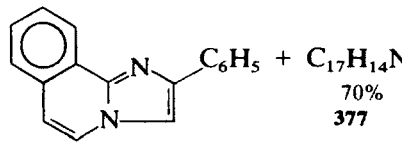


374 **375** (149)

The conversion of phenacylisoquinolinium bromide to an imidazoisoquinoline by action of ammonium acetate was postulated[40] as going through conversion of the carbonyl group to the imine **376**, cyclization, and dehydrogenation (Eq. 150). The structure of the imidazoisoquinoline was demonstrated by synthesis. This product was obtained only in small yield and was accompanied by a major product having two more hydrogens and at first was supposed to have the same skeletal structure. Cookson et al.[426] have now shown that the major product is the result of cyclization to position 3 and possesses structure **377**.

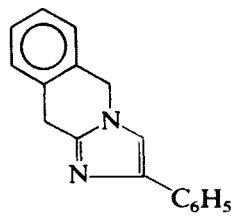


376



$$+ \underset{\substack{70\% \\ \textbf{377}}}{C_{17}H_{14}N_2} \quad (150)$$

12%

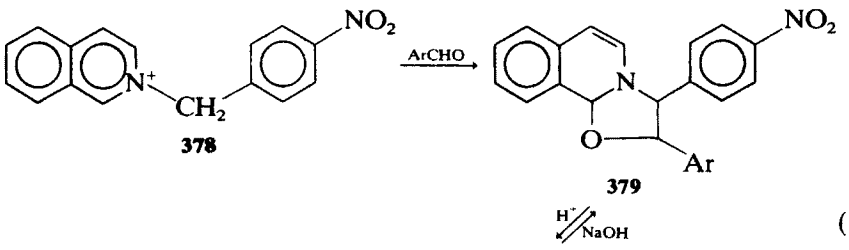


377

Albrecht and Kröhnke have found that the condensation of aryl aldehydes with a 2-(*p*-nitrobenzyl)isoquinolinium ion (**378**) gives not a betaine, as previously supposed,[382] but a cyclization product (**379**) derived from the initial condensation product **380** (Eq. 151).[427] It was shown that the ring could be opened and that, in the presence of alkali, the open chain product **380** recyclizes.[384] It seems clear that the role of the base in the cyclization is to create an alkoxide ion that can attack position 1 of the isoquinolinium ring.

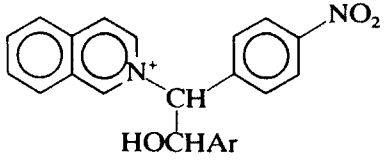
Wilson and DiNinno[428] were apparently the first to cyclize an isoquinolinium betaine in which the nucleophilic group was a carbanion. Cyclization of the hexanonyl side chain of **381** was effected by the action of sodium bicarbonate (Eq. 152). The product, the enamine **382**, was characterized by converting it to the benzoyl derivative **383** by the action of benzoyl chloride.

Finch and Gemenden[238] have shown that the 2-(3-aminopropyl)isoquinolinium ion **384** cyclizes in 95% yield in the presence of base (Eq. 153).

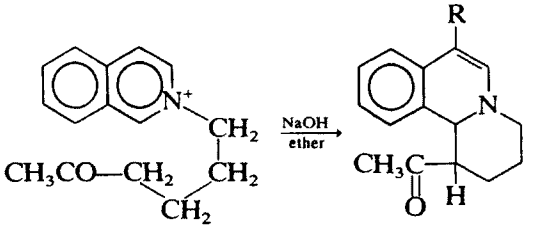


378 **379**

(151)

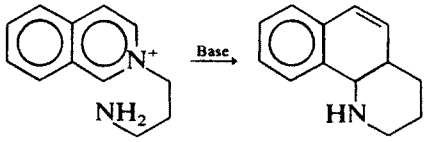


380



381 **382**, R = H
383, R = COC_6H_5

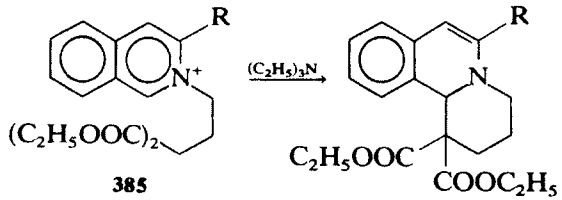
(152)



384 95%

(153)

Wimmer et al.[429] were able to cyclize isoquinolinium salts **385** that have 4,4-dicarbethoxybutyl as a side chain (Eq. 154). Nucleophilic cyclization



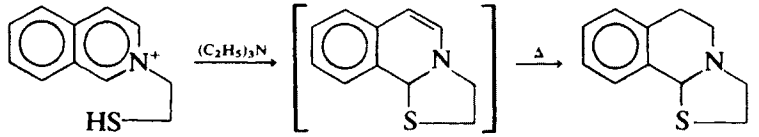
385

R = H, CH_3

(154)

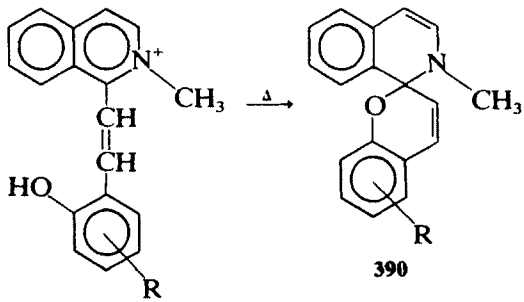
was also observed when the β-mercaptoethyl side chain in **386** was used, although the expected product **387** appeared to undergo disproportionation to afford **388** on attempted recrystallization (Eq. 155).

A nucleophilic cyclization of isoquinolinium salts in which the nucleophilic



386 387 388 (155)

group is not located on the quaternary chain is found in the work of Batshukaya and co-workers.[412,430] 1-(2-Hydroxystyryl)isoquinolinium salts **389** need only be heated in an aprotic solvent to form a spiropyran (**390**) (Eq. 156).

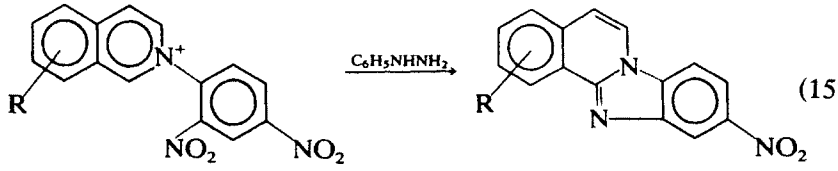


389 390 (156)

B. Other Cyclizations

In addition to the simple nucleophilic-type of cyclization, there have been a number of a more complex nature, mostly involving oxidation and reduction.

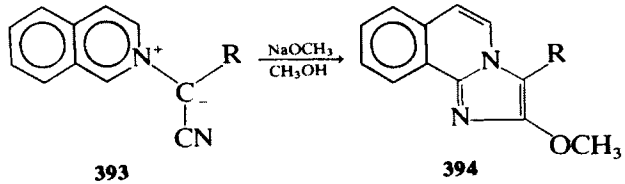
2-(2,4-Dinitrophenyl)isoquinolinium salts **391**, when warmed with phenylhydrazine (or *p*-bromophenylhydrazine) in acetic acid, yield benzimidazoisoquinoline **392** in good yield (Eq. 157).[431] The role of the phenylhydrazine is to serve as a reducing agent, for a similar cyclization can be accomplished by catalytic addition of 5 moles of hydrogen over palladium–charcoal. The product obtained by the hydrogenation–cyclization differs from that obtained with hydrazine in that the nitro group is reduced to amine.



391 392 (157)

R = H,OCH_3,Cl 40–90%

Kobayashi et al.[53] have shown that the ylide **393** from the 2-(cyanomethoxycarbonylmethyl)isoquinolinium ion or the closely related 2-dicyanomethylisoquinolinium ion reacts with sodium methoxide in methanol solution to afford an imidazoisoquinoline **394** (Eq. 158). The fully aromatic product may arise by disproportionation since the reported yields are less than 50%.

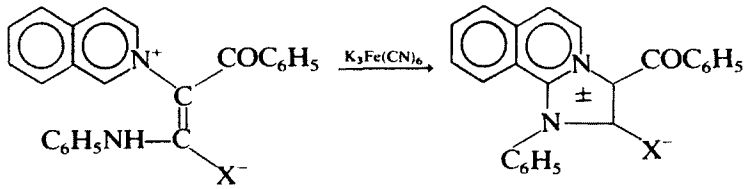


(158)

393 **394**

R = $COOCH_3$, CN

Sato and Ohta[393] have shown that sydnone-type derivatives **396** may be made by ferricyanide oxidation of the products **395** obtained when 2-phenacylisoquinolinium enolate reacts with phenylisocyanate or isothiocyanate (Eq. 159) [see Section VII.B(c)].

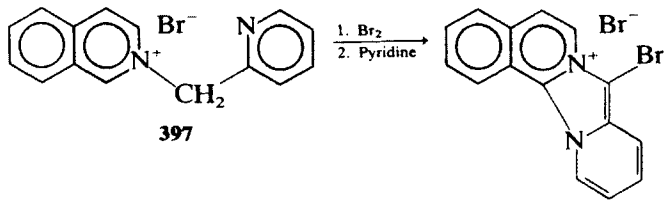


(159)

395 **396**

X = O,S

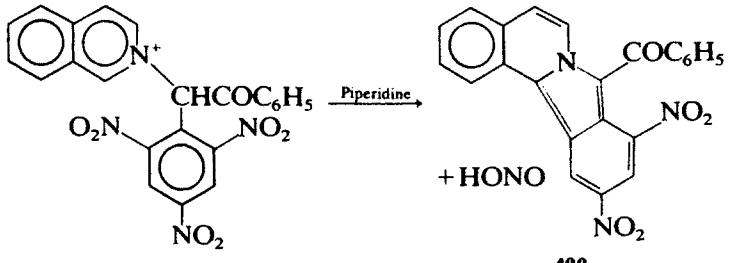
2-(2-Pyridylmethyl)isoquinolinium bromide **397**, when brominated and the bromination product subjected to the action of pyridine, affords a bromobenzimidazoisoquinolinium salt **398** (Eq. 160).[58]



(160)

397 **398**

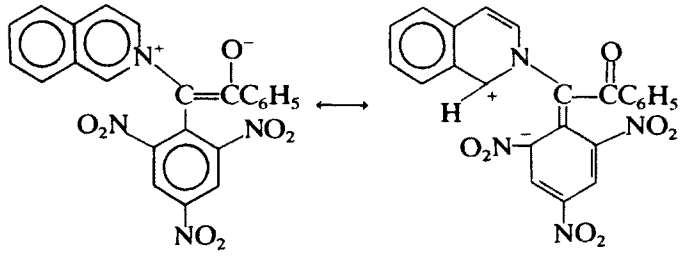
Augstein and Kröhnke[388] showed that a dibenzoindolizine derivative (**400**) may be obtained by heating a 2-(α-picrylphenacyl)isoquinolinium salt (**399**) in piperidine (Eq. 161). The reaction takes place by displacement of one nitro group as nitrous acid. The suggested mechanism assumes attack of one of the centers of negative charge in the enolate betaine **401** on a positively charged center.



(161)

399 **400**

78–83%



401

X. CYCLIZATIONS INVOLVING REACTION OF A MOLECULE OR ION WITH BOTH SIDE CHAIN AND NUCLEUS OF AN ISOQUINOLINIUM BETAINE

The reactions in this group include dipolar cycloadditions[432] as well as condensations–additions (or additions–condensations).

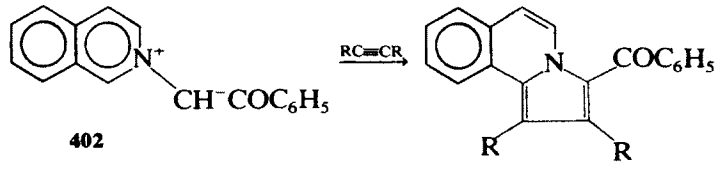
A. Dipolar Cycloadditions

The azomethine betaines derived from isoquinolinium quaternary salts undergo dipolar cycloaddition with alkynes, alkenes, and probably other systems that have multiple bonds.

(a) *Acetylenes*

Acetylenic compounds add to isoquinolinium betaines, but in nearly every case it is found that the major product isolated is not the expected primary adduct, but is rather a product resulting from prototropy, dehydrogenation, elimination, and skeletal rearrangement.

A fairly typical experiment might be the addition of dimethyl acetylenedicarboxylate to the betaine **402** obtained from a phenacylisoquinolinium

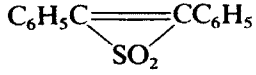


402 403 (162)

R = CN,$COOCH_3$

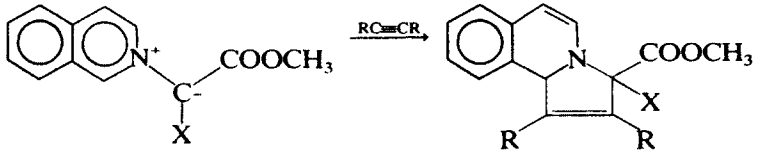
cation[433] that gives, in 27% yield, compound **403** (R = $COOCH_3$) formed by spontaneous dehydrogenation of the expected intermediate (Eq. 162). Similar results have been reported[434] when dicyanoacetylene was the addend (**403**, R = CN).

In view of its great angular strain, it would be expected that diphenylthiirine dioxide (**404**) would decompose readily into sulfur dioxide and acetylene. When the dioxide **404** was heated with the betaine **402**, the product (61% yield) was a typical cycloaddition adduct (**403**, R = C_6H_5).[435]



404

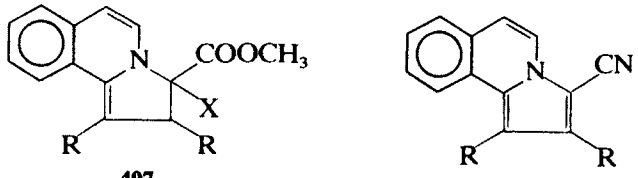
Kobayashi and co-workers[80,434,436,437] have studied the cycloaddition reactions of many isoquinolinium betaines **405** with acetylenes and have found a few examples in which the expected primary addition product **406** can actually be isolated. In each example the anionic carbon of the betaine was doubly substituted (Eq. 163).



405 406 (163)

X = $COOCH_3$, CN; R = $COOCH_3$

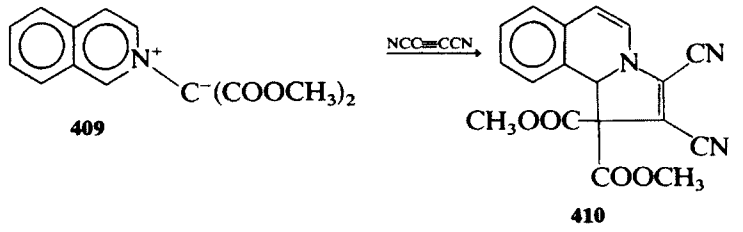
Two types of product (**407** and **408**) frequently observed in the addition of acetylenes to isoquinolinium betaines could be made from the primary products by isomerization to yield **407** or by elimination of methyl formate to yield **408**.



407 **408**

R = $COOCH_3$

It has also been claimed[436] that the betaine **409** from 2-(dicarbomethoxymethyl)isoquinolinium ion, on addition of dicyanoacetylene, can give a rearranged product **410** (Eq. 164).

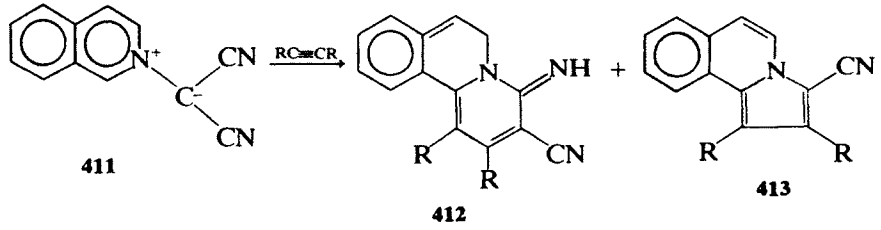


409 **410**

And other products

(164)

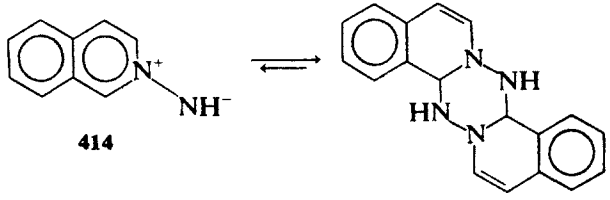
When the position of the functional groups is reversed, with the addition of dimethyl acetylenedicarboxylate to isoquinolinium dicyanomethylide (**411**), the product of the 1:1 addition has been formulated[117] as a benzo[*a*]quinolizine (**412**), in which the cyano and imino groups occupy positions that appear to be transposed from those that would be predicted for a simple 1,4-dipolar addition. The other product, a pyrrolo[2,1-*a*]isoquinoline (**413**), is probably formed by 1,3-dipolar cycloaddition followed by loss of hydrogen cyanide (Eq. 165).



411 **412** **413**

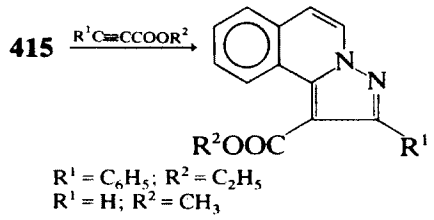
(165)

The use in cycloaddition of the betaine **414** from 2-aminoisoquinolinium ion is complicated by its tendency to undergo dimerization, thus affording **415** (Eq. 166). Fortunately, there is enough of the monomeric species present at ordinary temperatures to permit the use of the equilibrium mixture in cycloadditions (Eq. 167).[438]



414 **415**

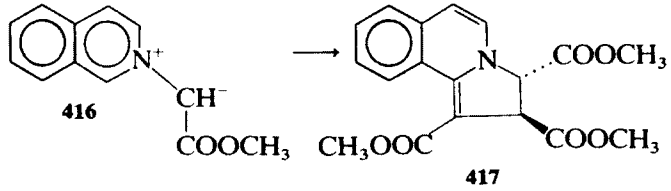
(166)



(167)

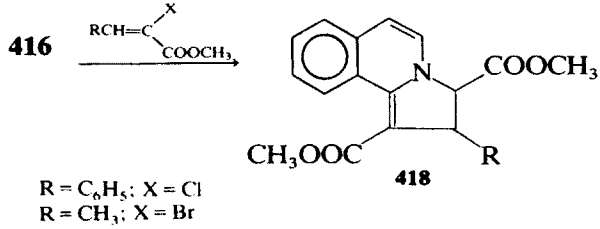
(b) *Alkenes*

The addition of electron-deficient alkenes to isoquinolinium methylides follows much the same pattern as that of acetylenes in that the primary addition product is rarely obtained and that there is a great tendency toward spontaneous dehydrogenation. The betaine **416** from the 2-(carbomethoxymethyl)isoquinolinium ion reacts with dimethyl fumarate at room temperature to afford a 28% yield of a dehydrogenated adduct **417**



(168)

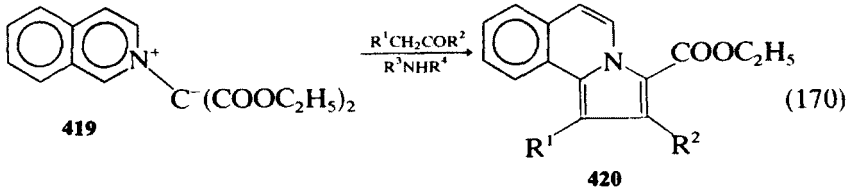
(Eq. 168). A dehydrohalogenated product **418** was obtained[439] when methyl esters of α-chlorocinnamic or α-bromoacrylic acids were used as addends (Eq. 169).



(169)

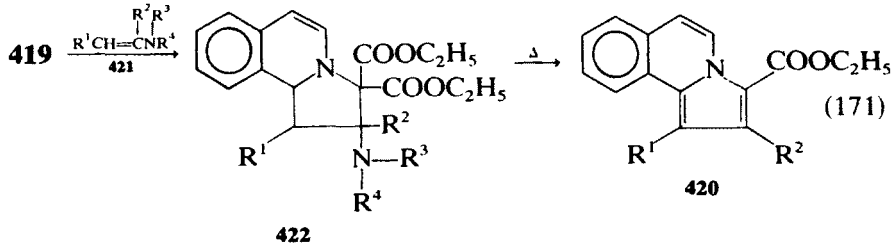
Basketter and Plunkett[440] have described an interesting route to indolizines (e.g., **420**) that probably takes place through a cycloaddition reaction. The betaine **419** from 2-(dicarboethoxymethyl)isoquinolinium ion is allowed to react with an aldehyde or ketone ($R^1CH_2COR^2$) in the presence of a primary or secondary amine (Eq. 170).

It was suggested[440] that the amine converts the ketone to an enamine, which then undergoes 1,3-dipolar cycloaddition. Support for this mechanism was offered by the demonstration that enamines **421** did undergo 1,3-dipolar cycloaddition with the betaine **419** and that the adduct **422** first



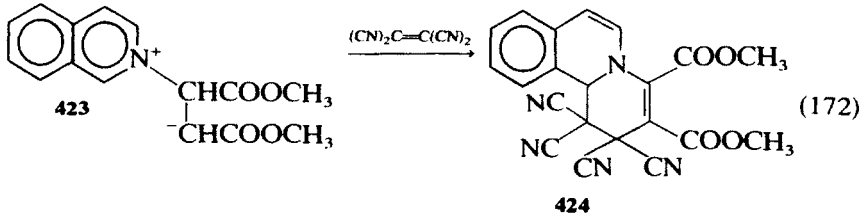
419 420 (170)

obtained underwent elimination and dehydrogenation on heating (Eq. 171).



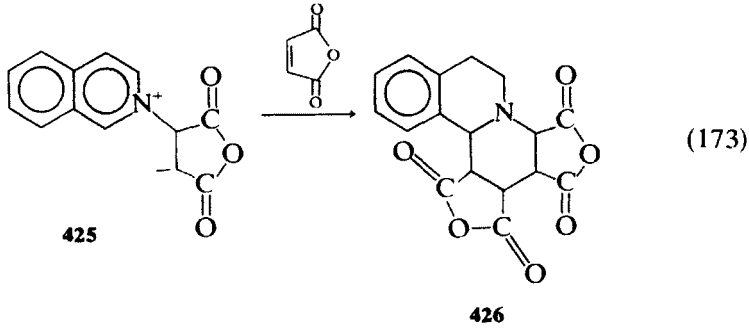
419 421 422 420 (171)

A 2-(1,2-dicarbomethoxyethyl)isoquinolinium ion can form a betaine by loss of a proton from either position 1 or position 2 of the ethyl group. It is believed that a betaine of the latter type (**423**) is involved in a 1,4-addition of tetracyanoethylene to yield a benzo[*a*]quinolizine **424** (Eq. 172).[441]



423 424 (172)

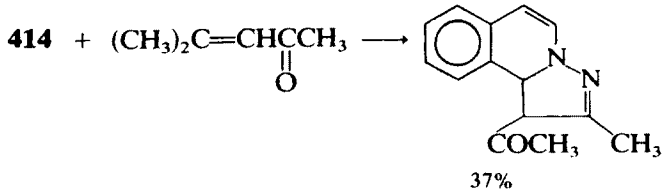
The betaine **425** formed by reaction of 1 mole of maleic anhydride and isoquinoline in dry benzene can react as a 1,4-dipole with an additional mole of maleic anhydride[110] to yield **426** (Eq. 173).



425 426 (173)

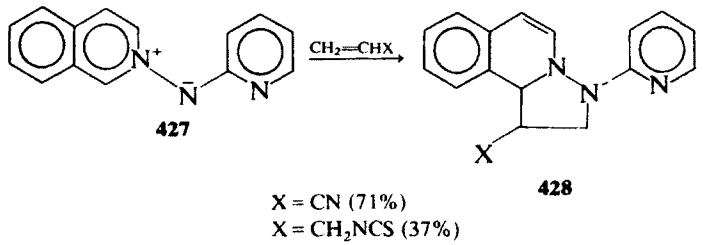
2-Iminoisoquinolinium betaine (**414**) adds polarophilic alkenes, usually with partial or complete aromatization of the initial addition product. An

example is the addition of mesityl oxide, which occurs with the loss of methane (Eq. 174).[438]



(174)

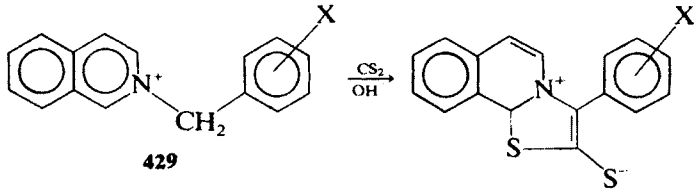
The addition of several polarophiles to the betaine **427** from 2-(2-pyridylamino)isoquinolinium ion appears to yield primary products **428** (Eq. 175).[441]



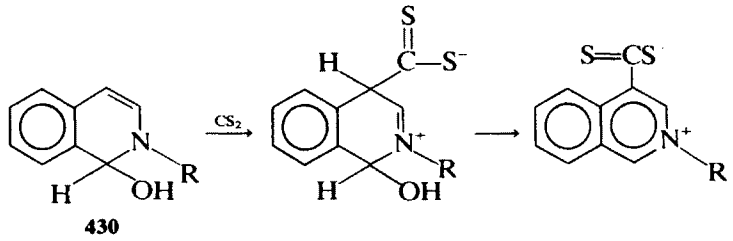
(175)

(c) *Other Polarophiles*

The addition of isoquinolinium methine betaines to polarophiles of other than acetylenic and ethylenic types has been observed. Perhaps the most studied polarophile for addition to isoquinolinium methines (e.g., **429**) has been carbon disulfide[137,442–444] (Eq. 176). The reaction is not clear-cut and is accompanied by side reactions,[137,444] the most remarkable of which is shown in Eq. 177.

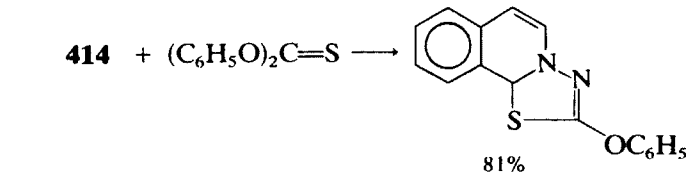


(176)



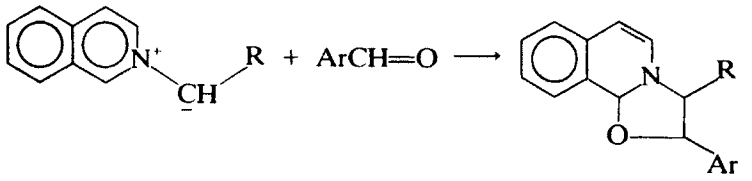
(177)

The carbinol amine **430**, formed when hydroxide ion is initially added, acts as an enamine leading to the introduction of a dithiocarboxylate group at position 4. Another example of 1,3-dipolar addition to a carbon–sulfur double bond is seen in Eq. 178.[438] The reaction occurs with loss of phenol.



(178)

There are also reactions that, on the basis of present evidence, could be envisaged as taking place by either stepwise aldol condensation followed by nucleophilic cyclization or, as Ahlbrecht and Kröhnke have pointed out,[427] could conceivably occur by 1,3-dipolar cycloaddition (Eq. 179).



(179)

B. Reactions that Proceed by Addition–Condensation or Condensation–Addition

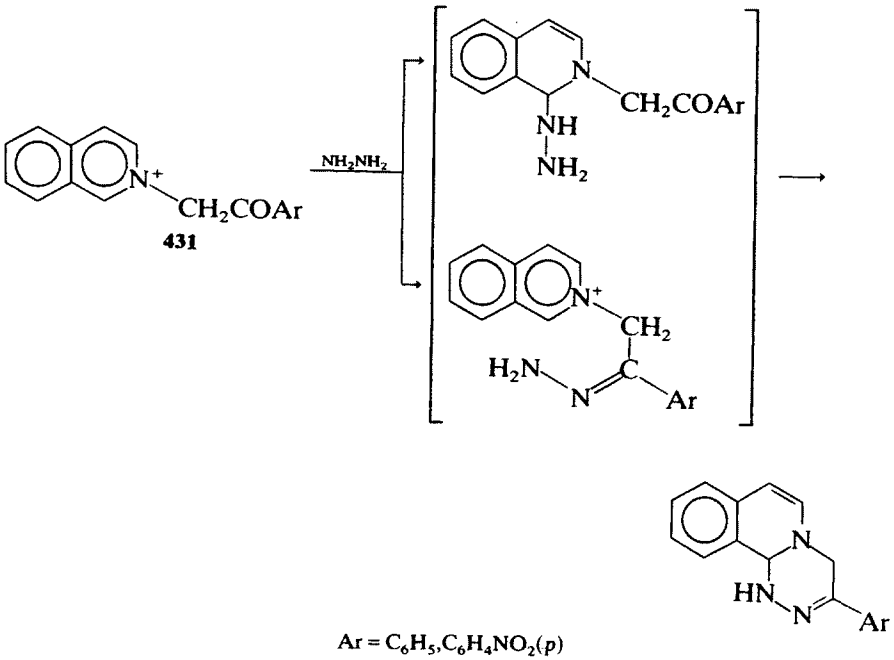
When the quaternary side chain has a carbonyl group, as in phenacyl isoquinolinium salts, two reactive centers for nucleophilic attack are presented and the reaction could proceed by either (or both) of two courses. An example is the reaction of hydrazine with the phenacylisoquinolinium ion **431** (Scheme 8).[445,446]

A similar ambiguity exists for the reaction reported by Kröhnke et al.[407] in which ammonium acetate reacts with a keto betaine **432** to afford the 2,3-dihydroimidazo[2,1-*a*]isoquinoline **433** (Eq. 180).

Another reaction belonging to this class is the base-catalyzed addition of nitromethane to phenacyl or acetonyl isoquinolinium salts[447] **434** (Eq. 181). Moderate yields of a mixture of cyclized products **435** arising from aromatization without loss of the nitro group, or by elimination of the nitro group, were obtained.

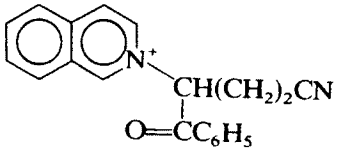
XI. CYCLIZATIONS INVOLVING SIDE CHAIN AND AN ALKYL OR ARYL GROUP ON NUCLEUS

Isoquinolinium quaternary salts suitably substituted in the quaternary side chain can undergo cyclization either directly or by a condensation reaction followed by a cyclization, or what may be essentially a double condensation.



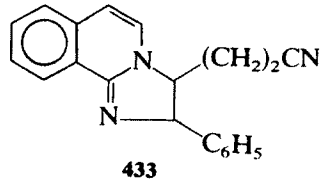
$Ar = C_6H_5, C_6H_4NO_2(p)$

Scheme 8



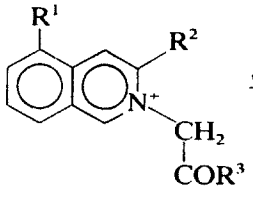
432

$\xrightarrow{NH_4OAc}$



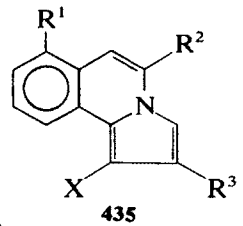
433

(180)



434

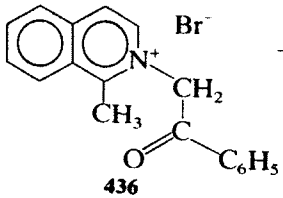
$\xrightarrow[Base]{CH_3NO_2}$



435

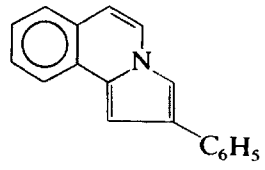
(181)

$R^1 = H$ or NO_2
$R^2 = H$ or CH_3
$R^3 = CH_3$ or Ar
$X = NO_2$ or H



436

$\xrightarrow{Base}$

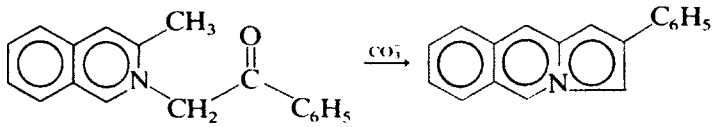


437

(182)

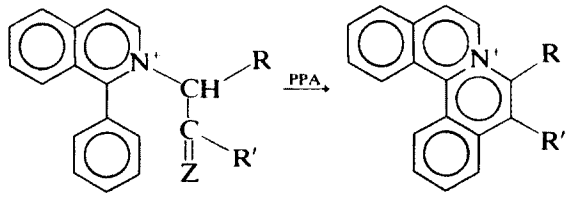
A. Simple Cyclization

Sprague[448] showed that when 1-methyl-2-phenacylisoquinolinium bromide (**436**) was treated with sodium carbonate, it cyclized to afford a pyrrolo[2,1-*a*]isoquinoline **437** (Eq. 182), thus providing another example of a reaction originally discovered by Tschitschibabin.[449] The same reaction was observed[445] when hydrazine was used as the base. It has also been observed[448] that cyclization involving the somewhat less highly activated 3-methyl group of the 2-phenacyl-3-methylisoquinolinium ion (**438**, Eq. 183) can take place.



438 (183)

From model experiments in the pyridine series,[450] it appeared likely that 1-phenyl-2-acetonylisoquinolinium ion (**439**) and its congeners should cyclize to the hitherto unknown dibenzo[*a*,*h*]quinolizinium system **440** (Eq. 184). Probably because of the difficulty with which the phenyl ring can



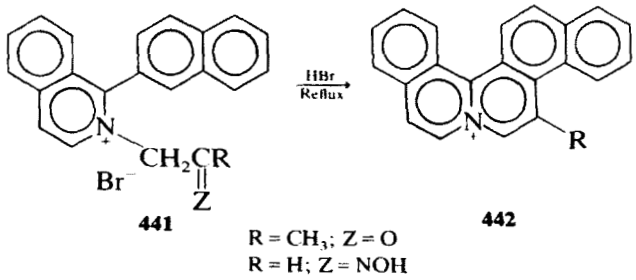
(184)

439 **440**

R = H, CH_3; R' = CH_3,C_6H_5, H
Z = O,NOH

achieve planarity in the presence of the peri hydrogen at position 8, it was found that cyclization in refluxing hydrobromic acid was not achieved[451] under conditions much more vigorous than were necessary in the phenylpyridine series except in a single instance[452] in which there was a methoxyl group para to the position of cyclization. It was later found[453] that the reaction could be carried out in good yields by cyclization at 200 to 220°C in either polyphosphoric acid or hydrobromic acid in a sealed tube. Under less drastic conditions the more highly activated 1-(2-naphthyl)isoquinolinium quaternary salts **441** afforded naphtho[2,1-*a*]benzo[*h*]quinolizinium salts **442** (Eq. 185).

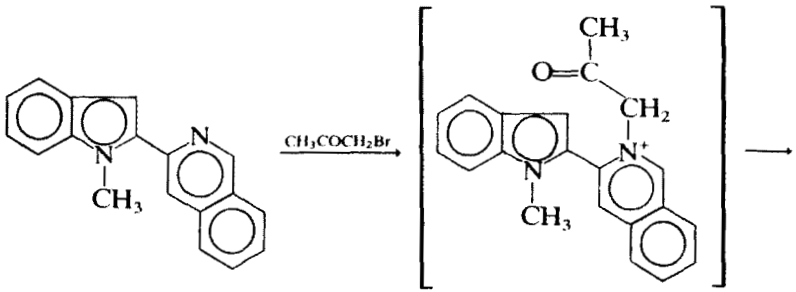
A cyclization of this type is also possible when the aryl group is at position 3.[454] When 3-(1-methyl-2-indolyl)isoquinoline **443** is quaternized with bromoacetone, spontaneous cyclization of the intermediate **444** occurs, thus leading to the 13H-indolo-[2,3-*a*]acridizinium system **445** (Eq. 186).



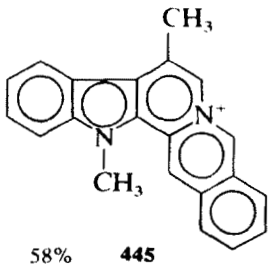
441 442

R = CH_3; Z = O
R = H; Z = NOH

(185)



443 444



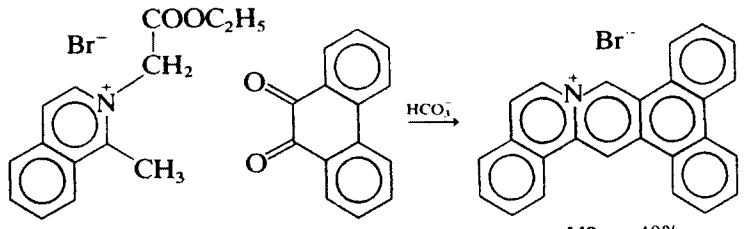
58% 445

(186)

B. Cyclization Involving a Double Condensation with Another Molecule

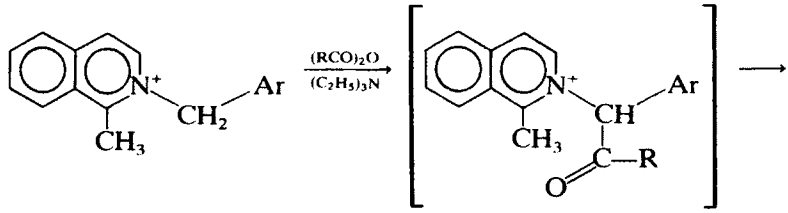
The convenient and versatile synthesis devised by Westphal et al.,[455] very useful with pyridinium salts, has also been applied in at least one instance to an isoquinolinium salt. A 1-methyl-2-carbethoxymethylisoquinolinium ion (**446**) in the presence of a bicarbonate ion condensed with phenanthraquinone (**447**) to afford tribenzo[*a*,*h*,*j*]acridizinium ion (**449**) in 40% yield (Eq. 187).

Another reaction involving both condensation and cyclization is seen when a 1-methyl-2-(4-nitrobenzyl)isoquinolinium ion (**449**) is heated with an acid anhydride in the presence of triethylamine.[456] The reaction appears

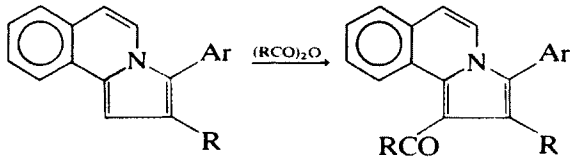


446 447 448 40% (187)

to involve an acylation affording **450**, followed by a cyclization of the type discussed earlier (Section XI.A) with at least partial acylation of the benzindolizine **451** formed (Eq. 188).



449 450 (188)



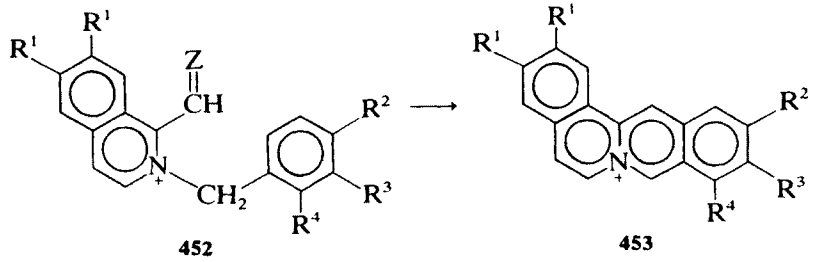
451

Ar = $(p\text{-}NO_2)C_6H_4$; R = CH_3, C_6H_5

XII. CYCLIZATIONS INVOLVING ATTACK ON QUATERNARY SIDE CHAIN BY A FUNCTIONAL GROUP ON ISOQUINOLINIUM NUCLEUS

Shortly after it was discovered that benzyl quaternary salts of picolinic aldehyde could be cyclized to the acridizinium ion,[457] efforts were begun to extend the reaction to the benzyl quaternary salts **452** of isoquinoline-1-carboxaldehyde[458] and its 6,7-dimethoxy[459–464] and 6,7-methylenedioxy[460,463–465] analogues (Eq. 189).

The benz[*a*]acridizinium derivatives **453** obtained can be reduced easily to afford tetrahydroberberines and their analogues. The yields in the cyclization reaction are good, making the route one of the most convenient and

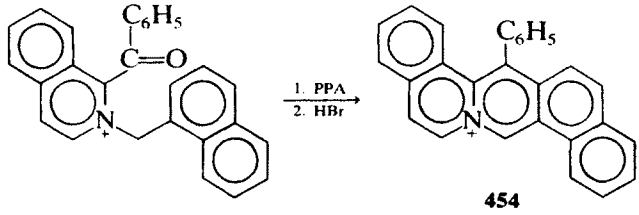


452 453 (189)

$R^1 = H,OCH_3,OCH_2O$; $R^2,R^3,R^4 = H,OCH_3,OCH_2O,OCH_2C_6H_5,OH$;
$Z = O,NOH,OCH_2CH_2O$

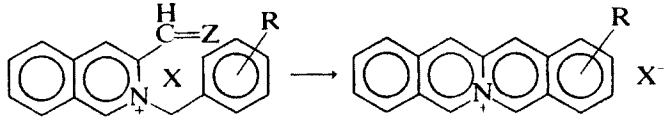
reliable of the berberine syntheses. The only notable failure, the attempted synthesis of stepharotine,[462,466] seems most likely to be due to the use of the wrong benzyl halide rather than to any rearrangement during the cyclization.

Through the use of 1-benzoyl instead of 1-formylisoquinoline and by carrying out the cyclization of the salt in polyphosphoric acid at 150 to 160°C, 13-phenylbenz[*a*]acridizinium derivatives are obtained.[467] The same type of cyclization afforded a dibenz[*a,h*]acridizinium salt **454** (Eq. 190).[467]



454 (190)

The cyclization of 2-benzyl-3-formylisoquinolinium salts **445** or, better, the oximes or acetals of such salts, afforded benz[*b*]acridizinium salts **456** (Eq. 191).[468,469] Fields et al.[470] have shown that the same type of cyclization

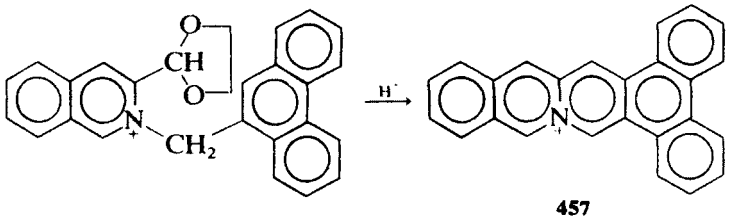


455 456 (191)

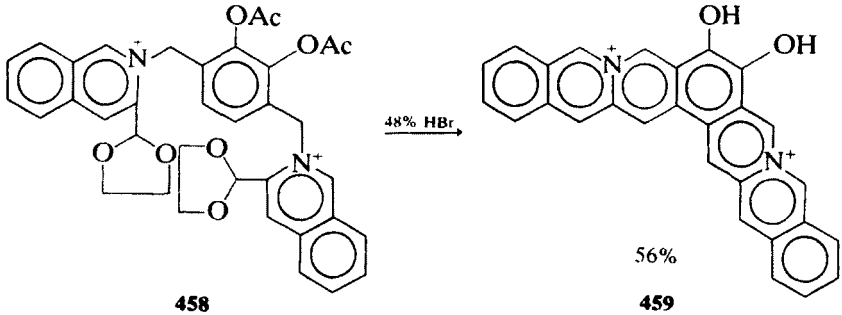
R = H,CH_3,OCH_3,OCH_2O

may be applied to the synthesis of the phenanthro[9,10-*b*]acridizinium cation **457** (Eq. 192). The most complex example of this type of cyclization is also found in the work of Fields et al.[471] Those authors prepared a crude bisquaternary salt **458** from 2,3-diacetoxy-1,4-bis(bromomethyl)benzene and an acetal of isoquinoline-3-carboxaldehyde and cyclized **458** in hydrobromic acid, thus affording a diazoniaheptaphene (**459**) (Eq. 193).

The recently developed[472] method for producing 11-aminoacridizinium derivatives through the cyclization of 1-benzyl-2-cyanopyridinium salts has

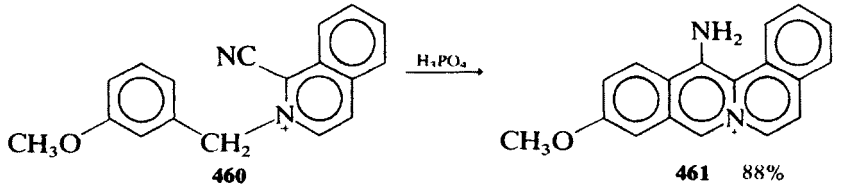


457 (192)



458 459 (193)

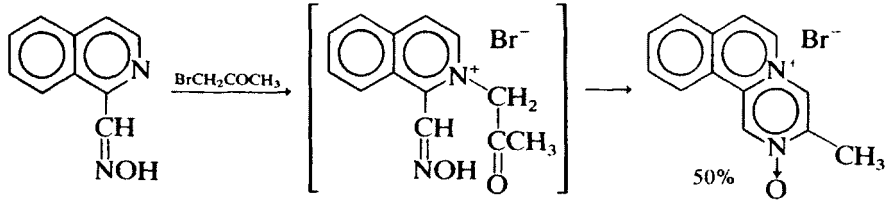
been extended to the isoquinolinium series (Eq. 194). The aminobenzacridizinium derivative **461** was obtained from 1-cyano-2-(3-methoxybenzyl)-isoquinolinium ion **460** in 88% yield.



460 461 88% (194)

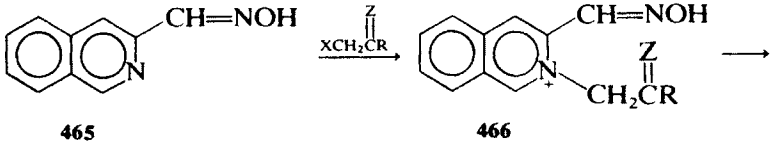
XIII. CYCLIZATIONS INVOLVING FUNCTIONAL GROUPS ON BOTH QUATERNARY SIDE CHAIN AND NUCLEUS

If the oxime **462** of 1-formylisoquinoline is refluxed in acetone with bromoacetone, the product is not the expected quaternary salt **463** but

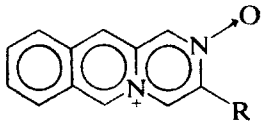


462 463 464 (195)

instead 3-methyl-2-azabenzo[*a*]quinolizinium 2-oxide (**454**), a cyclization product (Eq. 195).[473] A similar cyclization can be carried out by allowing a suitable halide to react with the oxime **465** of 3-formylisoquinoline (Eq. 196).[424,473] When the halide was bromoacetone, the product isolated after refluxing in acetone (55% yield) was the cyclization product 3-methyl-2-azabenzo[*b*]quinolizinium bromide 2-oxide (**467**, R = CH_3). With phenacyl bromide or with chloroacetaldehyde oxime, the quaternary salts **466** were actually isolated and cyclized by means of acid.



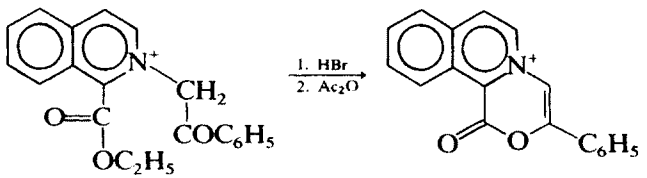
465 **466**



467 (196)

R = H; Z = NOH
R = CH_3,C_6H_5; Z = O

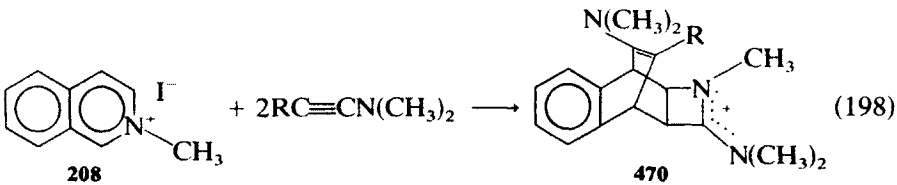
Kröhnke et al.[474] have shown that 1-ethoxycarbonyl-2-phenacylisoquinolinium (**468**), when refluxed with hydrobromic acid and then treated with acetic anhydride, gave the cyclization product **469** (Eq. 197).



468 **469** (197)

XIV. CYCLOADDITION REACTIONS INVOLVING ISOQUINOLINIUM NUCLEUS

The first cycloaddition reactions involving an isoquinolinium salt appear to have been carried out by Fuks et al.,[475] who observed that 2-methylisoquinolinium iodide (**208**) reacts with an excess of an ynamine to

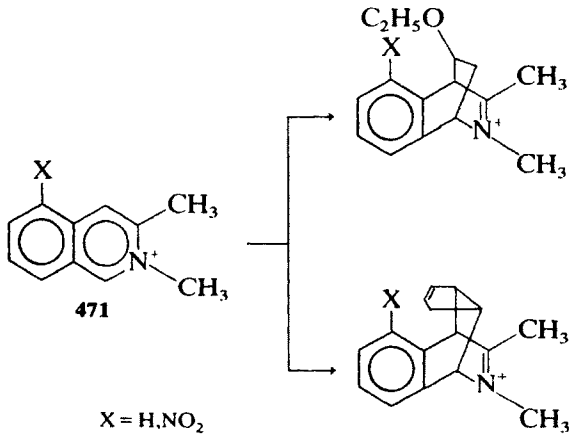


208 **470** (198)

give a 1:2 adduct. The structure of one of the products (R = *t*-butyl) has been demonstrated by single X-ray crystallography[475,476] to be **470** (Eq. 198). The reaction has been explained as involving 2+2 addition, ring enlargement, and finally 1,4-addition.

A. Polar Cycloaddition

Bradsher and Day[477] demonstrated that electron-rich alkenes such as alkyl vinyl ethers or cyclopentadiene would add 1,4 to 3-substituted isoquinolinium salts **471** (X = H, Scheme 9). These examples, which are representatives of a class of cycloadditions designated as polar cycloadditions[478,479] occur in a manner that is both regio- and stereounique.[480–482] The nature of the products obtained when there is no substituent present at position 3 is more complex[483] but easily understandable when it is realized that the initial product expected is a very reactive iminium salt.



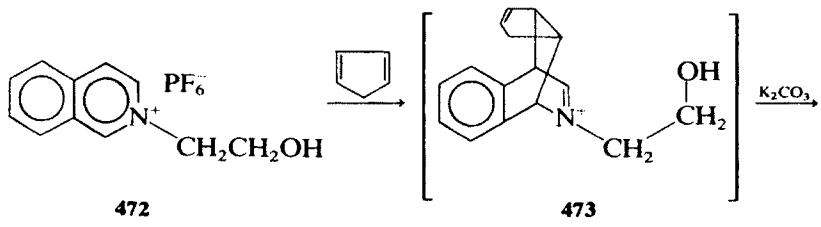
Scheme 9

A combination of cycloaddition and nucleophilic cyclization has been carried out on an isoquinolinium salt without a substituent at position 3 (Eq. 199).[429] 2-(2-Hydroxyethyl)isoquinolinium hexafluorophosphate (**472**) was allowed to react with cyclopentadiene and the crude adduct **473** treated with potassium carbonate, thus affording a 60% yield of a single stereoisomer **474** believed to be produced by endo cyclization.

The reactivity of 3-methylisoquinolinium salts is greatly enhanced if there is a nitro group at position 5[484] (Scheme 9, X = NO_2). Not only vinyl ethers and cyclopentadiene, but also indene, norbornene, β-pinene, and styrene react in good to excellent yields.

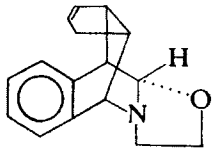
B. Dipolar Cycloaddition

The betaine **475** derived from a 2-methyl-4-hydroxyisoquinolinium ion can react with dipolarophiles across positions 1 and 3 to give in moderate



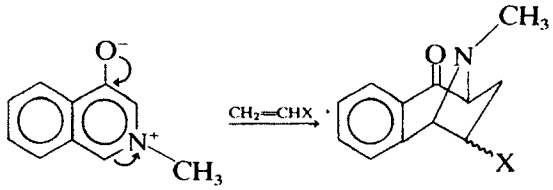
472 473

(199)



474 60% overall

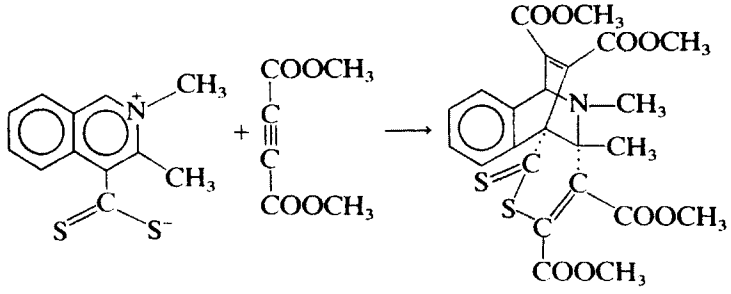
yields adducts **476**[485] (Eq. 200):



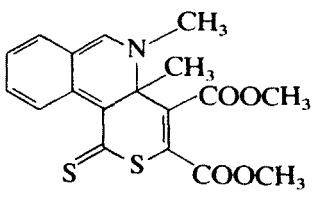
475 476 (200)

X = CN,COOCH3

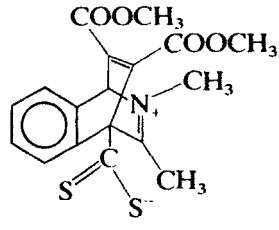
Another dipole has been studied by Mizuyama et al.,[486] who found that the 2,3-dimethylisoquinolinium-4-dithiocarboxylate (**477**) reacted with 2 moles of dimethyl acetylenedicarboxylate, thus affording **478** (Eq. 201). The authors have depicted the intermediate as being the product **479** of a 1,3-dipolar addition involving the thiocarboxylate anion and position 3 of the nucleus. In the absence of any proof, it would seem more logical to suppose that the more reactive dipole in the initial reaction would involve carbon atoms 1 and 4, thus leading to **480**. The latter intermediate would give a satisfactory explanation of how a positive charge could emerge at position 3 for dipole addition.



477 478 (201)



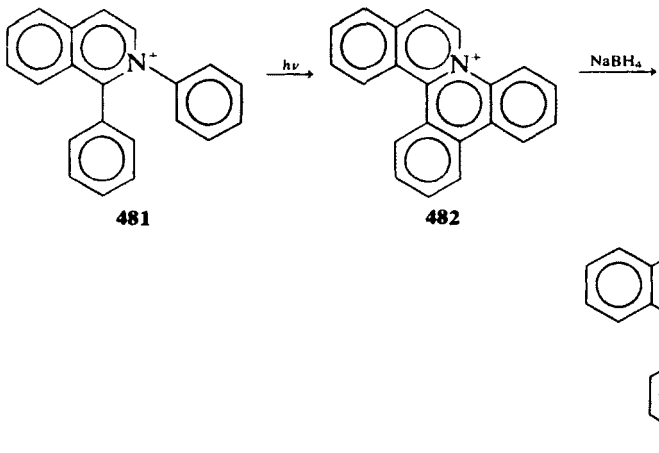
479



480

XV. CYCLODEHYDROGENATION REACTIONS OF QUATERNARY ISOQUINOLINIUM SALTS

Although cyclodehydrogenation of several pyridinium salts has been reported,[487,488] only a single example of a similar reaction involving an isoquinolinium salt has been found. Van Binst et al.[154] showed that 1,2-diphenylisoquinolinium ion (**481**), on irradiation, afforded what is presumably tribenzo[*a*,*c*,*h*]quinolizinium ion (**482**), which was identified by reduction to the quinolizine **483** by sodium borohydride (Eq. 202).



481 482 483 (202)

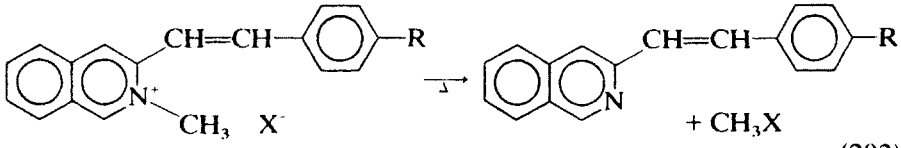
The reaction was complicated by the fact that the starting material was not pure but contained roughly one-third of the 3,4-dihydro derivative, but the yield (43%) was high enough to indicate that the fully aromatic salt participated in the dehydrogenation reaction.

XVI. DISSOCIATION AND HYDROGENOLYSIS

A. Thermal Dissociation

There appear to be relatively few examples of the removal of the position-2 substituent of a quaternary isoquinolinium salt, but occasionally it

has been necessary to carry out such a transformation. The classical approach to the problem has been thermal dissociation, taking advantage of the reversibility of the quaternization reaction. 3-(β-Styryl)-2-methylisoquinolinium ion (**484**, R = H) has been thermolyzed as the iodide[135] (at 200 to 220°C) and as the chloride[489] and the 3-(*p*-dimethylamino-β-styryl)2-methyl analogue **484** [R = $N(CH_3)_2$] as the iodide (Eq. 203), but in the absence of an explicit statement it might be inferred that the yields of the isoquinoline **485** were not very good. If, as it appears, the mechanism involves nucleophilic displacement of the methyl group by the halide anion, the iodide salt should be superior to the chloride.

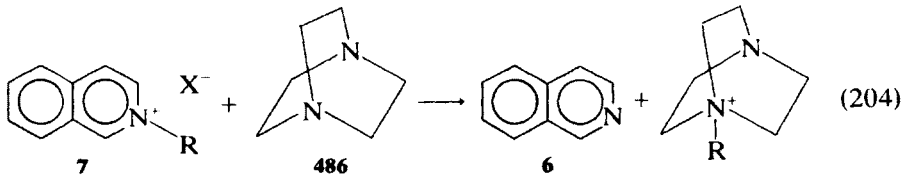


484 **485** (203)

R = H,$N(CH_3)_2$

B. By Action of Bases

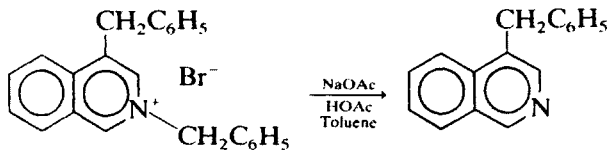
An alternate approach[490] makes use of a base, 1,4-diazabicyclo[2.2.2]-octane (**486**), which is characterized by low nucleophilicity (Eq. 204), and refluxing the mixture for 3 hr in dimethylformamide. The reported yields were fairly good.



7 **486** **6** (204)

R = CH_3; X = I; (75%)
R = $C_6H_5CH_2$; X = Cl; (55%)

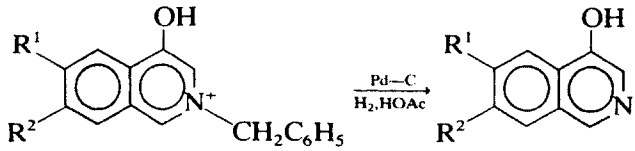
Removal of a 2-benzyl group from 2,4-dibenzylisoquinolinium bromide (**487**) has been accomplished by refluxing it for 20 hr in toluene with acetic acid and sodium acetate (Eq. 205).[136] Although the use of sodium phenyl selenide has been recommended for the cleavage of quaternary salts, it was ineffective when tried on papaverine methochloride.[491]



487 (205)

C. By Hydrogenolysis

When the group at position 2 of an isoquinolinium quaternary salt is benzyl, there is the possibility of removing it by hydrogenolysis. Grethe et al.[157] have obtained fair to good yields of 4-hydroxyisoquinolines **489** from the 2-benzylisoquinolium derivatives **488** by hydrogenolysis in acetic acid at 70°C over a palladium–charcoal catalyst (Eq. 206). In one case in which there was a chlorine at position 7 in the nucleus of the isoquinolinium salt, hydrogenolysis of the chlorine occurred concomitantly with that of the benzyl group.



(206)

488 **489**

$R^1 = H$; $R^2 = OCH_3$ (30%)
$R^1 = R^2 = OCH_3$ (86%)
$R^1 = H$; $R^2 = Cl$ (59%)

XVII. USES OF QUATERNARY ISOQUINOLINIUM SALTS

Although most of the quaternary isoquinolinium salts produced commercially are made for their fungicidal and bactericidal properties, many other applications have been suggested and, in many instances, patented. An attempt has been made to classify these uses as medical, agricultural, or industrial.

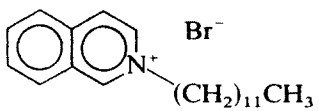
A. Medical Applications

In addition to being used as bactericides and fungicides, isoquinolinium salts have been tested as antineoplastic agents, curarelike agents, cholinesterase inhibitors, hypotensive agents, and local and general anesthetics and for other types of activity.

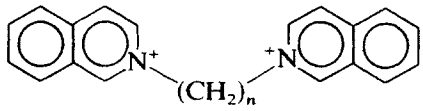
(a) *Bactericidal and Fungicidal Activity*

Dodecylisoquinolinium bromide (**490**) is a recognized bactericide[492,493] and fungicide that, in animal tests,[494] does not appear to be more than moderately toxic. Efforts have been made to modify the bacteriostatic or fungicidal activity by modifying the length[495] or nature[81,131,496–499] of the

side chain or nature of the anion.[500]



490

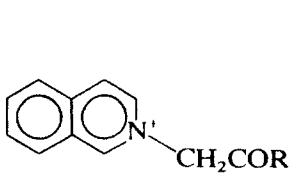


491

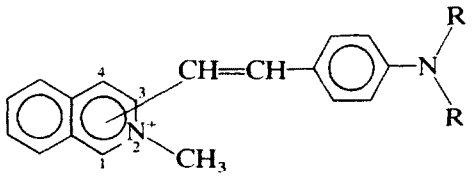
Bisquaternary salts such as **491** have been said to be active as antifungal[23,501–503] and bactericidal[22,23,26,502–505] agents. The bacteriostatic activity of quaternary isoquinolinium salts with a substituent in position 1 has also been studied.[506,507] Bisquaternary salts **491** have been tested for trypanocidal activity[508,509] and were reported[509] to prolong the lives of infected animals. Isoquinolinium analogues of active phenanthridine compounds showed no noteworthy activity.[510]

(b) *Antineoplastic and Carcinostatic Activity*

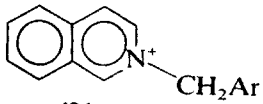
The observation that 2-phenacylisoquinolinium iodide (**492**, $R = C_6H_5$) inhibits sarcoma 37 tumors[511] led to the testing of many analogues.[39,512,513] Many bisquaternary isoquinolinium salts **491** were likewise synthesized for testing. Among the 1- and 3-styryl compounds **493** examined, the methiodides were found to be less active than were the free base.[514] Several compounds of the type represented by **494** have also been tested.[60,90,515]



492



493

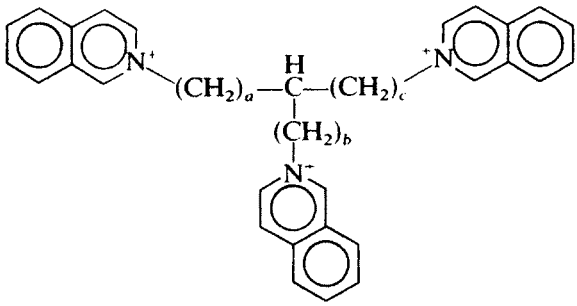


494

(c) *Curare Substitutes*

A search for compounds having muscle-relaxing properties[516] has led to the synthesis and testing of various isoquinolinium quaternary salts, some of which possess activity. With an occasional exception,[320] most of these isoquinolinium salts were bis-**491** and trisisoquinolinium salts **495** and their ring-substituted analogues.

Although activity was found in a large number of bisquaternary salts,[25,517]

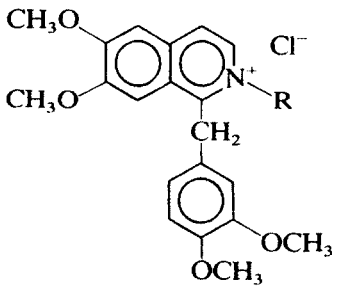


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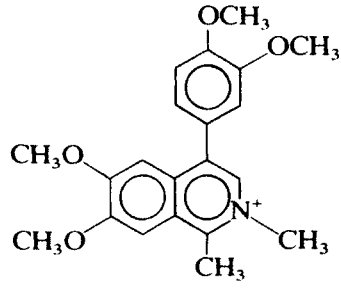
it was reported[517] that they were generally less active than their 1,2,3,4-tetrahydro analogues. Among the trisisoquinolinium salts tested,[27] one (**495**, $a = c = 3$; $b = 1$) proved outstanding.[518]

(d) *Cardiovascular Agents*

Quaternary papaverine (**496**) derivatives have been reported to have hypotensive and spasmolytic activity.[519] In **497**, where the 3,4-dimethoxyphenyl group is, in effect, moved to position 4, the hypotensive



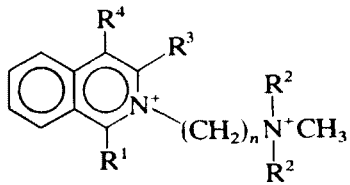
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497

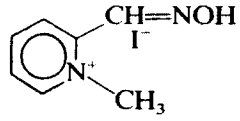
R = C_6H_5CO,CH_3CO,$C_6H_5SO_2$

activity is still found.[16] The activity of bisquaternary salts has been studied,[20,180,520,521] and several such compounds of type **498** have been shown to produce significant hypotensive effects that last for several hours.[521] Cardiovascular activity has been claimed for several other isoquinolinium quaternary salts.[522–525]



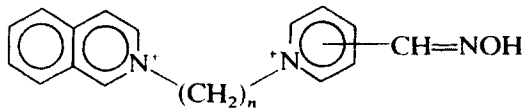
498

Picolinaldoxime methiodide (**499**) was developed as an important agent to reactivate acetylcholinesterase that has been deactivated by the action of nerve gases such as diisopropylfluorophosphate and its congeners.[526,527]

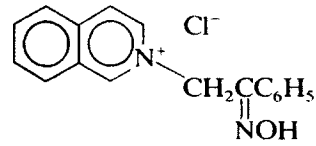


499

Various isoquinolinium salts have been tested for similar activity. The structural similarity of active compound types **500**[528] and **501**[529] to picolinaldoxime methiodide (**499**) is obvious. Testing of several other types of isoquinolinium salt has been reported.[216,281,530–533]



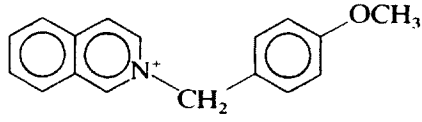
500



501

(e) *Local and General Anesthetics*

Some rather simple isoquinolinium salts show anesthetic properties. One of these salts is 2-(4-methoxybenzyl)isoquinolinium chloride (WIN 2173) (**502**), described[534] as a ganglionic blocking agent. Similar activity appears to be shown[20,505] by the type of bisquaternary salt **491** previously discussed as bactericides, curare substitutes, and cardiovascular agents. The anesthetic properties of several other isoquinolinium salts have been reported.[50,535,536]



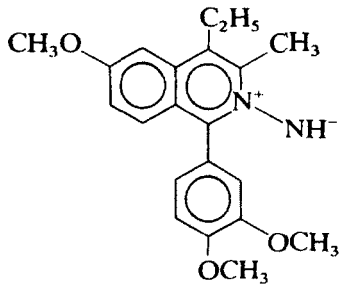
502

(f) *Other Types of Physiological Activity Shown by Isoquinolinium Salts*

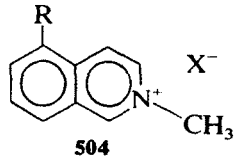
The activity of 1-benzyl-2-methylisoquinolinium iodide against an influenza virus has been reported,[537] and another isoquinolinium salt was stated[538] to be active against the virus of hoof-and-mouth disease.

It is reported[171] that the betaine **503** in animal tests was about five times as active as meprobamate and that certain 5-substituted isoquinolinium salts

504 have some reserpinelike activity.[539] The use of some 6-alkoxyisoquinolinium salts as antidiabetics has been patented.[540]



503



504

B. Agricultural Applications

Although the major agricultural use of isoquinolinium quaternary salts is as a pesticide, several other applications of these salts have been suggested.

(a) *As Pesticides for Agricultural Use*

The pronounced bactericidal and fungicidal activity of isoquinolinium salts that have a long quaternary side chain has made these, and in particular, 2-dodecylisoquinolinium bromide (Isothan, Q-15), of interest as pesticides. It appears that the latter salt has been used with variable results with a variety of fruit crops.[541–547] At least one bisquaternary salt has been tested as an agricultural fungicide, but results were not outstanding.[548]

(b) *Other Agricultural Uses*

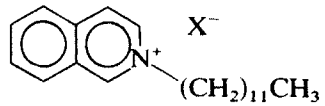
Other possible agricultural uses of isoquinolinium salts that have been investigated include insecticides,[549] defoliation control agents,[550] and soil conditioners.[551,552]

C. Industrial Uses

The largest industrial application of isoquinolinium salts has been in the preparation of cationic detergents and surfactants and as additives in metal plating, but there are a few more applications of some significance.

(a) *Detergents and Surfactants*

Although there is an occasional patent dealing with the application of isoquinolinium salts[553] or modification of the quaternary side chain,[497] nearly all the patents dealing with isoquinolinium salts as detergents–surfactants with antimicrobial activity have described new anions for laurylisoquinolinium salts (**505**). The anions include carboxylates,[554–556]



505

phenoxides,[557–560] phosphonates,[561] mercaptides,[562] alkylsulfates,[563,564] sulfonates,[561,565] sulfamates,[566] sulfimides,[567] enolates,[568] and imides.[568–570]

(b) *Brighteners in Metal Plating*

The addition of isoquinolinium quaternary salts to electroplating baths has been found to enhance the brightness of the plating. The major application appears to be in nickel plating,[33,571–580] although the use of salts of this type on the plating of zinc, cadmium,[581] and copper[582] has been mentioned. Most of the plating additives are monoquaternaries or betaines,[576,581,582] but a few bisquaternaries[572,577,583] have been used.

(c) *Textile Applications*

Aside from the application[584] of dodecylisoquinolinium salts as detergents, surfactants, and fungicides, their use by the textile industry as antistatic agents[585,586] and water repellants[585] has been suggested.

(d) *Corrosion Inhibitors*

It appears well established[587] that long-chained isoquinolinium salts inhibit the corrosion of steel exposed to salt,[587] or possibly acid[588–590] solutions. The use of other types of isoquinolinium salt in combination with phosphinate-[372,591] or dithiophosphinate-[592] derived anions as corrosion inhibitors for steel has been proposed.

(e) *Other Industrial Uses*

Patents have been issued[250,593,594] describing the use of isoquinolinium quaternary salts as demulsifiers for use in the petroleum industry. Dunaevskaya and co-workers[595,596] have described the use of isoquinolinium salts as flocculating agents.

Although isoquinoline methobisulfate has been described[89] as an activating agent in photographic development and an account of cyanine dyes that contain the isoquinolinium nucleus has been published,[597] it is not clear whether isoquinolinium salts play any part in modern photography.

Other suggested uses of isoquinolinium salts have been as organic semiconductors[28,598,599] and reaction catalysts or cocatalysts for polymerization[600] or ring opening of an epoxide.[601]

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