PYRROLES

Part One

This is a part of the forty-eighth volume in the series

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

A SERIES OF MONOGRAPHS

EDWARD C. TAYLOR, *Editor*

ARNOLD WEISSBERGER, *Founding Editor*

PYRROLES

Part One
THE SYNTHESIS AND THE PHYSICAL AND CHEMICAL ASPECTS OF THE PYRROLE RING

Edited by

R. Alan Jones

School of Chemical Sciences
University of East Anglia
Norwich, U.K.

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Contributors

Hugh J. Anderson
Department of Chemistry
Memorial University of Newfoundland
St. John's, Newfoundland, Canada

Marino Artico
Dipartimento di Studi Farmaceutici
Facoltà di Farmacia
Università degli Studi di Roma "La Sapienza"
Rome, Italy

Gerritt P. Bean[a]
Department of Chemistry
Western Illinois University
Macomb, Illinois

Derek J. Chadwick[b]
Department of Organic Chemistry
The Robert Robinson Laboratories
University of Liverpool
Liverpool, U.K.

Nicholas Dennis[c]
School of Chemical Sciences
University of East Anglia
Norwich, U.K.

Albert Gossauer
Institut für Organishe Chemie der Universität Freiburg
Freiburg, Switzerland

Anthony H. Jackson
School of Chemistry and Applied Chemistry
University of Wales College of Cardiff
Cardiff, U.K.

Charles E. Loader
Department of Chemistry
Memorial University of Newfoundland
St. John's, Newfoundland, Canada

Petr Nesvadba
Institut für Organishe Chemie der Universität Freiburg
Freiburg, Switzerland

Michael P. Sammes
Department of Chemistry
University of Hong Kong
Hong Kong

[a] *Present affiliation*: Department of Chemistry and Biochemistry, University of Boulder, Boulder, Colorado.
[b] *Present affiliation*: The Ciba Foundation, 41 Portland Place, London W1N 4BN.
[c] *Present affiliation*: Graduate School of Science and Technology, Bond University, Gold Coast, Queensland 4229, Australia.

The Chemistry of Heterocyclic Compounds
Introduction to the Series

The chemistry of heterocyclic compounds is one of the most complex and intriguing branches of organic chemistry. It is of equal interest for its theoretical implications, for the diversity of its synthetic procedures, and for the physiological and industrial significance of heterocyclic compounds.

The Chemistry of Heterocyclic Compounds, published since 1950 under the initial editorship of Arnold Weissberger, and later, until Dr. Weissberger's death in 1984, under our joint editorship, has attempted to make the extraordinarily complex and diverse field of heterocyclic chemistry as organized and readily accessible as possible. Each volume has dealt with syntheses, reactions, properties, structure, physical chemistry and utility of compounds belonging to a specific ring system or class (e.g., pyridines, thiophenes, pyrimidines, three-membered ring systems). This series has become the basic reference collection for information on heterocyclic compounds.

Many broader aspects of heterocyclic chemistry are recognized as disciplines of general significance which impinge on almost all aspects of modern organic and medicinal chemistry, and for this reason we initiated several years ago a parallel series entitled *General Heterocyclic Chemistry* which treated such topics as nuclear magnetic resonance, mass spectra, and photochemistry of heterocyclic compounds, the utility of heterocyclic compounds in organic synthesis, and the synthesis of heterocyclic compounds by means of 1,3-dipolar cycloaddition reactions. These volumes were intended to be of interest to all organic and medicinal chemists, as well as to those whose particular concern is heterocyclic chemistry.

It has become increasingly clear that this arbitrary distinction creates as many problems as it solves, and we have therefore elected to discontinue the more recently initiated series *General Heterocyclic Chemistry*, and to publish all forthcoming volumes in the general area of heterocyclic chemistry in *The Chemistry of Heterocyclic Compounds* series.

EDWARD C. TAYLOR

Department of Chemistry
Princeton University
Princeton, New Jersey 08544

Foreword

Pyrrole is a remarkable substance; it is highly reactive, versatile in that reactivity and is of crucial importance for living systems. In both animal and plant kingdoms, the brightly colored materials which have become known as the pigments of life such as haem, chlorophyll, vitamin B_{12}, and the cytochromes are constructed largely from the relatively simple monopyrrolic building block porphobilinogen. Their biological interest has been one major driving force, though by no means the only one, which has caused the massive surge of interest in and research effort on the chemistry of pyrroles. There is now available an amazing variety of chemistry amassed from these studies. What stands out plainly is the powerful effect substituents on the pyrrole nucleus have on the reactivity of the system, whether they be attached at carbon or at nitrogen. Those who have worked personally with pyrrolic substances are acutely aware of this aspect of their chemistry and, for example, use it to steer safely along a synthetic route avoiding Scylla on the one hand and Charybdis on the other, Professor Woodward's synthesis of chlorophyll is a perfect example.

This topic of reactivity and all other relevant ones ranging from synthetic methods, spectroscopic properties, and the physical and theoretical aspects are all fully reviewed, in this first volume of several, by those who are authorities on each particular area. In addition, I was pleased to see that there is extensive authoritative coverage of the chemistry of those important isomers of pyrrole itself, namely, the 2*H*-pyrroles and 3*H*-pyrroles.

Chemists working on pyrroles and their relatives, and it is a growing group, should be grateful that the editor and his colleagues have worked together to produce this invaluable assembly of information and analysis. This set of volumes is certain to be a constant source of reference for all who enjoy the chemistry of pyrroles and who wish to add further building blocks to the marvelous edifice which is still evolving.

ALAN R. BATTERSBY

Cambridge, U.K.
April 1989

Preface

This book, which is the first of a series devoted to the chemistry of pyrrole and its derivatives, presents the basic structural, physical, and chemical properties of 1*H*-pyrrole and of the less prevalent 2*H*- and 3*H*-isomers, together the synthesis of the three systems.

Since its initial detection in coal tar and bone oil by Runge in 1834, pyrrole has been an intriguing compound; one which, although highly susceptible to oxidation and polymerization, occupies a key role in life. Such was its importance as the basic nitrogen heterocycle in porphins and chlorins that much of our early knowledge of the simple ring system revolved around the biologically more important derivatives. This is reflected to a large extent in the early authoritative texts by Fischer and Orth, who provided the chemist with a comprehensive review of the synthesis and basic chemical properties of the more stable substituted pyrrole derivatives. The advent of sophisticated analytical and separation techniques, developed over the past twenty years, and our ability with faster computers to undertake more complex theoretical calculations, has widened our horizons and we are now in a position to present a fuller, if not yet complete, picture of the chemistry of pyrrole.

In the compilation of this first part of the series, I am indebted to the contributing authors for their successful endeavors in providing comprehensive surveys of the physical, theoretical, synthetic, and chemical aspects of our present-day knowledge of the chemistry of the pyrrole ring. In particular, I acknowledge the forebearance of the authors, who allowed me to conflate their individual contributions on the chemical reactivity of the pyrrole ring into a single cohesive chapter. My sincere thanks also go to my university colleagues for their support and helpful advice and last, but by no means least, to my wife for her continuing patience and understanding.

R. ALAN JONES

Norwich, U.K.
July 1989

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Abbreviations Used in the Text, Tables, and Formulas

ac	acetyl
acac	acetylacetonate
Ar	aryl
t-BOC	*tert*-butyloxycarbonyl
9-BBN	9-borobicyclo[3.3.1]nonane
BPR	by-product
Bu	butyl
CASSCF	complete-active-space self-consistent-field theory
CNDO	complete neglect of differential overlap (molecular orbital calculations)
CNDO/S	CNDO adapted for spectroscopy
cr	crude
Dabco	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undecene
DDQ	2,3-dichloro-5,6-dicyano-1,4-quinone
DIBAL	diisobutylaluminum hydride
DMAD	dimethyl acetylenedicarboxylate
DMF	dimethylformamide
DMSO	dimethylsulfoxide
E	electrophilic agent
EHT	extended Hückel theoretical (calculations)
Et	ethyl
GC	gas chromatography
HAM	'hydrogenic atoms in molecules' modified SCF
HOMO	highest occupied molecular orbital
HMO	Hückel molecular orbital (calculations)
HMPA	hexamethylphosphoric triamide
HSAB	hard–soft acid–base (theory)

INDO	intermediate neglect of differential overlap (molecular orbital calculations)
INDO/S	INDO adapted for spectroscopy
LCAO	linear combination of atomic orbital (calculations)
LCGO–SCF	linear combination of Gaussian orbitals–SCF calculations
LNMP	lithium *N*-methylpiperazide
LUMO	lowest unoccupied molecular oribital
M	component of a mixture
Me	methyl
MINDO	modified intermediate neglect of differential overlap (molecular orbital calculations)
MM–MNDO	molecular mechanics approach to MNDO
MNDO	modified neglect of differential overlap (molecular orbital calculations)
MORT	molecular orbital resonance theory
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NPM	*N*-phenylmaleimide
NI	not isolated
NIS	*N*-iodosuccinimide
NY	no yield given
PBG	porphobilinogen
Ph	phenyl
Pr	propyl
PPP	Pariser–Parr–Pople (molecular orbital calculations)
QCFF/pi	quantum chemical extension of the force field method to π-electron systems
R	alkyl group (unless otherwise stated)
SAC	symmetry-adapted cluster theory
SCF	self-consistent field theory
SEM	$CH_2O(CH_2)_2SiMe_3$
SINDO	symmetry-orthogonalized INDO
STO	Slater-type orbital
Tf	triflyl (CF_3SO_2)
THF	tetrahydrofuran

TMED	*N*,*N*,*N*′,*N*′-tetramethylethylenediamine
TMS	trimethylsilyl
Tol	tolyl
Tos	*p*-toluenesulfonyl
TOSMIC	*p*-toluenemethylisocyanide
UHF	unrestricted Hartree–Fock (calculations)
VEH	valence-effective Hamiltonian (calculations)

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CHAPTER 1

Physical and Theoretical Aspects of 1*H*-Pyrroles

Derek J. Chadwick

Department of Organic Chemistry
The Robert Robinson Laboratories
University of Liverpool
*Liverpool, U.K.**

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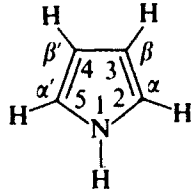
1.1. INTRODUCTION

The term *pyrrole* stems from Runge's observation in 1834[1] that coal tar and bone oil contain a substance that imparts a red color to pine splinters moistened with mineral acid. The compound was isolated from bone oil and

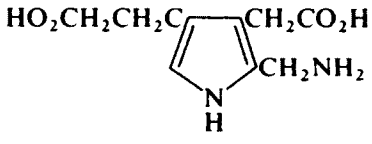
* *Present address*: The Ciba Foundation, 41 Portland Place, London W1N 4BN.

purified by conversion into its potassium salt by Anderson in 1857.[2,3] The structural formula was established in 1870.[4] The International Union of Pure and Applied Chemistry (IUPAC) numbering system is given in **1** along with the commonly used nomenclature wherein the 2(5) positions are designated $\alpha(\alpha')$ and the 3(4) positions $\beta(\beta')$.



1

The ring system, which is widely distributed in nature, is a subunit of haem, the chlorophylls, vitamin B_{12}, and the bile pigments. Porphobilinogen (**2**) is an important monopyrrolic natural product, since it is the biosynthetic precursor to the porphyrins and corrins. The pyrrole ring occurs in a number of naturally occurring antibiotics, including the increasingly important netropsin (**3**) and distamycin structures. Polymers based on the pyrrole ring system show considerable promise as semiconducting and conducting materials.



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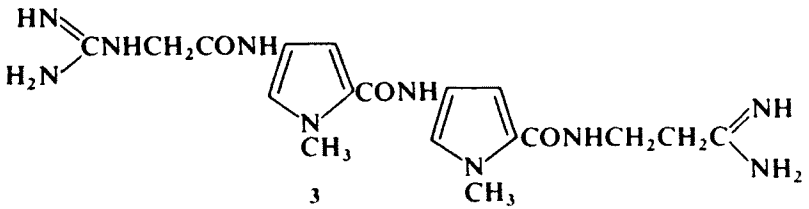

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Pyrrole chemistry prior to the early 1930s is reviewed in the comprehensive work by Fischer and Orth.[5] More recent general reviews are available in Refs. 6–12 and in the exhaustive monographs of Gossauer[13] and Jones and Bean.[14] This survey draws heavily on these reviews and extends the literature coverage to 1987 (*Chemical Abstracts*, Vol. 106).

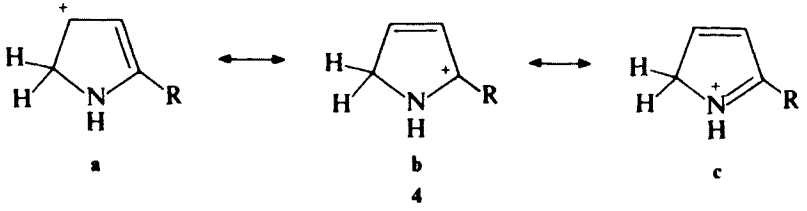
Pyrrole is a colorless liquid, b.p. 129.8°C at 760 torr, m.p. 23.4°C, density 0.970 g ml^{-1} at 20°C, with an odor somewhat resembling that of chloroform. It gradually turns brown in air and is slightly hygroscopic, taking up approximately 3% by weight of water at room temperature. It has a low solubility in

water (ca. 6%) but is miscible with most organic solvents. Useful tabulations of macroscopic physical constants are available in Ref. 13 (pp. 4–6) and Refs. 15 and 16.

The physical and chemical properties of pyrrole are in accord with those expected for an aromatic system (see Section 1.5) in which the nitrogen lone pair is delocalized into the ring; as a consequence, the compound has negligible basicity, compared with typical secondary amines. The pK_a in water for *N*-protonated pyrrole has been estimated[17] as -10 (cf. 11.3 for pyrrolidine), so protonation occurs preferentially at carbon rather than nitrogen [$pK_a^{H_2O}$ $C_\alpha = -3.80$,[18] -4.44[19]]: this is supported by the results of most molecular orbital (MO) calculations and nuclear magnetic resonance (NMR) measurements.[18,20,21] The N–H hydrogen atom undergoes rapid exchange with protic solvents at all pH values; exchange of the C–H hydrogen atoms is catalyzed by acid and occurs more rapidly at β than α positions, although the α-protonated salts are generally the thermodynamically more stable species (see Chapter 3.2). This thermodynamic preference is also evident in the results of $^3H/^1H$ exchange experiments[22] (see also Ref. 23) and is supported by modified neglect of differential overlap (MNDO) and ab initio calculations.[24,25] The basicity of the pyrrole ring increases considerably with alkyl substitution; representative examples taken from Ref. 18 are given in Table 1.1, and further data are available in Refs. 14, 18, and 19. Alkyl derivatives of pyrrole display, in their hydrogen-exchange reactions, the largest "Baker–Nathan" order ever observed for a chemical reaction;[26] this is argued as illustrating the importance of steric hindrance to solvation. The canonical forms of the 5-protonated intermediate derived from a 2-alkylated pyrrole are **4a–c**. Solvation of **4b** and also partly of **4c** is hindered; the latter effect is particularly significant since **4c** is the most important contributor to the resonance hybrid. Thus, for deuteriation in aqueous dioxan,[27] a very high Me:*t*-Bu rate ratio (1.75) is observed. For deuteriation at the 2 position of 3-alkylpyrroles, the rate ratio for the methyl and *t*-butyl compounds is even larger (2.87); the relevant canonical forms are **5a–c**, of which **5a** is the most important. In the deuterium exchange at the 3 position of 2-alkylpyrroles, the Me:Et rate ratio is a very high (2.3), since both canonical

TABLE 1.1. BASE STRENGTHS OF ALKYLPYRROLES FOR α-PROTONATION

Substituent	pK_a
H	−3.80
1-Methyl	−2.90
2-Methyl	−0.21
3-Methyl	−1.00
2,4-Dimethyl	2.55
2,5-Dimethyl	−0.71
3,4-Dimethyl	0.66
1,2,5-Trimethyl	−0.24
2,3,5-Trimethyl	2.00



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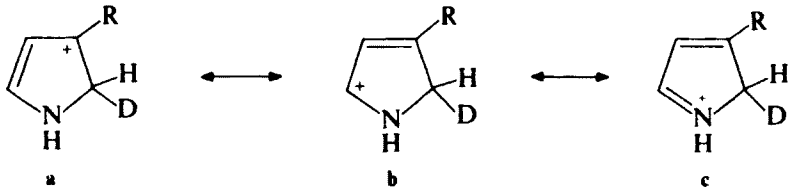

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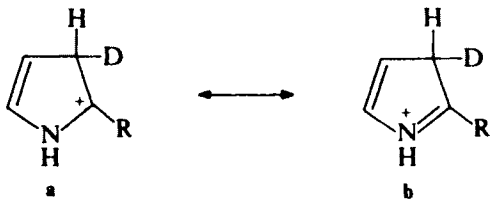
structures **6a**, **b** are hindered. Pyrroles bearing electron-withdrawing substituents are considerably less basic than their alkyl or aryl counterparts, and protonation may occur preferentially on the substituent. The basicity of pyrrole toward uranyl hexafluoroacetylacetonate (U) $\{UO_2[(CF_3CO)_2CH]_2\}$, obtained



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by monitoring of the ^1H NMR signals due to the α-CH_2's of THF in the equilibrium

$$U \cdot THF + \text{pyrrole} \rightleftarrows U \cdot \text{pyrrole} + THF$$

gave a value of $\Delta G^0 = +19.3$ kJ M^{-1} (cf. values of -5.0 for pyridine, $+5.7$ for 2,6-dimethylpyridine, and $+14.7$ for acetonitrile[28]).

Estimates of the pK_a of pyrrole for N–H ionization to give the pyrrolyl anion vary somewhat depending on the solvent and analytical methodology. Recent values are 23.05 in dimethylsulfoxide (DMSO)[29] and 21.9 in 5% H_2O–95% DMSO;[30] the former values should be compared with the value of 44 estimated for pyrrolidine, showing the stabilizing effect of two α carbon–carbon double bonds. A note of caution has been expressed in relation to the determination of pK_a values of NH acids by transmetalation, since such evaluations can display a differential sensitivity to solvent depending on the particular countercation used.[31] The NH acidity of substituted pyrroles increases with increasing electron withdrawal by substituents; those in α positions have a greater effect than in

the β position. Nitro- and nitrosopyrroles are especially acidic and dissolve in dilute aqueous alkali (e.g., the pK_a of 2-nitropyrrole is 10.60 and of 2,5-dinitropyrrole, 3.16; see Refs. 13, 14, and 32 for further examples). Carbon-13 NMR spectroscopy has been used for the estimation of the pK_a values of 1-methyl- and 1-dimethylaminopyrrole for α-C–H ionization in THF; values of 39.5 and 39.7 are quoted for the former and 36.9 and 37.1 for the latter compound, showing that the pyrroles are insufficiently acidic for complete metalation by a lithiated amine. (The pK_a of diisopropylamine in THF is 35.7.) It is interesting to compare these values with those determined for α-C–H ionization of furan (35.6), thiophene (33.0), and *N*-methylindole (38.1).[33]

The involvement of the nitrogen lone pair in the pyrrole π-system is reflected in its dipole moment; *N*-methylation of pyrrolidine leads to a reduction in the overall moment from 1.58 to 1.10D,[34] whereas *N*-methylation of pyrrole leads to an increase in moment from 1.76 to 1.91D.[35] This indicates that the moments of pyrrole and pyrrolidine are in opposite directions and that the σ-moment of pyrrole is opposed by the π-moment;[36] a view supported by ^{1}H NMR chemical-shift data measured for CCl_4, C_6D_6, and C_6F_6 solutions.[34] The quoted values for the dipole moment of pyrrole[13,14] vary with methodology and state or solvent. In the gas phase, values given are 1.74 and 1.84; in nonpolar solvents, such as CS_2, CCl_4, and cyclohexane, they range from 1.66 to 1.79D; in the neat liquid a value of 1.55D is typical, while in solvents to which pyrrole can hydrogen-bond the value may be considerably higher (e.g., in dioxan ca. 2.1D and in triethylamine ca. 3.0D). Many theoretical techniques have been applied to the calculation of dipole moments, often with considerable success (see Ref. 13 for a tabulation and also many of the references cited in Section 1.2). There is a wealth of experimental information on the dipole moments of substituted pyrroles; a selection is given in Table 1.2 for solutions in benzene at 25°C. Further examples may be found in Refs. 13 and 14. Additionally, extensive information on substituted 1-vinylpyrroles is available.[42] Group dipole moments for a range of substituents at the 2 and 3 positions of pyrrole have been evaluated from published dipole moment data.[40] The role of dipole moment studies in the conformational analysis of substituted pyrroles is addressed in Section 1.6. Recent studies on the macroscopic magnetic, electric, and optical properties of pyrrole derivatives include Refs. 43 and 44 (dipole moments and Kerr constants), Refs. 45–47 (dielectric absorption and relaxation), Ref. 48 (molecular optical anisotropy), and Refs. 49 and 50. (The latter two contain extensive compilations of magnetic and magnetooptical parameters). Polypyrrole is currently under intensive investigation because of its promise as a conducting polymer. Doped polypyrrole films, generally prepared electrochemically, display metallic conductivity typically in the range 40–200 $\Omega^{-1}\,cm^{-1}$, whereas films derived from *N*-methylpyrrole have much lower conductivity (ca. $10^{-3}\,\Omega^{-1}\,cm^{-1}$), which is more characteristic of a semiconductor. Films from the copolymerization of mixtures of pyrrole and *N*-methylpyrrole have redox potentials intermediate between those of either monomer, suggesting random copolymerization; there does not appear to be an abrupt metal–semiconductor

TABLE 1.2. DIPOLE MOMENTS OF SUBSTITUTED PYRROLES IN BENZENE AT 298 K

Substituents						
1	2	3	4	5	μ(D)	Ref.
Me	H	H	H	H	1.96	37
H	Me	H	H	H	1.95	37
H	Me	H	Me	H	1.75	38
H	Me	H	H	Me	2.03	38
Me	Me	H	H	Me	2.08	38
H	CHO	H	H	H	2.18	37
Me	CHO	H	H	H	2.84	37
H	H	CHO	H	H	4.96	39
H	$COCH_3$	H	H	H	1.82	37
H	H	$COCH_3$	H	H	5.03	37
H	COPh	H	H	H	1.81	37
H	CO_2Me	H	H	H	1.77	37
H	$CONMe_2$	H	H	H	2.07	37
H	H	CO_2Me	H	H	3.60	37
H	NO_2	H	H	H	4.33	37
H	I	I	I	I	2.54	37
H	CN	H	H	H	3.76	39
Me	CN	H	H	H	4.17	37
H	Ph	H	H	H	1.66	37
Ph	Ph	H	Ph	Ph	2.04	40
H	2-furyl	H	H	H	1.58	41
H	2-thienyl	H	H	H	1.82	41

transition[51] (see also Refs. 52–54 and references cited therein). The magnetic susceptibility of doped polypyrrole is discussed in Ref. 55, and the electrochemical oxidation of pyrroles is reviewed in Ref. 56 [see Section 3.5.4].

Polarographic data for pyrrole derivatives are reviewed extensively in Ref. 13 and discussed also in Ref. 14. Pyrrole and its *N*- and *C*-alkyl- and *N*-acyl derivatives are not reduced polarographically at a mercury electrode over a wide pH range, nor are simple pyrrole carboxylic acid esters, although the presence of an ester group may aid the reduction of other substituents. The half-wave potential for the reduction of *C*-acyl and *C*-nitropyrrole derivatives depends on the position of the substituent and the pH of the medium. It is generally true that β-substituents are more readily reduced than an α-substituent and nitropyrroles more readily reduced than acylpyrroles. The anodic oxidation potentials for a series of 117 pyrrole derivatives have recently been measured by cyclic voltammetry and substituent partial potentials for common substituents derived largely by least-squares analysis. From these, with only a few exceptions (e.g., when two strongly electron-withdrawing substituents are located at the α positions, or when one α position is vacant while the other bears a strongly electron-withdrawing group), it is possible to deduce accurate calculated oxidation potentials for virtually any common substituted pyrrole. The substituent

contributions to observed oxidation potentials are given in Table 1.3.[57] Some trends are apparent in these numbers; for example, the strongly electron-withdrawing effect of β-methoxycarbonyl (+273 mV) drops to −12 mV, when a methylene is inserted to give CH_2CO_2Me, and successive methylene insertions lead to further reductions so that the substituent contributions approach that for ethyl (−95 mV). When the 2-methyl group (substituent contribution −398 mV) is converted into CH_2Br, CH_2OAc, or CH_2Cl, the values, not surprisingly, become less negative (−204, −169, and −163 mV, respectively). Similarly, replacement of CH_2CH_3 by CH_2CH_2OAc or CH_2CH_2Cl leads to increases in the substituent contributions from −95 to −84 and −54 mV, respectively, as expected from qualitative electronegativity considerations. However, there does not appear to be a demonstrable correlation between the substituent contributions and σ_m and σ_p coefficients. For pyrroles bearing

TABLE 1.3. SUBSTITUENT CONTRIBUTIONS TO OBSERVED OXIDATION POTENTIALS OF SUBSTITUTED PYRROLES (in mV)[a]

Substituent	At α Position	At β Position
Me	−398	−125
Et		−95
Pr		−89
i-Bu		−95
CH_2OCOMe	−169	
CH_2Cl	−163	
CH_2Br	−204	
$(CH_2)_2Cl$		−54
$(CH_2)_2OCOMe$		−84
$CH{=}CMe_2$		−195
CH=CHPr		−255
CO_2CH_2Ph	569	257
CO_2Et	549	240
CO_2t-Bu	533	252
CO_2Me	560	273
CO_2H	581	265
CH_2CO_2Et		−11
CH_2CO_2Me		−12
$(CH_2)_2CO_2Et$		−72
$(CH_2)_2CO_2Me$		−63
$(CH_2)_3CO_2Me$		−75
$CH{=}CHCO_2Et$		63
$CH{=}CHCO_2H$		70
$CONMe_2$	341	
COMe	531	241
CHO	651	348
CN	781	365
Br		68
Cl		124
I	−257	135

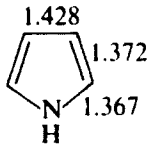
[a] Contribution of the unsubstituted pyrrole ring is 920 mV.

electron-withdrawing groups at both α positions, the observed oxidation potentials are lower than those predicted from additivity, usually by about 300–500 mV, suggesting that the presence of two directly conjugated, electron-withdrawing groups does not double the π-electron depletion in the system and that only between 60 and 80% of the double substituent is felt. This effect is not observed when the substituents are arranged in the 2,3- and 2,4-dispositions.

1.2. THEORETICAL METHODS

Pyrrole continues to be the subject of a wide variety of theoretical investigations spanning the complete range of sophistication from simple Hückel (HMO) theory, through semiempirical CNDO, INDO, SINDO, MINDO, MNDO, and HAM methods, to minimal and (increasingly) split-valence basis set ab initio calculations. Semiempirical methods continue to be the most popular, although increasing computer power and the ready availability of packaged software is stimulating the increased application of ab initio methods. Correspondingly, the number of applications of HMO theory is diminishing. A recent phenomenon is the emergence of reliable molecular mechanics (force-field) calculations on heteroaromatic systems, including pyrrole.

In simple HMO theory, the wave function for each π-type MO is constructed by the LCAO approach. Orbital overlap between nonneighboring atoms is neglected, and the sigma electrons are ignored. The Coulomb integral α (roughly corresponding to the energy of an electron in an isolated carbon 2*p*-orbital) is the arbitrary value assigned to integrals involving only one atom, while the resonance integral β is the value assigned to integrals involving neighboring atoms; integrals involving atoms separated by more than one bond are ignored. For the theory to cope successfully with heteroaromatic compounds, the effects of heteroatoms on the values of α and β have been accommodated through the introduction of adjustable parameters and via the ω technique, which makes α depend, through a proportionality constant ω, on the π-electron density at a particular atom. HMO theory has been widely applied, with some success, to a range of problems in pyrrole chemistry, including the refinement of the molecular geometry, the estimation of π-electron densities, and the calculation of the ionization potential, heat of formation, and wavelengths of optical absorption. Bond lengths so determined are shown in 7.[58] The area (now largely of historical interest) is particularly well reviewed in Ref. 14, and additional references are cited in Ref. 12. Further recent work includes the use of the ω technique in the evaluation of the ionization potential (8.03–8.18 eV; experimental 8.22 eV),[59] the use of HMO and Del Re methods for the calculation of atomic charges,[60] and the application of HMO and Rayleigh–Schrödinger calculations to some magnetic properties of pyrrole.[61] HMO theory and the ω technique have also been used to calculate the energies of a range of 5-membered heteroaromatic compounds (including pyrrole) bearing OH, SH, NH_2, and alkyl groups in a study of the tautomeric equilibria (see Section 1.7).[62]



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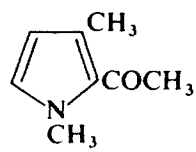

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In the more powerful extended Hückel theory (EHT) method, allowance is made for the effects of σ-electrons and orbital overlap. The technique has been applied to problems such as the pyrrole–pyridine hydrogen-bonded system,[63] the estimation of the geometry of the 2-acetyl derivative **8** (in which the plane of the acetyl group is predicted to be 40° from the pyrrole plane[64]), and the calculation of the geometries of *N*- and *C*-phenylpyrroles and of bipyrroles, for most of which twisted conformations are predicted.[65,66] The EHT method is also finding application in calculations on the band structure of polypyrrole and other conducting polymers.[67–69]

The semiempirical Pariser–Parr–Pople (PPP), complete neglect of differential overlap (CNDO), intermediate NDO (INDO), modified INDO (MINDO), and modified NDO (MNDO) methods represent attempts to relax the approximations of Hückel theory. The CNDO approach continues to be the most popular, although the use of MNDO is increasing. In the PPP technique, one- and two-center repulsion integrals are included, but orbital overlap is neglected. In CNDO (as the term indicates) all integrals involving differential overlap are neglected, whereas in INDO one-electron core resonance integrals are included. The MINDO technique is an INDO-based treatment in which allowance is made for electron correlation by modification of the electron repulsion integrals, while in MNDO some of the shortcomings of the INDO approximation are avoided. The applications of these methods to pyrroles is well reviewed in Refs. 13 and 14, and more recent work is cited in Ref. 12.

The semiempirical method, molecular orbital resonance theory (MORT), which retains the concept of the valence-bond resonance structure but treats each bond in the MO sense, has been used to calculate the heat of atomization of pyrrole as -44.409 and -44.546 eV (cf. the observed value of -44.77 eV).[70] Recent applications of the PPP method have been directed primarily at the interpretation of UV and PES data,[71–73] Ref. 73 is a correction to earlier work (cf. Ref. 74). Recently, PPP and CNDO/S methods have been applied to the calculation of the absorption spectra of the important antibiotics netropsin and distamycin-A.[75]

Many of the recent exampes of the use of the CNDO method in pyrrole chemistry are routine, including geometry optimization,[76] the study of activity and selectivity in electrophilic substitution reactions via calculation of the localization energies of a range of substituted pyrroles,[77,78] study of the interaction energies and electron distributions in pyrrole during reactions with a range of electrophiles,[79] and calculations on pyrrole protonation[80] (cf. Ref. 81). The method has also been applied generally to the calculation of ground and excited-

state properties, including electronic structure, UV and PES spectra, dipole moment, polarizability, and diamagnetic susceptibility,[82-91] to the calculation of spin density distribution in anion and dianion radicals derived from nitropyrroles[92] and (along with ab initio methods) to the valence-bond (Dewar and valene) isomers of pyrrole; the latter isomer is calculated as being significantly more stable than the former.[93] An interesting comparison of values for pyrrole MO energies and ionization potentials calculated by the semiempirical HAM/3, INDO/S, and CNDO/S (with and without the inclusion of *d*-orbitals) methods and by minimal (STO/3G) and split-valence (4-31G) ab initio methods is available in Ref. 94. The results, given in Table 1.4, show that the MO energies and their sequences are highly dependent on the calculation method; the inclusion of *d*-orbitals in the CNDO/S calculations does not affect the MO energies greatly. The INDO/S and CNDO/S methods give improved results over CNDO/2 and INDO for the low binding energy region, but there is a tendency toward overestimation in the high binding energy region. Ab initio results are highly basis-set-dependent; the minimal basis set underestimates the lower IPs, while the split-valence basis set overestimates the higher ones. The HAM/3 results, obtained in a low computation time, seem to be the best and are comparable with the best ab initio approaches taking into account electron correlation and relaxation (see later). The same authors[82] have applied INDO/S and CINDO methods to the study of the electronic spectrum of pyrrole and the calculation of ground and excited-state dipole moments. These results are discussed in Section 1.4.4.

The CNDO/2 technique has been used (along with other theoretical tools) to model the structure of polypyrrole.[96] Calculations of partial atomic charges on α,α'-bipyrrole show that they are not a function of the relative orientation of the ring planes. The charge distribution in polypyrrole is thus determined by calculations on successively larger planar oligomers; the converged partial

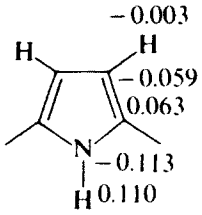
TABLE 1.4. MO ENERGIES AND IONIZATION POTENTIALS (eV) FOR PYRROLE CALCULATED BY SEMIEMPIRICAL AND ab initio METHODS

			CNDO/S[b]			ab initio			
MO[a]	HAM/3	INDO/S	I	II	III	STO/3G	4-31G	Nature	Expt.[c]
$1a_2$	8.84	8.28	8.77	8.86	8.94	6.28	7.89	π	8.02
$2b_1$	9.74	9.64	10.22	10.19	10.49	7.61	9.25	π	9.05
$6a_1$	12.86	13.02	13.32	13.35	13.42	12.16	13.81	σ	12.85
$1b_1$	13.46	15.16	15.73	15.69	15.91	14.11	15.32	π	13.57
$4b_2$	13.61	13.18	13.34	13.37	13.44	12.85	14.45	σ	
$5a_1$	14.49	14.94	14.87	14.91	15.03	14.34	15.92	σ	14.27
$3b_2$	15.20	15.74	15.71	15.68	15.90	14.58	16.02	σ	14.80

[a] MO numbering refers to the minimal basis set.

[b] Column I: *d*-orbitals excluded; column II: *d*-orbitals included for N; column III: *d*-orbitals included for C and N.

[c] Taken from Ref. 95.



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charges, shown in **9**, are comparable with those previously determined for pyrrole by the CNDO/2 approach.[14]. These results are close to those obtained by the MNDO method and although differing quantitatively from those predicted by ab initio calculations (see, e.g., Ref. 97), they give the same qualitative indications. Calculations of the torsional barriers for polypyrrole by CNDO/2 and MNDO reveal the well-known deficiencies of the latter when dealing with rotations involving deconjugation of π systems; CNDO/2 yields a barrier of approximately 14.7 kJ M^{-1} and predicts the cis and trans structures to have similar energies, whereas STO-3G ab initio calculations,[98] while indicating a similar value for the trans–cis barrier, suggest that the cis form is approximately 10.5 kJ M^{-1} less stable than the trans structure.

The spectroscopically parameterized CNDO/S3 model has been used to analyze the ultraviolet (UV) photoemission and optical absorption spectra of pyrrole and polypyrrole[99] (see also Ref. 100). The reported charge densities calculated for pyrrole (based on the molecular geometry determined by microwave spectroscopy by Bak et al.[101]), the antisymmetric α, α'-dimer, and polypyrrole ($d_{\alpha\alpha'}$ = 1.49 Å), shown in Figure 1.1, differ significantly from those shown in **9** and from those listed in Ref. 14. The computed bond orders for pyrrole and the

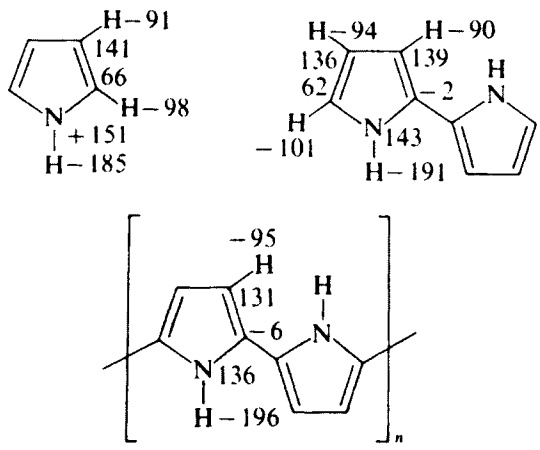


Figure 1.1. CNDO/S3 charge densities ($\times 10^{-3}$ *e*) for pyrrole, the antisymmetric α,α'-dimer, and polypyrrole.

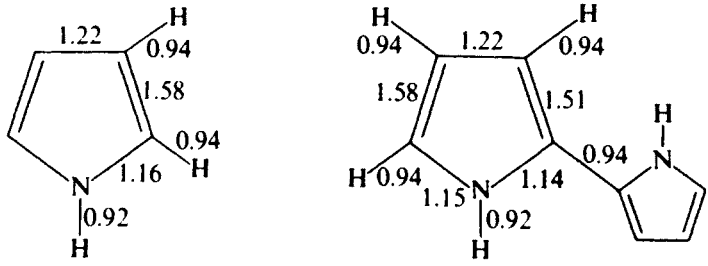
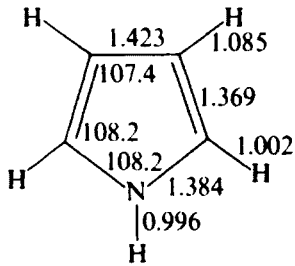


Figure 1.2. CNDO/S3 bond orders for pyrrole and the antisymmetric α,α'-dimer.

dimer, shown in Figure 1.2, are consistent with the aromaticity of the pyrrole ring; the dipole moment for pyrrole is predicted to be 1.52D with the positive pole directed toward nitrogen.

The INDO procedure has been used in the calculation of charge distribution in pyrrole and a number of C-substituted[102] and, more recently, N-substituted derivatives.[103] In the latter work, a clear distinction between +R (i.e., CF_3, CN, $COCH_3$, $COCF_3$) and −R (i.e., NH_2, OH, F) substituents is demonstrated, such that the former show a marked overall π-electron withdrawal accompanied by a smaller σ-electron back-donation coupled with a redistribution of π-electrons within the ring system, whereas the dominant feature of the latter is σ-electron withdrawal with a negligibly small effect on the π-electrons. INDO-optimized geometries with scaling of CH and NH bond lengths have been used as input to STO-3G ab initio calculations on 35 azoles; the geometry for pyrrole is given in **10**, the dipole moment is calculated as 1.90D and that for *N*-methylpyrrole as 2.01D.[104] The INDO method has been applied to the calculation of electronic transition energies [5.73 $B_2(\pi\rightarrow\pi^*)$, 5.86 $A_2(\pi\rightarrow\sigma^*)$, 6.15 $A_2(\pi\rightarrow\sigma^*)$, 6.71 $A_2(n\rightarrow\sigma^*)$, 6.94 $B_2(n\rightarrow\sigma^*)$, 7.18 $B_2(n\rightarrow\sigma^*)$, and 7.66 eV $B_2(n\rightarrow\sigma^*)$], charge distribution, and ionization potentials [9.57 a_2 (π), 10.63 $b_2(n)$, 12.89 $b_1(\sigma)$, 12.98 $a_1(\sigma)$, and 14.23 eV a_1 (σ)] for pyrrole; the dipole moment is estimated as 1.52D.[105] The use of INDO calculations in the study of pyrrole ring tautomerism[106] and in the conformational analysis of bipyrroles[107] and of 2- and 3-(2- and 3-furanyl)pyrroles [108] will be discussed in later sections. The technique has



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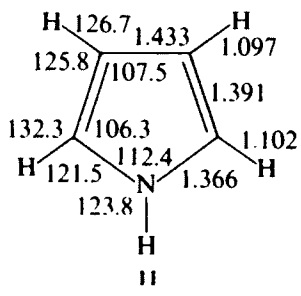
also been applied to the study of electron correlation in pyrrole[109] and to its electropolymerization.[110] In the latter study, INDO and CNDO calculations are used to predict the spin density of the radical cations derived from pyrrole, *anti*-2,2′-bipyrrole, and 2,2′:5′,2″-terpyrrole and to explore the dependence of the spin density distribution in the dimer and trimer on the interring torsion angles. It seems that during electropolymerization, as the oligomeric units increase in chain length, the α positions may no longer remain the exclusively reactive sites and that the reactivity of the pyrrole dimer and trimer radical cations is not greatly affected by small deviations from planarity.

In a study of the assignment of electronic transitions by geometry optimization, Mishra and Jug[111] have applied the SINDO/1 semiempirical method with configuration interaction to the calculation of adiabatic excitation energies, excited-state geometries, bond orders, and dipole moments for a host of molecules, including pyrrole; agreement with experiment and with the results of ab initio calculations is generally good. The pyrrole ring is not planar in all the excited states investigated; the first triplet and first two singlet states adopt a chairtype geometry, while the next three singlets are boatlike. Jug has also applied SINDO/1 in an approach to aromaticity related to bond order (see later).[112]

The MINDO/3 method has been applied by several groups to pyrrole geometry refinement. The results, summarized in **11**, are essentially the same; the agreement between calculated and experimental values is excellent, and the error nowhere exceeds 0.02 Å in bond lengths and 2° in bond angles.[113–115] These values are close to, but not identical with, those from more recent MNDO treatments shown in **12**; differences are most apparent in the region of the heteroatom.[116,117] These techniques have also been applied to the calculations



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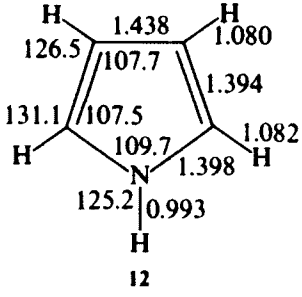
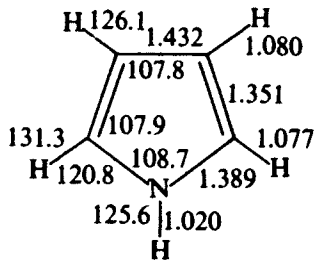


12

of geometries for the pyrrole mono- and dications,[115] to the evaluation of polarizabilities for pyrrole and its molecular ion,[118] and to calculations of proton affinities for the α and β positions, which confirm the well-known preference for α-protonation.[25,119] Also available in these papers are calculations of heats of formation and dipole moments, valence-shell gross atomic populations, and ionization potentials. The MINDO/3 technique has been used in the calculation of molecular vibration frequencies for pyrrole;[120] in the study

of 1,2-proton shifts in protonated furan, pyrrole, and thiophene;[121] in an analysis of activity and selectivity in the electrophilic substitution reactions of these systems;[122] and for the estimation of orbital energies as a function of conformation in *N*-arylpyrroles.[123] The MNDO method has been used for calculations of geometries and heats of formation for a range of molecules including pyrrole[124] and of anions and σ- and π-radicals.[125] Heats of formation so calculated (in kJ M^{-1}) for the pyrrole anion and its σ- and π-radicals are 59.73, 406.57 and 233.78. The applications of MINDO/3 and MNDO calculations to the study of tautomerism in pyrrole derivatives[114,126] and of MINDO/3 to the study of the conformational preferences of some 2-substituted pyrroles[127] are discussed in later sections. The MNDO technique has also found limited application in studies of the structure[96] and energy band gaps[128] of polypyrrole.

As the power of computers increases, it is becoming increasingly common to see applications of ab initio methods not only to the evaluation of charge distribution and single point absolute energy but also to more complex problems, including the optimization of molecular geometry. Geometries obtained for pyrrole with a minimal STO-3G basis set (**a**) and with split-valence 3-21G (**b**) and 6-31G (**c**) basis sets are shown in **13**;[129] the geometry in **13a** is essentially the same as that reported in Ref. 130, and **13b** is the same as that reported in Ref. 131. The STO-3G minimal basis set tends to overestimate the N–H and



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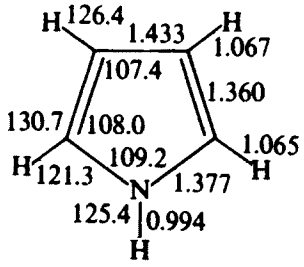

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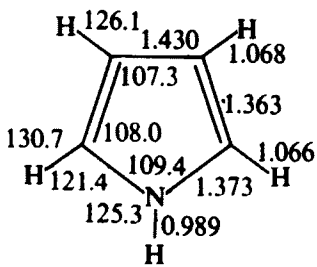


c

underestimate the C(2)=C(3) bond lengths. In general, better agreement is obtained between 6-31G optimized structures and experimental microwave data. The 6-31G* dipole moment is calculated as 1.83D[129,131] and the orbital energies (in electron volts) as $-7.95(a_2)$, $-9.15(b_1)$, $-14.09(a_1)$, $-14.83(b_2)$, $-15.19(b_1)$, $-15.71(b_2)$, $-16.01(a_1)$, $-19.96(a_1)$, $-20.71(b_2)$, $-21.46(a_1)$, $-26.47(b_2)$, $-28.18(a_1)$, and $-34.98(a_2)$. The results presented in Ref. 129 supersede those reported earlier[104] based on STO-3G calculations on INDO-optimized molecular geometry. Split-valence 4-31G ab initio calculations have been used for the evaluation of electron-density maps and localized molecular orbitals for pyrrole, furan, and thiophene,[132,133] and 4-21G-optimized geometries for these systems (the geometry for pyrrole differs only slightly from the split-valence geometries **13b** and **13c**) are also available.[134] The molecular electron densities calculated for pyrrole in position and the much less familiar momentum space are compared pictorially in Ref. 135. In position space, pyrrole has C_{2v} symmetry, but the transformation to momentum space introduces inversion symmetry, leading to D_{2h} symmetry in the momentum density. A new minimum basis set has been developed for use in the computation of excitation energies of large molecules. As a prelude to the application of this method to porphyrins, excitation energies and oscillator strengths have been evaluated for pyrrole.[136] The results are discussed in a later section.

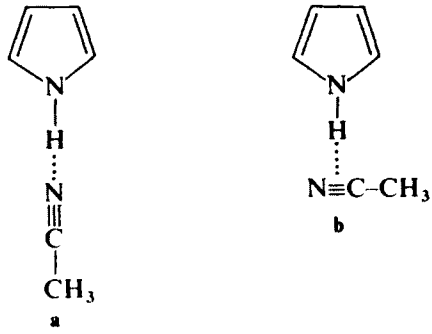
An ab initio multibody approach including the effect of electron correlation and reorganization beyond the Hartree–Fock approximation has been used to calculate orbital energies and one-electron properties (e.g., dipole and quadrupole moments, diamagnetic susceptibility) for pyrrole.[137] The latter properties are listed (along with prior experimental and theoretical values) in Table 1.5. Agreement between calculated and experimental values for the dipole moment is quite good, and the experimental and theoretical values of the electronic part of the second moments, which measure the extent of the electronic charge cloud,

TABLE 1.5. ONE-ELECTRON PROPERTIES FOR PYRROLE FROM REF. 137 (PRIOR EXPERIMENTAL OR THEORETICAL VALUES IN PARENTHESES)[a]

	Dipole Moment, D
μ	1.992 (1.74 ± 0.02;[b] 1.977[c])
	Electronic Part of Second Moments, 10^{-16} *cm*^{2}
$\langle x^2 \rangle$	39.72 (38.6 ± 0.7[d])
$\langle y^2 \rangle$	39.50 (39.1 ± 0.7[d])
$\langle z^2 \rangle$	7.28 (7.5 ± 0.7[d])
$\langle r^2 \rangle$	86.50 (85.2 ± 2.1[d])
	Second Moments (Total), 10^{-16} *cm*^{2}
Q_{xx}	−5.691
Q_{yy}	−5.015
Q_{zz}	−7.281

TABLE 1.5. *(Contd.)*

Quadrupole Moments, 10^{-26} esu cm^3	
θ_{xx}	2.195 (5.8 ± 1.6; 2.717[c])
θ_{yy}	7.065 (6.6 ± 1.2; 7.121[c])
θ_{zz}	−9.259 (−12.4 ± 2.3;[d] −9.837[c])
Third Moments, 10^{-24} cm^3	
R_{xxy}	0.683
R_{yyy}	2.746
R_{yzz}	0.488
R_{yrr}	3.917
Octupole Moments, 10^{-34} esu cm^3	
Ω_{xxy}	−1.205
Ω_{yyy}	4.755
Ω_{yzz}	−3.550
Charge Density, e/a_0^3	
$\langle\delta(r - C_1)\rangle$	119.913
$\langle\delta(r - C_3)\rangle$	119.931
$\langle\delta(r - H_1)\rangle$	0.3674
$\langle\delta(r - H_3)\rangle$	0.3677
$\langle\delta(r - N)\rangle$	194.698
$\langle\delta(r - H_5)\rangle$	0.3344
Average Diamagnetic Shielding, ppm	
$\sigma^d(C_1)$	419.37
$\sigma^d(C_3)$	422.21
$\sigma^d(H_1)$	171.20
$\sigma^d(H_3)$	172.90
$\sigma^d(N)$	480.11
$\sigma^d(H_5)$	179.07
Diamagnetic Susceptibility, 10^{-6} erg/(G^2 mol)	
χ_{xx}	−198.45 (−197.6 ± 2.1[d])
χ_{yy}	−199.40 (−195.7 ± 1.9[d])
χ_{zz}	−336.07 (−329.8 ± 2.5[d])
Potential at the Nuclei, au	
$\phi(C_1)$	−14.74
$\phi(C_3)$	−14.69
$\phi(H_1)$	−1.088
$\phi(H_3)$	−1.062
$\phi(N)$	−18.30
$\phi(H_5)$	−0.964
Electric Field at Nuclei $\mathbf{E} = (E_x, E_y, E_z)$, *au*	
$\mathbf{E}(C_1)$	(−0.011, −0.024, 0)
$\mathbf{E}(C_3)$	(−0.035, −0.013, 0)



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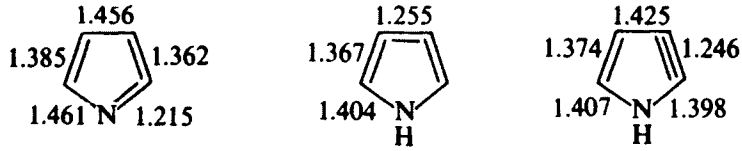
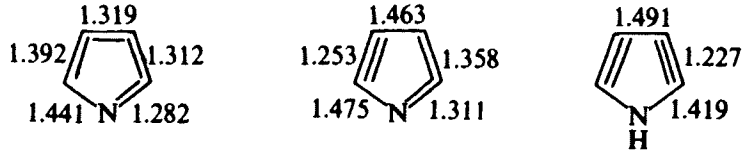
The complete harmonic vibrational force field of pyrrole has been calculated by the ab initio gradient method using the 4–21 basis set and the resultant force field scaled with a set of six factors transferred from benzene, allowing the calculation of the vibrational spectrum.[152] The results are discussed in Section 1.4.5. STO-3G calculations on INDO-optimized geometries yield gas-phase proton affinities for α- and β-protonation of pyrrole as 874.4 and 858.9 kJ M^{-1}, respectively, indicating that the α-protonated form is thermodynamically more stable than the β-protonated form.[24] Nonetheless, the C_{1s} orbital energies of the α and β positions (−11.0387 and −10.992 au, respectively) suggest that C_β is the more basic center and thus the one that should undergo *kinetically* controlled protonation. This is in agreement with the results of a kinetic analysis of gas-phase electrophilic substitutions of pyrrole.[153]

The results of the first theoretical studies of the isomers of pyrryne and tetradehydropyrrole [at the UHF/6-31G and complete-active-space self-consistent field (CASSCF) 3–21G levels] have been published.[154] Optimized geometries at the 3–21G level and relative energies (in kJ M^{-1}) are given in Figure 1.3. Judging from comparative calculations on the parent pyrrole, there is a systematic tendency to overestimate the degree of bond alternation in these calculations. Ab initio studies on the conformations of 70 monosubstituted pyrroles,[130] bipentaheteroarenes,[41,155–159] and pyrrole tautomerism[106] are discussed in later sections. Other applications include the study of the mechanisms of photorecyclization and photoisomerization of pyrrole,[160] the geometry of the carbon radicals of pyrrole,[161] and of pyrrole's resonance energy.[162]

Ab initio Hartree–Fock and valence-effective Hamiltonian (VEH) calculations[163,164] are increasingly being applied to the understanding of the structure and properties of polypyrrole (see, e.g., Ref. 98 and references cited therein). In Ref. 98, the length of the interannular bond as a function of the interannular torsion angle in 2,2′-bipyrrole, its 1,1′-dimethyl-, and 3,3′-dimethyl-derivatives is evaluated by STO-3G calculations (the intraannular geometry is fixed at that obtained from previous STO-3G optimizations on the corresponding tetramers), and the resulting geometries for a range of torsion angles ω then serve as input for VEH calculations on the polymer chains. In agreement with previous



Relative 6–31G	79	0	22
Energies 3–21G	40	0	33



6–31G	41	31	0
3–21G	138	139	0

Figure 1.3. Ab initio calculations of the structures and relative energies (kJ M^{-1}) of the isomers of pyrryne and tetradehydropyrrole.[154]

results, the most stable conformation of 2,2′-bipyrrole is trans coplanar (defined as $\omega = 0°$) with the heteroatoms pointing in opposite directions, which is preferred over the cis-conformation to the extent of 10.5 kJ M^{-1}. The barrier to the trans–cis interconversion is about 17 kJ M^{-1}. The interring bond increases in length from 1.477 Å in the trans conformation to 1.491 Å in the orthogonal conformation. This is in fair agreement with the comparison of X-ray-diffraction data on bipyrrole and *N*-methyltetrapyrrole where, in the latter compound, the bond between rings, which are tilted at approximately 66° with respect to each other, is 1.461 Å; that is, 0.013 Å longer than the experimental value of 1.448 Å in coplanar bipyrrole. In both 3,3′-dimethyl-2,2′-bipyrrole and 1-methylbipyrrole two energy minima are located as the interannular torsion angle ω is varied; one conformation has C_2 symmetry and the other only C_1 symmetry. Optimum values for ω are 37.7° (C_2) and 51.5° (C_1), for the former molecule, and 51.5° (C_2) and 64.1° (C_1), for the latter system. Interestingly, in the crystal structure of *N*-methyltetrapyrrole, there are two crystallographically distinct molecules. One has all $\omega \approx 50°$, while the other has $\omega \approx 50°$ between the inner rings, but $\approx 66°$ between the inner and outer rings. The correspondence with the possible values calculated for 1-methylbipyrrole is remarkable. Two distinct molecules are also present in the crystal structure of 3,3′-dimethyl-2,2′-bipyrrole. One molecule has $\omega \approx 55°$ (i.e., C_1 symmetry) but the other, $\approx 110°$. Since the latter conformation was not located in the ab initio calculations, it is assumed to be an artifact of the crystal packing. As ω in bipyrrole increases, so does the value of the ionization potential; its dependence on ω is well accommodated by a cosine function. In the polymer, as ω increases, the ionization potential and band-gap values increase and the bandwidth of the highest occupied bands decreases. The conclusion is that substituents that do not lead to $\omega > \approx 40°$ are acceptable, since such an angle would not have too negative an effect on the polymer's electronic properties (see

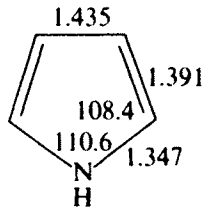
also Ref. 96). However, the four orders of magnitude difference in maximum conductivity achieved for poly-3,3′-dimethyl-2,2′-bipyrrole and poly-*N*-methylpyrrole suggests that the possibility of achieving a coplanar conformation after doping can be of importance for the intrachain mobility of polarons or bipolarons. The density of states computed from the band structure of neutral polypyrrole calculated at the Hartree–Fock ab initio level compares very well with photoelectron spectroscopic data on polypyrrole.[97] MNDO-optimized geometries for pyrrole oligomers have been used as input to VEH calculations of ionization potentials, optical transition energies and electron affinities for polypyrrole; the theoretical results generally compare favorably with experimental data.[165] The VEH method has also been used to provide band-gap estimates in polypyrrole as a function of pyrrole geometry; the conclusion is that the band gap decreases linearly as a function of increasing quinonoid character.[166] The effects of dopants on the geometry and electronic structure of polypyrrole have also been addressed by ab initio methods.[167,169] As a result of charge transfer with electron-donating dopants, extra charges appear on the polymer chains, inducing strong geometric modifications, with the lattice evolving from the aromatic to the quinonoid structure.[168]

A relatively recent development in pyrrole chemistry is the application of molecular mechanics methods to the system.[169–171] Central to the success of the calculations is the prediction of a reliable set of atomic charges, and to this end Abraham and co-workers have developed a charge scheme based on the transmission of charge by polar atoms through a one-bond α effect, a two-bond β effect, and a three-bond γ effect. The α effect is proportional to the electronegativity difference between the bonded atoms, the β effect is a function of the electronegativity difference and the polarizability of the β atom, and the γ effect is proportional to the β effect for the two atoms (see Ref. 169 and references cited therein). For conjugated systems, a method for the calculation of π-charges based on HMO theory is added to this; the parameterization of the Hückel Coulomb and resonance integrals is based on either the CNDO π-derivatives (PI method) or on the observed dipole moments (DM). The latter basis for calculation gives, in general, more consistent results and is to be preferred. A comparison of π-charges (total charges in parentheses) and dipole moments

TABLE 1.7. π-CHARGES (TOTAL CHARGES IN PARENTHESES) AND DIPOLE MOMENTS (D) FOR PYRROLE PREDICTED BY STO-3G, CNDO, DM, AND PI METHODS

	STO-3G	CNDO	DM	PI
N	383(−308)	395(−66)	240(−200)	396(−17)
C-2	−100(20)	−104(33)	−29(−26)	−41(−63)
C-3	−91(−101)	−94(−47)	−90(−153)	−157(−208)
NH	0(223)	0(101)	0(222)	0(222)
H-2	0(67)	0(−2)	0(88)	0(88)
H-3	0(56)	0(−1)	0(81)	0(81)
μ	1.90	2.11	1.78	3.14

predicted for pyrrole by a variety of methods is given in Table 1.7.[171] In a related approach, Allinger's MM2 program has been extended through the incorporation of MNDO calculations for that portion of a molecule designated for MO treatment and the related force-field parameters are modified accordingly. The steric energy is then minimized with respect to geometry. If the geometry changes significantly during the minimization, the MNDO calculations are repeated and all the parameters dependent on the MO calculations are reassigned. The MM–MNDO cycle is repeated until total self-consistency is achieved. The structure obtained in this way for pyrrole (**15**) does not seem to



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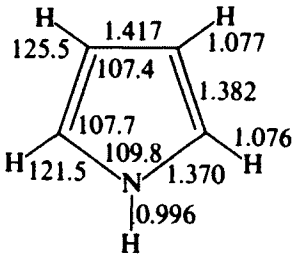
compare very favorably with experiment.[170] Force-field calculations have also been applied to the interpretation of the vibrational spectra of pyrrole (see, e.g., Refs. 152, 172, and 173 and references cited therein). A force-field parameterization for the conformational analysis of linear di-, tri-, and tetrapyrrolic pigments is available in Ref. 174. The conformational energy of polypyrrole as a function of interannular torsion angle has been mapped by molecular mechanics calculations[96] and the crystal packing energy minimized as a function of the unit cell variables and the chain setting angle (the angle between the molecular plane and the crystal **b** axis). The calculations indicate that the planar conjugated structure is the most stable and provide energetically feasible monoclinic and orthorhombic unit cells.

1.3. MOLECULAR STRUCTURE

The planarity and C_{2v} symmetry of pyrrole follow from analyses of the microwave spectra of pyrrole itself and of six derivatives labeled with ^{2}H, ^{13}C, and ^{15}N isotopes. Bond lengths and angles so determined are shown in **16**.[138] These values are similar to those of an earlier microwave study[101] but differ appreciably from those in Ref. 175. Electron diffraction data are also available.[14] The molecular geometry is a reflection of the cyclic delocalization implied by the canonical structures **17a–f**; the N–C_α and C_β–$C_{\beta'}$ bonds are shorter than normal single bonds, whereas the C_α–C_β bonds are longer than normal double bonds. Bak has estimated, on the basis of an empirical relationship between bond length and bond order, that the contributions of the canonical forms to the ground state are **17a** 62%, **17b** 1%, **17(c+d)** 29%, and **17(e+f)** 8%.[176] Both



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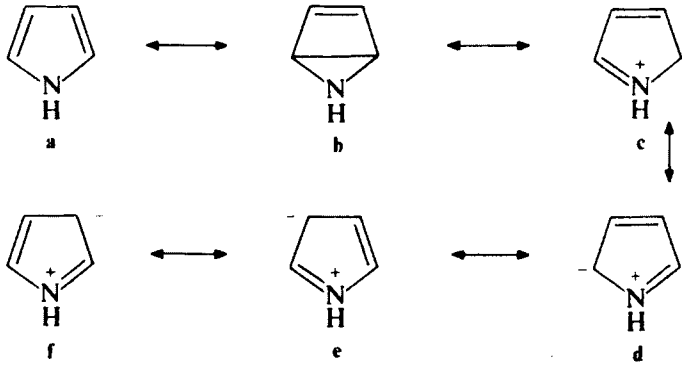

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N–^{1}H- and N–^{2}H–2-cyanopyrrole have been subjected to microwave analysis.[177] Since some 21 parameters are required to define the structure and only four rotational constants are available, an infinite number of solutions are possible; the model favored by the authors differs from **16** only slightly; the N–C(2) and C(2)–C(3) bonds are both shortened by 0.009 Å; that is, the pyrrole ring is slightly squashed at the site of substitution. Calculations on ^{14}N nuclear quadrupole coupling constants in 1-methylpyrrole[145] have cast doubt on earlier interpretations of the microwave spectrum of this molecule.[138,147]

The complete structure of pyrrole, based on the dipole–dipole coupling constants of pyrrole–^{15}N in three thermotropic nematic liquid crystals (ZLI1167, ZLI1132, and Phase 1083), has been reported.[178] Distances and angles obtained for pyrrole in each liquid crystalline environment are listed in Table 1.8. Differences between the three sets of data are ascribed to variations in hydrogen bonding between the pyrrole and liquid-crystal molecules. 1-Methylpyrrole has also been subjected to geometric analysis in liquid crystalline media, and significant solvent effects have again been observed; it is concluded that the minimium energy conformation has one C–H of the methyl group in a plane perpendicular to the ring.[179]

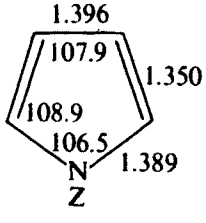
A search of the Cambridge Crystallographic Database (updated to January 1988, containing 63589 references) for molecules containing the pyrrole subunit not fused to another ring yielded 179 "hits". Many of these correspond to

TABLE 1.8. BOND DISTANCES (pm) AND ANGLES (°) FOR PYRROLE IN LIQUID CRYSTALS ZLI1167, ZLI1132, AND PHASE 1083

	ZLI1167	ZLI1132	Phase 1083	**16**
N–H	95.61(12)	96.37(6)	96.20(7)	99.6(4)
C(2)–H	104.37(11)	106.96(21)	106.01(20)	107.6(3)
C(3)–H	105.93(11)	106.42(7)	106.03(8)	107.7(4)
N–C(2)	136.12(16)	136.66(9)	136.42(10)	137.0
C(2)–C(3)	137.22(27)	137.34(28)	138.51(27)	138.2(5)
H–N–C(2)	124.29(6)	125.43(11)	125.03(11)	125.1
H–C(2)–N	121.80(10)	120.39(14)	120.84(14)	121.5
H–C(2)–C(3)	131.55(4)	131.34(2)	131.29(3)	130.8
H–C(3)–C(2)	125.36(6)	125.48(7)	125.22(7)	125.5
H–C(3)–C(4)	126.99(5)	127.36(5)	127.63(5)	127.1
N–C(2)–C(3)	106.64(9)	108.27(15)	107.86(15)	107.7
C(2)–C(3)–C(4)	107.65(4)	107.15(5)	107.16(5)	107.4
C(2)–N–C(5)	111.42(12)	109.14(22)	109.94(22)	109.8

structures of di-, tri- and tetrapyrroles related to the bile pigments, and to porphyrin and related systems, wherein the pyrrole geometry may be substantially perturbed when the ring represents part of an extended π-system. For the remainder, the geometry of the pyrrole ring has been calculated (where coordinates are available on file) and the results listed in Table 1.9. With very few exceptions, the mean values of the intra-annular torsion angles are zero to within experimental error; thus, the pyrrole ring is planar. Exceptions to this rule are generally a consequence of inadequacies in the crystallographic solutions rather than of truly chemical origin.

Among the simplest pyrrole derivatives for which X-ray data are available are the tri-1-pyrrolyl phosphine and arsine compounds, BEYCEN and BEYCIR.[189] Mean values of bond distances and angles averaged over the six pyrrole rings are presented in **18**. Compared with **16**, the geometry appears to be somewhat perturbed at the nitrogen, perhaps a consequence of bulky N-substitution. Interestingly, the geometry of the pyrrole ring in 1-methylpyrrole-chromium tricarbonyl π-complex (CYMPYR) **19** shows little perturbation from that of **16**, although the *N*-methyl group is bent out of the ring plane by 8.9° in the direction opposite to the chromium; the complex is considerably weaker than



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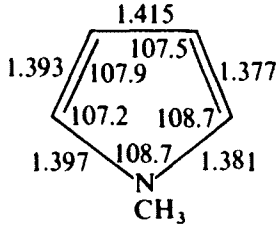
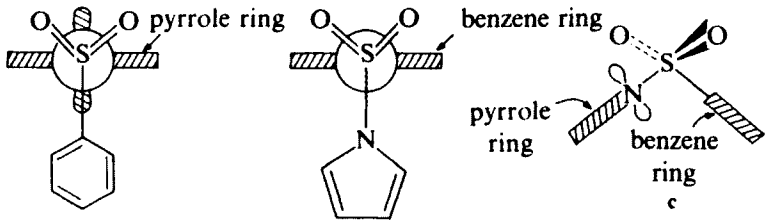


19

the benzene analog, and the structure presumably reflects this weakness. Beddoes et al.[235] have reviewed the geometries of 26 N-substituted pyrroles in which the pyrrole ring is not embedded as part of another ring system. The intraannular angles were found to be in the range 105.1–111.1°, whereas the external angles are more variable, ranging from 120.4 to 130.7° depending on the presence and size of the substituent. The sum of the angles at nitrogen is more consistent; 22 out of the 26 examples have angle sums between 359.5 and 360° and the furthest deviation from 360° is 356.4°. Pyrrole rings embedded in another ring system show wider geometry variations. These authors also report the geometry of 1-benzenesulfonylpyrrole (DUPTAJ) in which the relative orientations of the phenyl and pyrrole rings and of the sulfonyl moiety are as shown in **20a–c**. Other simple N-substituted pyrroles for which data are available include PYEIDO and the metal complexes BEHTIR, BIFKOQ, CAJMUV, CAZSIF, CESJOZ, CIFRAK, COLGEP, CONSED, and DOBMAI.



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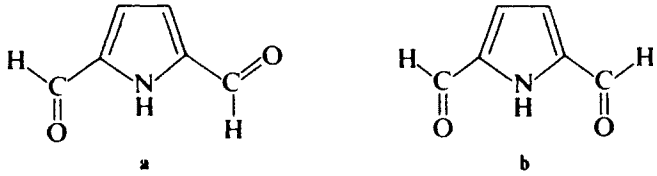
Substituent groups capable of direct conjugative interaction with the pyrrole π-system tend to be coplanar with the ring system, unless steric effects prevent this. Thus, in the aldehydes DASRIY, DASROE, DASRUK, and DIZGOI, the formyl groups are at maximum rotated out of this plane by only about 8°. The crystal structure of 2,5-diformylpyrrole (DIZGOI) is interesting in that it comprises four crystallographically independent molecules that are hydrogen-bonded from pyrrole nitrogen to an aldehyde oxygen atom to form a continuous chain parallel to the unit-cell **b** axis. Two of these molecules adopt syn, anti aldehyde conformations (**21a**), and two adopt the syn, syn conformation (**21b**); with this exception, the structural parameters for the four molecules are close. The intraannular angle at C(4) in the three aldehydes DASROE, DASRIY, and DASRUK is substituent-dependent, varying from 106.8 through 107.7 to 109.4°;



a **b**

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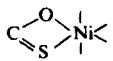
TABLE 1.9. BOND LENGTHS AND BOND ANGLES CALCULATED FOR PYRROLE DERIVATIVES ON THE CAMBRIDGE CRYSTALLOGRAPHIC DATABASE

Compound ID[a]	R^1	R^2	R^3	R^4	R^5	r_{12}	r_{15}	r_{23}	r_{34}	r_{45}	θ_{215}	θ_{123}	θ_{234}	θ_{345}	θ_{154}	Ref.
ABSBPP	*t*-Bu	NMe_2	Ph	$NHSO_2Ph$	H	1.371	1.354	1.350	1.392	1.349	106.8	110.8	104.5	109.9	108.0	180
AEMPYC	H	CO_2Et	Et	COMe	Me	1.396	1.330	1.382	1.417	1.404	110.6	107.4	106.7	107.8	107.5	181
ANTBPE	H	COR	H	H	H	1.363	1.347	1.355	1.382	1.362	107.2	109.0	107.3	106.9	109.5	182
BATROD	H	Br	Br	H	CONHR	1.372	1.410	1.388	1.373	1.373	111.2	105.4	108.7	110.4	104.0	183
BATRUJ	H	CONHR	H	Br	H	1.348	1.354	1.321	1.368	1.294	108.2	108.1	106.4	110.1	106.9	183
						1.322	1.374	1.387	1.401	1.224	108.1	107.7	103.2	111.8	108.8	183
BEHTIR	CS_2=	H	H	H	H	1.394	1.402	1.378	1.452	1.356	109.0	107.3	108.0	107.1	108.6	184
						1.393	1.373	1.349	1.426	1.368	109.6	107.6	107.6	108.1	106.9	184
						1.377	1.388	1.346	1.427	1.352	108.6	108.2	107.9	107.4	107.9	184
BEJDUP	H	CH_2Ar	NO_2	Cl	Cl	1.367	1.354	1.408	1.424	1.360	110.0	106.1	107.8	105.9	110.1	185
BENSES	Ar	CO_2H	H	COMe	Me	1.401	1.360	1.358	1.416	1.394	109.6	107.5	108.1	107.4	107.4	186
BESROG	NHPh	Ph	Ph	CO_2Et	Me	1.403	1.359	1.362	1.434	1.385	111.1	106.4	108.0	107.8	106.7	187
BEXJAP	Me	PFN_2=	H	H	H	1.376	1.354	1.364	1.389	1.341	106.9	107.9	108.0	106.6	110.6	188
BEYCEN	$P(N=)_2$	H	H	H	H	1.376	1.400	1.357	1.402	1.341	107.1	108.8	107.4	108.5	108.2	189
						1.387	1.408	1.333	1.401	1.351	107.2	109.5	107.1	109.8	106.3	189
						1.380	1.376	1.369	1.401	1.333	105.1	109.5	107.0	106.8	111.5	189
BEYCIR	$As(N=)_2$	H	H	H	H	1.366	1.397	1.369	1.416	1.347	106.7	111.0	104.7	109.7	108.0	189
						1.373	1.404	1.382	1.340	1.344	108.3	107.1	107.4	111.6	105.5	189
						1.383	1.417	1.348	1.417	1.321	104.4	110.9	106.4	108.3	109.9	189
BIFKOQ		H	H	H	H	1.364	1.379	1.348	1.411	1.333	108.8	110.0	104.1	111.5	105.6	190
						1.386	1.373	1.331	1.414	1.369	108.7	108.9	107.3	108.4	106.7	190
BIFVOB	N=	SCF_3	SCF_3	SCF_3	SCF_3	1.406	1.406	1.447	1.466	1.447	110.0	108.1	106.8	106.8	108.1	191
						1.393	1.393	1.356	1.402	1.356	108.3	107.4	108.4	108.4	107.4	191
BIMGUZ10	Me	Me	CO_2Et		H	1.352	1.383	1.392	1.433	1.361	109.0	107.8	106.8	107.2	108.2	192
BNOVCM	H	CO_2R	H	H	Me	1.375	1.378	1.390	1.385	1.388	109.1	107.7	107.6	108.3	107.3	193
BPACUA10	Cu⋹	CH=N*t*-Bu	H	H	H	1.455	1.353	1.349	1.410	1.370	105.3	106.5	111.1	104.2	113.0	194
						1.374	1.348	1.387	1.359	1.398	105.0	109.7	107.5	105.9	111.4	194
BPACUA11	Cu⋹	CH=N*t*-Bu	H	H	H	1.388	1.380	1.399	1.428	1.360	103.9	112.3	103.5	108.0	111.7	194
BPYACO10	Co⋹	CH=N*t*-Bu	H	H	H	1.362	1.373	1.376	1.392	1.410	106.4	111.9	105.5	107.8	108.4	195
BPYANI10	Ni⋹	CH=N*t*-Bu	H	H	H	1.370	1.344	1.369	1.371	1.382	105.9	111.4	104.8	108.8	109.1	196
BUFNEV	H	Ph	Me	CO_2Me	CO_2Me	1.369	1.371	1.390	1.411	1.381	109.9	107.7	107.0	108.0	107.5	197
BUWZIC	Cu⋹	COR	H	H	H	1.363	1.349	1.404	1.389	1.396	107.7	110.2	104.8	108.4	108.8	198
						1.369	1.356	1.362	1.408	1.340	105.8	110.1	106.2	106.7	111.3	198

BZPYRA	H	COPh	H	H	H	1.375	1.355	1.393	1.397	1.378	109.2	107.2	107.6	107.2	108.8	199
BZPYRB	H	COAr	H	H	H	1.370	1.331	1.381	1.384	1.364	109.2	106.9	107.6	107.1	109.2	199
BZPYRC	H	COAr	H	H	H	1.380	1.359	1.384	1.389	1.381	109.0	107.1	108.1	107.3	108.5	199
CALPCE	H	CO_2R	H	H	H	1.376	1.338	1.363	1.412	1.365	108.6	108.0	107.4	106.4	109.7	200
CAJMUV	CS_2=	H	H	H	H	1.391	1.372	1.336	1.404	1.331	108.2	107.4	108.0	108.4	108.0	201
						1.386	1.388	1.336	1.406	1.344	109.0	107.3	108.3	108.8	106.6	201
						1.382	1.388	1.336	1.394	1.340	107.8	107.4	109.2	107.6	108.0	201
						1.384	1.376	1.349	1.403	1.339	107.8	107.8	108.0	107.8	108.6	201
CANTDHIO	H	COR	H	H	H	1.388	1.326	1.440	1.519	1.393	112.3	107.8	103.4	106.6	109.7	202
						1.464	1.359	1.444	1.458	1.423	110.1	103.1	111.3	103.5	112.0	202
CANTETIO	H	COR	H	H	H	1.312	1.451	1.451	1.387	1.378	103.6	115.2	101.3	110.9	108.4	203
						1.363	1.395	1.416	1.418	1.410	116.1	102.4	110.3	107.8	103.4	203
CAPYIB	Me	H	$C(CN)=C(CN)_2$	H	H	1.329	1.384	1.393	1.429	1.354	109.2	109.1	105.9	107.1	108.6	204
CAZSIF	CS_2=	H	H	H	H	1.390	1.358	1.315	1.372	1.387	107.7	109.3	108.0	108.5	106.4	205
						1.385	1.389	1.319	1.452	1.350	107.8	109.1	108.0	106.3	108.5	205
CEDGUN	H	$NH(CO)_2OEt$	CN	Me	Me	1.346	1.388	1.390	1.427	1.372	110.4	107.5	107.5	106.9	107.6	206
CESJOZ	Hf≪	H	H	H	H	1.381	1.379	1.341	1.362	1.415	109.6	107.1	110.5	107.3	105.5	207
						1.384	1.399	1.330	1.420	1.347	104.8	110.3	108.4	105.7	110.8	207
CIDREM	Ph	Cl	CO_2Me	CO_2Me	Ph	1.367	1.385	1.361	1.430	1.382	108.5	109.9	106.4	107.7	107.5	208
CIFRAK	≫Mo≪	H	H	H	H	1.404	1.351	1.330	1.409	1.405	106.1	110.8	107.3	106.3	109.3	209
						1.418	1.401	1.313	1.414	1.317	100.4	113.9	105.1	108.2	112.2	209
CIHHUW	CO_2Et	CO_2Et	Ph	H	Ph	1.406	1.385	1.387	1.391	1.392	110.7	106.1	107.8	110.2	105.1	210
CIHJAE	CO_2Et	CO_2Et	2-ClC_6H_4	H	Ph	1.390	1.389	1.376	1.426	1.368	108.4	108.7	106.5	108.6	107.8	210
CIYZAL	CH=	CH_2OH	H	H	CH=NR	1.383	1.396	1.366	1.390	1.377	108.7	107.8	108.3	108.6	106.7	211
CMPYCR[b]	Me	H	H	H	H	1.381	1.397	1.377	1.415	1.393	108.7	108.7	107.5	107.9	107.2	212
COLGEP	Zr≪	H	H	H	H	1.331	1.428	1.410	1.410	1.373	110.0	106.5	109.8	105.8	107.9	213
CONSED	Fe≪	H	H	H	H	1.388	1.366	1.358	1.345	1.386	104.9	110.6	107.0	108.6	108.9	214
						1.409	1.271	1.350	1.618	1.243	109.4	108.7	101.0	104.0	116.1	214
COWPOT	H	COR	H	H	H	1.377	1.350	1.380	1.390	1.362	108.8	107.1	107.7	107.4	109.0	215
COYKUWIO	H	CH=NNHCOMe	H	H	H	1.369	1.360	1.381	1.401	1.362	109.0	107.6	107.1	107.7	108.4	216
COYLADIO	H	CH=N–	H	H	H	1.373	1.348	1.377	1.392	1.354	109.2	106.8	107.6	107.6	108.7	217
COYLEHIO	H	CH=N–	H	H	H	1.358	1.349	1.384	1.383	1.358	109.3	106.8	108.0	107.0	109.0	216
						1.359	1.359	1.382	1.381	1.360	109.2	107.1	107.9	107.6	108.3	216
COZPOW	Me	$OSiMe_3$	P≪	P≪	$OSiMe_3$	1.388	1.381	1.380	1.456	1.376	108.7	108.6	106.8	106.7	109.1	218
COZRAK	Me	OCOMe	P≪	P≪	OCOMe	1.382	1.387	1.352	1.426	1.364	107.0	109.7	107.2	107.1	109.0	218
CUFXIK	NHCOAr	Me	CO_2Me	$CONEt_2$	Me	1.362	1.387	1.377	1.430	1.353	111.7	105.9	108.0	108.0	106.4	219

TABLE 1.9. (*Contd.*)

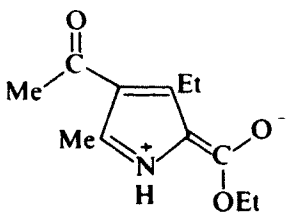
Compound ID[a]	R^1	R^2	R^3	R^4	R^5	r_{12}	r_{15}	r_{23}	r_{34}	r_{45}	θ_{215}	θ_{123}	θ_{234}	θ_{345}	θ_{154}	Ref.
CUVCUR	H	COPh	H	H	Ph	1.368	1.355	1.387	1.378	1.395	111.3	106.3	108.0	108.5	106.0	220
						1.378	1.356	1.387	1.377	1.393	110.1	106.8	107.9	108.3	106.9	220
CXANTI	H	COR	H	H	H	1.374	1.347	1.379	1.403	1.374	109.2	107.7	107.2	107.3	108.6	221
DAJRUB	H	Me	CH=NN=CR_2	CHO	Me	1.359	1.355	1.376	1.432	1.373	111.9	107.1	106.5	108.0	106.4	222
DASRIY	H	CHO	Me	H	H	1.378	1.343	1.393	1.400	1.377	109.1	107.8	106.5	107.7	108.9	223
DASROE	H	CHO	Me	Et	H	1.375	1.354	1.401	1.414	1.387	108.8	108.2	106.8	106.8	109.5	223
DASRUK	H	CHO	Me	Cl	H	1.386	1.336	1.408	1.392	1.387	110.2	107.3	105.7	109.4	107.5	223
DEDMII	H	CO_2Et	COMe	SR	Ph	1.373	1.359	1.374	1.402	1.395	110.5	107.4	107.7	107.7	106.8	224
DEGBAS	H	COR	H	H	H	1.389	1.359	1.368	1.439	1.359	109.9	106.9	107.7	106.8	108.7	225
						1.411	1.377	1.341	1.422	1.362	107.7	108.0	108.2	107.5	108.5	225
DEGEW	Cu<	CH=NR	H	H	H	1.379	1.344	1.388	1.384	1.397	106.9	109.8	106.2	107.3	109.7	225
						1.382	1.342	1.391	1.384	1.399	106.9	109.4	106.7	106.8	110.1	225
DERROH	Cu<	CH=NR	H	H	H	1.381	1.347	1.391	1.392	1.390	106.5	109.8	106.3	106.8	110.6	226
DERRUN	Ni<	CH=NR	H	H	H	1.383	1.347	1.392	1.392	1.390	106.5	110.4	105.2	108.0	109.8	226
DICJUU	H	Ph	Ar	Ar	Ph	1.367	1.369	1.372	1.412	1.384	110.6	107.3	107.7	107.7	106.7	227
DIHCEC	H	CH=C<	Me	Me	CO_2t-Bu	1.362	1.476	1.382	1.425	1.194	102.6	108.4	106.8	108.5	112.4	228
DIHCECOI	H	CH=C<	Me	Me	CO_2t-Bu	1.360	1.393	1.373	1.425	1.383	109.4	108.5	107.6	107.2	107.3	228
DIHCIG	H	CH=C<	Me	Me	CO_2t-Bu	1.380	1.377	1.398	1.405	1.392	110.0	106.6	108.4	107.2	107.8	228
DIZGOI	H	CHO	H	H	CHO	1.362	1.365	1.386	1.383	1.379	108.0	108.2	107.9	106.7	109.2	229
						1.363	1.369	1.393	1.376	1.388	109.7	107.1	108.0	108.0	107.2	229
						1.358	1.373	1.387	1.384	1.363	108.2	107.9	107.7	107.3	108.9	229
						1.365	1.382	1.398	1.379	1.391	108.4	108.4	107.4	108.1	107.8	229
DIYCET	Rh<	CH=N–	H	H	H	1.363	1.361	1.374	1.384	1.375	105.9	110.1	107.0	106.4	110.5	230
DMDAPY	H	Me	COMe	COMe	Me	1.377	1.369	1.361	1.459	1.392	110.0	109.0	106.6	106.7	107.7	231
DOBMAI	CS_2=	H	H	H	H	1.423	1.414	1.364	1.457	1.362	109.9	106.6	108.1	109.0	106.4	232
						1.405	1.413	1.372	1.427	1.407	113.0	105.9	108.0	110.8	102.4	232
DUBDUZ	H	CO_2Et	H	CO_2Et	CH_2CO_2Et	1.374	1.343	1.358	1.398	1.396	110.0	107.8	107.8	107.2	107.2	233
DULJEZ	H	CN	C≡CTMS	TMS	$N(TMS)_2$	1.385	1.368	1.388	1.428	1.387	108.5	107.8	108.1	105.6	110.0	234
DUMBOC	H	CH=N–	H	H	H	1.373	1.349	1.379	1.394	1.351	109.1	106.8	107.6	107.6	108.9	217
DUMBUI	H	CH=N	H	H	H	1.373	1.343	1.370	1.402	1.370	109.1	107.5	107.7	106.7	109.1	217
DUPTAJ	SO_2Ph	H	H	H	H	1.374	1.373	1.442	1.452	1.364	112.6	105.0	106.5	108.0	107.9	235
ECMPCA	Me	Me	CO_2Et	CHO	H	1.381	1.346	1.384	1.435	1.374	110.5	106.6	107.7	106.3	109.0	236
ECTEPM	H	CO_2Et	Et	Et	CH_2Ar	1.391	1.371	1.376	1.410	1.387	108.4	108.5	107.2	107.7	108.2	237
						1.386	1.357	1.390	1.414	1.390	109.6	107.7	107.0	107.6	108.1	237

EXCDPK	H	CO_2Et	Me	Et	COAr	1.369	1.359	1.390	1.404	1.391	109.7	107.9	107.1	107.5	107.8	238
	H	COAr	Me	Et	Me	1.374	1.347	1.399	1.404	1.384	110.1	107.3	106.6	108.0	108.0	238
FADSUY	Zr≪	Me	H	H	Me	1.403	1.406	1.346	1.413	1.348	106.3	108.4	108.7	107.4	109.1	239
						1.408	1.402	1.344	1.393	1.339	106.4	108.4	107.9	109.4	107.9	239
						1.400	1.417	1.353	1.409	1.343	106.0	108.8	108.2	108.1	108.8	239
						1.410	1.393	1.328	1.411	1.333	106.2	109.0	107.5	108.9	108.4	239
FADTAF	Zr≪	Me	H	H	Me	1.390	1.427	1.397	1.439	1.381	106.0	109.7	107.9	106.1	110.4	239
						1.456	1.411	1.333	1.438	1.376	105.5	108.4	109.8	106.6	109.6	239
FATPEV	Ph	Li	H	H	H	1.412	1.395	1.386	1.419	1.371	111.8	102.8	111.6	106.8	106.9	240
FMTPHG	Hg	SCF_3	SCF_3	SCF_3	SCF_3	1.358	1.377	1.391	1.419	1.366	107.8	109.7	105.7	107.7	109.1	241
FPYNIT	H	H	Cl	Ar	H	1.387	1.399	1.397	1.358	1.375	112.5	103.6	109.4	111.0	103.4	242
MFPPYR1O	H	PF_4	H	H	Me	1.355	1.373	1.387	1.370	1.353	110.4	105.8	108.3	108.7	106.7	243
MPPRDS	Me	3-Pyridyl	S	H	H	1.377	1.377	1.390	1.423	1.364	109.5	107.0	107.7	107.2	108.6	244
MPYPAL	H	CH=CMeCHO	H	H	H	1.368	1.367	1.388	1.398	1.356	110.2	106.6	107.2	108.6	107.3	245
NETRSN	Me	CONHR	H	NHCO–	H	1.397	1.346	1.390	1.409	1.358	109.1	106.5	107.3	107.7	109.4	246
						1.355	1.372	1.368	1.353	1.366	108.3	107.9	108.0	108.5	107.2	246
NPMPRD	R	Me	H	H	Me	1.398	1.379	1.384	1.411	1.362	109.4	106.4	108.1	108.1	108.0	247
PCVAPP	Ph	Ph	NPhR	H	Ph	1.381	1.387	1.369	1.416	1.376	110.0	106.3	109.5	106.6	107.6	248
PRTHIK	H	COAr	H	H	H	1.375	1.345	1.388	1.394	1.377	109.5	107.0	107.6	107.2	108.7	249
PYALCU	Cu≪	CH=N–	H	H	H	1.360	1.354	1.401	1.424	1.421	107.2	111.4	105.2	106.1	107.2	250
PYCICU	Cu≪	CH=N–	H	H	H	1.328	1.356	1.378	1.418	1.405	106.5	111.5	107.0	103.6	111.4	251
PYDPYR1O	H	R	H	H	R	1.377	1.363	1.356	1.415	1.358	109.7	107.3	107.7	107.8	107.6	252
PYEIDO	NR_2	H	H	H	H	1.363	1.369	1.353	1.401	1.330	110.4	106.6	107.4	109.3	106.4	253
						1.370	1.365	1.354	1.402	1.350	110.5	106.4	108.1	108.4	106.6	253
PYMANI	Ni≪	CH=N	H	H	H	1.363	1.385	1.415	1.386	1.396	106.4	110.5	105.7	108.1	109.3	254
						1.381	1.366	1.370	1.392	1.372	106.1	110.1	106.3	107.8	109.6	254
TRPAMN	Mn(CO)$_3$	CH=N–	H	H	H	1.410	1.307	1.352	1.349	1.399	105.6	108.9	108.2	106.3	111.0	255
VERUCE	H	H	CH_2OH	COMe	H	1.370	1.342	1.361	1.439	1.385	109.9	108.8	106.3	106.7	108.3	256
						1.381	1.342	1.350	1.431	1.383	109.0	109.1	106.5	106.9	108.4	256
VERUCH	H	H	CH_2OH	COMe	H	1.362	1.345	1.355	1.439	1.383	109.8	109.1	106.4	106.5	108.2	256
						1.378	1.336	1.354	1.431	1.386	109.3	108.7	106.9	106.3	108.8	256
						1.375	1.345	1.365	1.438	1.388	110.1	108.2	107.0	106.4	108.4	256
VIMNOL1O	CH_2Ar	CH(OH)R	H	H	H	1.382	1.372	1.367	1.407	1.360	108.5	107.2	108.5	106.8	108.9	257

[a] The compound ID is the code used by the Cambridge Crystallographic Data Centre for compound identification. Where the point of connection to the substituent is ambiguous, the convention has been chosen that the pyrrole ring is attached at the leftmost atom.

[b] $Cr(CO)_3$ complex.

in other words, electron-releasing substituents close the angle whereas electron-withdrawing substituents have the opposite effect.[223] In the keto-ester AEMPYC, the shortening of the N–C(5) bond and the lengthening of the N–C(2) and C(4)–C(5) bonds is presumably evidence of a resonance interaction of the kind represented by **22**. These bond length distortions, coupled with the observation that the plane of the acetyl group makes an angle of approximately 15° with the pyrrole ring whereas the ethoxycarbonyl group is twisted out of the ring plane by only about 1°, support the view that conjugation between the pyrrole ring and a carbonyl group is greater at the α than the β positions. This effect can also be discerned in the esters DUBDUZ, BUFNEV, and DEDMII, the preferred conformations for which in the crystal are **23**, **24**, and **25** respectively. Whereas in **23** where there is little steric hindrance between abutting groups so that both the ester groups are coplanar with the pyrrole ring, steric hindrance in **24** and **25** forces, in both cases, the β-carbonyl-containing substituent out of the ring plane (to the extent of ca. 60° in **24** and ca. 80° in **25**; i.e., the ketone function in the latter is almost orthogonal to the pyrrole ring). Nonetheless, the α-carbonyl-containing substituent remains coplanar in both compounds. The α-phenyl rings in **24** and **25** deviate from coplanarity with the pyrrole ring by approximately 36° and 25°, respectively. Considerably out-of-pyrrole-plane carbonyl-containing β-substituents are also to be found in DMDAPY (crystal conformation **26**), where the ketone groups are rotated about 25° and 40° from the ring plane, CIDREM (conformation **27**), where the ester groups are rotated about 45° and 32° from the plane, BESROG (conformation **28**), ester rotation about 30° from the plane, and CUFXIK (conformation **29**). In the last compound, whereas the ester group is coplanar with the pyrrole ring, the amide is orthogonal to it presumably reflecting reduced conjugative demand by the latter because of the involvement of the diethylamino group's electron density.



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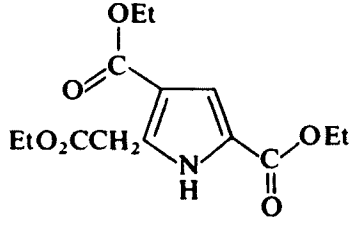

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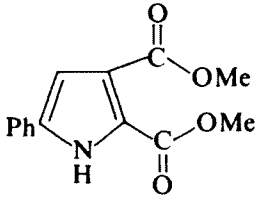

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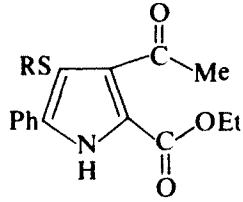

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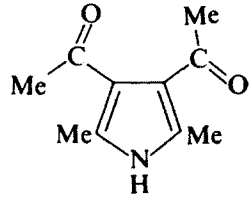

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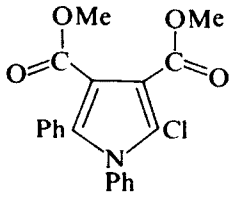

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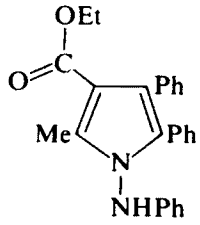

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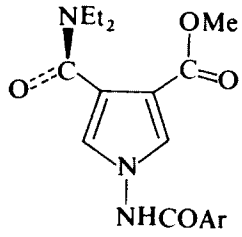

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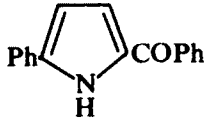
The 2-aroylpyrroles BZPYRA, BZPYRB (Ar = *p*-ClC_6H_4), BZPYRC (Ar = *p*-$MeOC_6H_4$), EXCDPK (Ar = substituted pyrrolyl), PRTHIK (Ar = 3-thienyl), and CUVCUR commonly form intermolecular hydrogen-bonded dimers via a syn-disposed carbonyl group (with respect to the pyrrole NH); they also have their pyrrole rings close to coplanarity with the carbonyl group whereas the aryl rings are rotated far from the carbonyl plane (45–52° in the first three compounds, 35–44° in the last two), presumably reflecting favored conjugation between the carbonyl group and the π-excessive pyrrole ring. Aryl substituents directly bonded to the pyrrole ring always deviate somewhat from coplanarity the extent of the deviation varying with the degree of congestion and the position of substitution. Thus, in the unhindered compound CUVCUR (**30**), the deviation is only about 10° whereas in the highly hindered DICJUU (**31**) deviations range from about 35° to 60°. Not suprisingly, aryl substituents at pyrrole α positions deviate less from planarity than those at β positions. The related esters CIHHUW and CIHJAE (**32** and **33**) illustrate these features and also demonstrate the lack of availability of the ring nitrogen lone pair (which is "occupied" as part of the pyrrole aromatic sextet) for conjugation into N-



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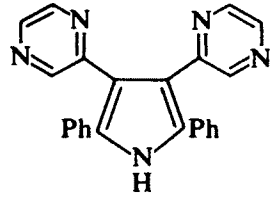

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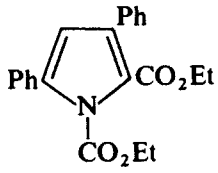

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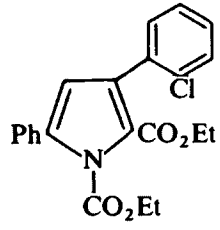
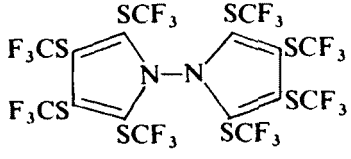


33

substituents. Thus the deviations of the planes of the substituents from the pyrrole ring plane are (for **32**) at N≈75°, at C(2)≈8°, at C(3)≈53°, and at C(5)≈30°, and (for **33**) at N≈67°, at C(2)≈8°, at C(3)≈56°, and at C(5)≈36°. This lack of conjugation into carbonyl (and related) groups substituted on the pyrrole nitrogen has important consequences for their chemistry.

Reference has already been made in the previous section to theoretical and X-ray-diffraction studies on 2,2′-di- and 2,2′-oligopyrroles in relation to the electrical properties of polypyrrole (see also Ref. 258). In BIFVOB (**34**), a substituted 1,1′-dipyrrole, the two rings are mutually orthogonal and the N–N′ bond distance is 1.382 Å.



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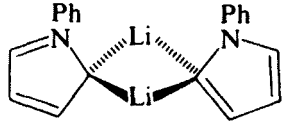
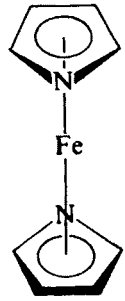


35

The fascinating structure of the *N*,*N*′-tetramethylethylenediamine (TMEDA) complex of 2-lithio-1-phenylpyrrole (FATPEV) has been reported (shown in **35** with TMEDA omitted).[240] The structure is dimeric, having C_2 symmetry with the pyrrole C(2) atom equidistant from two lithium atoms, with each serving to bridge between two pyrrole rings; the latter are syn-disposed and coplanar with respect to each other and are orthogonal to the C(2)LiC(2)′Li′ ring. The average C–Li distance is 2.188(5) Å, the Li–Li separation 2.691(9) Å, and the LiC(2)Li′ angle 75.9(2)°. Each lithium atom is also involved in a chelated interaction with one TMEDA molecule. The intra-annular NC(2)C(3) angle at 102.8° is among the smallest recorded in Table 1.9, presumably a consequence of the unusual bonding at C(2) and also a manifestation of the phenomenon noted earlier that electron-releasing substituents serve to close the intraannular angle at the carbon to which they are attached.

The structure of the important pyrrole antibiotic Netropsin (as the pentahydrated sulfate) NETRSN has been determined.[246]



36

The crystal structure of azaferrocene (**36**) is disordered at room temperature. Heat capacity measurements in the range 10–300° K indicate many crystalline phases; the thermal effects are very dependent on thermal history and crystal size.[259] Scanning electron microscopy has been used extensively in structural studies on polypyrrole (see, e.g., Refs. 258 and 260–262), from which it has been deduced that the chains lie flat in the plane of the polymer film. Unfortunately, the polymer is only poorly crystalline, so limited data are available from X-ray-diffraction measurements; the results are interpretable in terms of scattering from pyrrole chains at interplanar spacings close to the van der Waals distance for aromatic groups.[262]

1.4. MOLECULAR SPECTROSCOPY

1.4.1. ^{1}H NMR Spectra

The literature up to the mid-1970s is exhaustively reviewed in the books by Gossauer[13] and Jones and Bean[14] and the coverage extended into the early 1980s in Ref. 12. Information is also available in Ref. 263.

The spectrum of neat pyrrole at 60 MHz consists of two closely overlapping multiplets centred at δ 6.32 (H-2,5) and 6.14 (H-3,4) and a broad low-field resonance (at ca. δ 7.25) due to the imino hydrogen, whose relaxation time is shortened by the adjacent quadrupolar ^{14}N nucleus.[264] The pyrrole self-association is broken down on dilution with solvent, and a general increase in the chemical shift difference between the ring-proton resonances is observed. Substantial changes in chemical shifts may also result from specific solvation via

TABLE 1.10. VARIATION OF RING HYDROGEN CHEMICAL SHIFTS WITH SOLVENT FOR PYRROLE

Solvent[a]	H-2,5[b]	H-3,4[b]	Ref.
Hexane	6.32	5.94	265
Cyclohexane	6.51	6.11	266
Cyclohexane[c]	6.57	6.11	267
CCl_4	6.62	6.05	268
CCl_4[c]	6.64	6.07	267
Benzene	5.85	5.80	265
$CDCl_3$	6.68	6.22	[d]
Acetone	6.58	5.89	265
Acetone[c]	6.78	6.07	267
THF	6.52	5.92	270

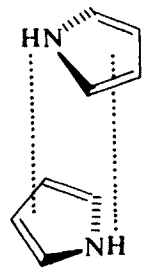
[a] Various concentrations were used.

[b] Shifts are in parts per million downfield from TMS; the chemical shift of the N–H resonance is strongly solvent dependent.

[c] Infinite dilution shifts are reported.

[d] Varian catalog.

hydrogen-bonding to electronegative atoms or dipolar interactions with aromatic π-systems (Table 1.10). Attempts to correlate chemical-shift differences in cyclohexane and acetone with reactivity parameters calculated from HMO theory were unsuccessful.[267] Care needs to be exercised in the interpretation of solvent-induced chemical-shift changes since these can depend profoundly on the choice of standard. Thus, with TMS as internal standard, the shift differences for pyrrole between CCl_4 and C_6H_6 are reported in Ref. 269 as −0.227 (α-H) and −0.225 (β-H) and between CCl_4 and C_6F_6 as 0.202 (α-H) and −0.004 (β-H), whereas the *reference-independent* solvent shifts between CCl_4 and C_6H_6 are found to be 0.383 (α-H) and 0.385 (β-H) and between CCl_4 and C_6F_6 are 0.742 (α-H) and 0.536 (β-H); the important conclusion is that the negative shifts simply arise from the choice of reference. The concentration- and temperature-dependence of the hydrogen chemical shifts in pyrrole have been used to estimate the enthalpy for self-association as approximately $-6.7\ kJ\,mol^{-1}$.[271] The "closed" NH π-bonded dimeric structure **37** seems to be favored by the evidence, although the data are not definitive. The ^{14}N relaxation times of pyrrole dissolved in 1,4-dioxan, pyridine, 3,5-lutidine, 2-fluoropyridine, cyclohexane, carbon tetrachloride, and pentafluoropyridine have been determined at several temperatures via line-shape analysis of the pyrrole N–H signal and the results discussed in terms of solvent effects on the pyrrole association equilibrium.[272,273]



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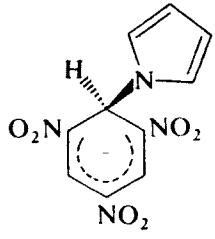
The interactions between pyrrole and other aromatic systems (particularly benzene) and hydrogen-bonding between pyrrole and molecules containing electronegative atoms (especially pyridine) have been widely studied by ^1H NMR spectroscopy. NMR data on the pyrrole–benzene complex seem best accommodated by a π-dipole complex in which the aromatic rings are inclined with respect to each other,[34] although other conclusions have been drawn from other physical techniques.[14] ^1H NMR has been used to estimate thermodynamic parameters for the association between pyrrole and pyridine as $-\Delta H = 18.0\ kJ\,mol^{-1}$, $-\Delta S = 33.4\ J\,K^{-1}\,mol^{-1}$,[266] values not too dissimilar from those determined by calorimetry or IR spectroscopy. The pyrrole–pyridine complex has recently been studied by ^2H and ^{14}N nuclear quadrupole resonance with the field-cycling double-resonance method,[274] the conclusion being that only one kind of complex is present having a nitrogen–nitrogen

distance of 2.92 Å (based on an empirical correlation between deuterium quadrupole coupling constants and hydrogen-bond geometry).

Whereas pyrrole binds only weakly to lanthanide shift reagents,[275] the Ag(*fod*)/Pr(*fod*)$_3$ mixture seems more successful, as upfield-induced shifts have been reported for a range of heteroaromatic compounds, including pyrrole.[276] ^{1}H NMR spectra have been recorded for a number of η^5-pyrrolyl complexes of zirconium[277] and iron.[278] Azaferrocene (**36**) undergoes ready reaction with π-acidic ligands (e.g., L = CO, RNC, and R_2NPF_2) to afford η^1-*N*-pyrrolyl complexes of the type $(\eta^5\text{-}C_5H_5)FeL_2$ ($\eta^1\text{-}NC_4H_4$) characterized by substantial low-field ^{1}H NMR shifts from δ 5.26 (α-H) and 4.45 (β-H) in the η^5-parent to δ 6.27–6.55 (α-H) and 6.03–6.15 (β-H) in the η^1-derivatives.[278] NMR data (including $^{31}P^1H$ coupling constants) are available on a wide range of N-pyrrolyl phosphorus compounds containing P(III) or P(V). Chemical shifts lie in the ranges δ 6.71–6.88 (α-H) and 6.22–6.40 (β-H) for P(III) and 6.89–7.25 (α-H) and 6.17–6.36 (β-H) for P(V) derivatives; $^{31}P^1H$ coupling constants are of the order of 3.1–4.8 Hz for α-H and < 0.5–2.9 Hz for β-H interactions; the very small β-H couplings occur in the P(III) compounds.[279]

Transformation of pyrrole into its anion (in DMSO with Na^+ as the countercation) leads to upfield displacements of the ring-hydrogen signals (H-2,5 δ 0.23 ppm, H-3,4 δ 0.31 ppm).[280] The ^{1}H NMR spectrum of pyrrolylmagnesium chloride in diethyl ether consists of two triplets (δ 7.10 and 6.37; J = 2 Hz) whose general appearance is very similar to those found in the NMR spectra of pyrrole-N-^{2}H and pyrrolylsodium in ether (δ 6.84 and 6.26; J = 2 Hz). This similarity suggests that the association of magnesium is with nitrogen and not ring carbon.[281] The ^{1}H NMR spectrum of 1-pyrrolylthallium(I) has been interpreted in terms of an ionic structure, although this is difficult to reconcile with the compound's solution chemistry.[14] Treatment of pyrrole (and its 2,5-dimethyl- and 3-ethyl-2,4-dimethyl-analogs) with methoxide ion (in DMSO or acetonitrile solvent) in the presence of 1,3,5-trinitrobenzene yields Meisenheimer salts of the kind shown in **38** whose ^{1}H NMR chemical shifts suggest that the cyclohexadienyl moiety diminishes the electron density on the pyrrole ring.[30]



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Substitution of an alkyl group for hydrogen on pyrrole N or C atoms leads to upfield shifts (ca. 0.1–0.3 ppm) in the remaining ring hydrogen resonances. Electron-withdrawing substituents (e.g., formyl, acyl, or alkoxycarbonyl) on nitrogen cause substantial downfield shifts of the α-hydrogen resonances and much smaller downfield shifts for those of the β-hydrogens (Table 1.11). Data

TABLE 1.11. VARIATION OF RING HYDROGEN CHEMICAL SHIFTS WITH 1-SUBSTITUENT FOR PYRROLE DERIVATIVES

1-Substituent (Solvent)	$\Delta\delta$(H-2,5)[a]	$\Delta\delta$(H-3,4)[a]	Ref.
Me (CCl_4)	− 0.25	− 0.13	268
$CH{=}CH_2$ (CCl_4)	+ 0.09	+ 0.02	282
CHO ($CDCl_3$)	+ 0.59	+ 0.18	283
COMe (CCl_4)	+ 0.53	+ 0.08	284
CO*t*-Bu ($CDCl_3$)	+ 0.77	+ 0.03	12
CO_2Me (CCl_4)	+ 0.51	+ 0.05	284
Ph (CCl_4)	+ 0.30	+ 0.10	284

[a] $\Delta\delta = \delta_{N-R} - \delta_{N-H}$ in ppm.

TABLE 1.12. VARIATION OF RING HYDROGEN CHEMICAL SHIFTS WITH RING SUBSTITUENT FOR PYRROLE DERIVATIVES

Substituent (Solvent)	$\Delta\delta$(H-2)[a]	$\Delta\delta$(H-3)[a]	$\Delta\delta$(H-4)[a]	$\Delta\delta$(H-5)[a]	Ref.
2-CHO ($CDCl_3$)	–	+ 0.80	+ 0.13	+ 0.52	287
2-COMe ($^2H_8$-dioxan)	—	+ 0.73	+ 0.02	+ 0.29	288
2-CN ($^2H_6$-Me_2CO)	–	+ 0.75	+ 0.14	+ 0.33	289
2-CO_2Me (CCl_4)	—	+ 0.65	+ 0.01	+ 0.18	12
3-CO_2*t*-Bu ($CDCl_3$)	+ 0.67	–	+ 0.38	+ 0.04	12
3-CO_2CH_2Ph ($CDCl_3$)	+ 0.70	—	+ 0.47	+ 0.06	12
3-CHO ($CDCl_3$)	+ 0.79	–	+ 0.64	+ 0.01	287
2-Me (CCl_4)	—	− 0.33	− 0.16	− 0.26	268
3-Me (CCl_4)	− 0.34	—	− 0.20	− 0.20	268

[a] $\Delta\delta = \delta_{Ar-R} - \delta_{Ar-H}$.

are also available for a range of 1-substituted 2,5-dimethylpyrroles.[285,286] The shifts in the ring hydrogen resonances in C-substituted pyrroles (Table 1.12) are in accord with general expectations of inductive and resonance effects. Chlorine or bromine as ring substituents have little effect on the positions of the remaining ring-hydrogen resonances. Substituent effects on ring-hydrogen chemical shifts have been analyzed for a very wide range of aromatic compounds, including pyrrole and many derivatives, with a view to the empirical prediction of chemical shifts; values so obtained are reliable to $\pm$ 0.2–0.3 ppm.[290]

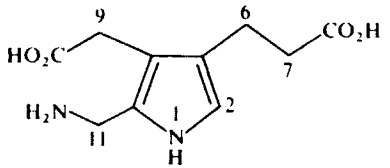
Proton–proton coupling constants have been accurately measured for pyrrole by direct fine-structure analysis, ^{14}N- and ^{2}H-decoupling on deuteriated pyrrole, ^{14}N- and ^{1}H-decoupling with spectrum simulation, and analysis of the 60- and 100-MHz spectra of ^{15}N-pyrrole. Agreement between the results from the various methods is generally good.[13] Replacement of ^{14}N by ^{15}N removes quadrupolar broadening and yields (at 100 MHz) an *AA'BB'CX* spectrum consisting of some 57 lines for the hydrogens bonded to ring carbon and 20 lines for the N–H from which iterative analysis yields values of the coupling constants

as $J_{1,2}$ $(= J_{1,5}) = +2.579 \pm 0.006$, J_{13} $(= J_{1,4}) = +2.458 \pm 0.006$, $J_{2,3}$ $(= J_{4,5}) = +2.660 \pm 0.011$, $J_{2,4}$ $(= J_{3,5}) = +1.491 \pm 0.011$, $J_{2,5} = +1.845 \pm 0.009$, and $J_{3,4} = 3.359 \pm 0.01$ Hz.[291,292] The compound ^{15}N-pyrrole has been subjected to a number of ^{1}H NMR determinations of ring geometry in nematic solvents;[178,293,294] differences between data measured in different liquid crystals are ascribed to variations in hydrogen bonding[178] (see Section 1.3). The ^{1}H NMR spectra of 1-methylpyrrole oriented in the nematic phases of liquid crystals with positive and negative diamagnetic anisotropies and in their mixtures have also been reported.[179] Ring proton coupling constants in substituted pyrroles are diagnostic of the position of substitution; the usual order is and typical ranges are $J_{2,4}$ $(= J_{3,5})$ 1.35–1.80 $< J_{2,5}$ 1.95–2.30 $< J_{2,3}$ $(= J_{4,5})$ 2.40–3.10 $< J_{3,4}$ 3.40–3.80 Hz.[14] The applications of ^{1}H NMR to conformational studies on pyrrole derivatives (in particular of long-range couplings between ring and aldehyde hydrogens) are discussed in a later section.

^{1}H (and more recently ^{3}H) NMR has played an important role in the study of the biogenesis of porphyrins and corrins from porphobilinogen (PBG); the ^{1}H NMR assignment is given in Table 1.13.[295] Also included in this paper are the ^{3}H NMR spectrum of PBG and the results of studies of the effects of change of pH on the PBG ^{1}H NMR spectrum. Hydrogen-3 NMR has permitted the detection of a PBG–PBG-deaminase complex in which the PBG appears to be bound via a thiol group. Tentative evidence has also been presented for the intermediacy of an azafulvene species during the formation of [^{3}H]uroporphyrinogen I.[296] Radiolysis of pyrrole, 1-methylpyrrole, and 2,5-dimethylpyrrole in CCl_3F at 77 K by ^{60}Co γ-rays yields cations, the ESR spectra of which indicate that the unpaired electrons occupy the $^1a_2(\pi_3)$ orbital having a node through the heteroatom. The hyperfine coupling constants for $H_{2,5}$ in pyrrole and 1-methylpyrrole are remarkably high (16 and 15.5 G, respectively) whereas those for $H_{3,4}$ are normal (3.0 and 3.6 G). 2,5-Dimethylpyrrole also displays an enhanced coupling to the methyl groups (17.5 G). The small coupling (3–3.5 G) observed to ^{14}N is characteristic of σ-orbital spin polarization.[297]

^{1}H and ^{19}F NMR studies of polypyrrole-BF_4 show that, whereas ^{19}F relaxation is dominated by BF^- ion rotation, ^{1}H relaxation is controlled by

TABLE 1.13. ^{1}H NMR ASSIGNMENT OF PORPHOBILINOGEN AT pH 8.0 IN D_2O/Na_2CO_3 REFERENCED INTERNALLY TO $Me_3SiCD_2CD_2CO_2^-Na^+$



Hydrogen:	7	6	9	11	2
δ (ppm):	2.41	2.67	3.41	4.16	6.69

electronic-spin motion on the polymer backbone.[298] ESR spectroscopy has been used to study the electronic structure of pyrrole and doped polypyrrole (see, e.g., Refs. 262 and 299–301); conduction does not appear to be dependent on the presence of free spins.

1.4.2. ^{13}C NMR Spectra

Both ^{14}N- and ^{15}N-pyrrole have been subjected to extensive analyses for the evaluation of accurate ^{13}C chemical shifts and heteronuclear coupling constants. The α-carbon resonance in ^{14}N-pyrrole is broadened as a result of quadrupolar relaxation by, and nonzero coupling to, the ^{14}N nucleus.

The undecoupled ^{13}C NMR spectrum of ^{15}N-pyrrole has been studied exhaustively, with iterative computer analysis of 64 assigned transitions for each of the α- and β-carbon atoms as the X part of *AA'BCDMX* spectra. This has yielded chemical shifts and unequivocal assignments and precise values (along with several signs) of the $^{13}C-^{1}H$ and $^{13}C-^{15}N$ coupling constants. Long-range ^{13}C isotope effects on the ^{1}H chemical shifts (ca. 0.0–0.3 Hz) and ^{2}H isotope effects on the ^{13}C chemical shifts in 1-$^{15}N^{2}H$-pyrrole (ca. 0.03–0.18 Hz) have also been investigated. Some of the results of this study are given in Table 1.14.[302]

The positions of the ^{13}C resonances for pyrrole and 1-methylpyrrole are solvent-dependent; similar effects are apparent in the two molecules (Table 1.15).

TABLE 1.14. ^{13}C NMR DATA FOR ^{15}N-PYRROLE

Ring Position (*n*)	$\delta(^{13}C)$	$J_{C(n)-H(1)}$	$J_{C(n)-H(2)}$	$J_{C(n)-H(3)}$	$J_{C(n)-H(4)}$	$J_{C(n)-H(5)}$	$J_{C(n)-N}$
2	118.14	+ 3.80	+ 183.28	+ 8.69	+ 7.45	+ 6.63	− 12.97
3	108.11	+ 7.11	+ 8.34	+ 168.80	+ 4.61	+ 7.43	− 3.92

TABLE 1.15. SOLVENT-DEPENDENCE OF ^{13}C CHEMICAL SHIFTS FOR PYRROLE AND 1-METHYLPYRROLE[a]

	Pyrrole		1-Methylpyrrole		
Solvent	C-2,5	C-3,4	C-2,5	C-3,4	NMe
Neat (+ 10% cyclohexane)	118.9	108.6	122.4	109.4	36.0
CS_2	118.7	108.3	121.1	109.1	—
Cyclohexane	118.2	108.6	121.5	109.0	35.7
$CDCl_3$	117.3	107.6	121.1	107.8	35.8
CH_2Cl_2	118.8	109.2	122.6	109.4	36.9
Dioxan	117.7	108.0	121.6	108.0	35.4
Acetone	118.0	107.8	121.7	108.1	35.4
Benzene	118.1	108.7	122.1	109.2	35.6
DMSO	116.3	106.1	120.2	106.1	34.3

[a] Data from Refs. 303 and 14 given relative to TMS.

N-Methylation leads to downfield shifts of the α-carbon resonances of approximately 3.8 ppm, but the effect on the β-carbon resonances is smaller. Only small changes in ring carbon shifts are discernible with variation in the *N*-alkyl group for 1-substituted 2,5-dimethylpyrrole derivatives (Table 1.16),[304] and the effects of *N*-methylation on the ring carbon chemical shifts of tetrasubstituted pyrroles seem somewhat variable.[102]

From a study embracing 54 substituted pyrroles, substituent ^{13}C chemical-shift parameters have been derived that allow the prediction of ^{13}C shifts to about 0.5 ppm (Table 1.17). Account must be taken, however, of 'steric compression shifts' between adjacent substituents and of interactions between two electron-withdrawing groups leading to some reduction in the overall degree of

TABLE 1.16. ^{13}C CHEMICAL SHIFTS OF 1-SUBSTITUTED 2,5-DIMETHYLPYRROLE DERIVATIVES IN $CDCl_3$ RELATIVE TO INTERNAL TMS

1-Substituent	C-α	C-β	CH_3
CH_2Ph	127.6	105.7	12.3
Ph	128.4	106.1	12.9
CH_2CHMe_2	127.3	105.5	12.8
CH_2CHPh_2	127.8	105.4	12.3
CH_2t-Bu	127.1	106.3	13.8
i-Pr	127.3	106.4	14.1
PhCHMe	127.8	106.5	13.8
PhCHPh	[a]	107.1	14.2
Et	128.2	105.8	12.5
1-Naphthyl	126.5	105.4	12.3

[a] Signal overlapped with 1-substituent carbon signals.

TABLE 1.17. ^{13}C SUBSTITUENT CHEMICAL-SHIFT PARAMETERS FOR PYRROLE DERIVATIVES[a]

Substituent	C-2	C-3	C-4	C-5
2-Me	10.8	− 1.2	1.1	− 2.1
2-CHO	14.9	13.2	3.7	10.9
2-COMe	14.5	9.9	2.6	8.1
$2\text{-}CO_2R$	4.7	7.3	3.2	5.9
$2\text{-}NO_2$[b]	19.3	2.5	2.5	6.2
3-Me	− 2.4	12.7	1.1	− 0.9
3-Et	− 3.7	18.3	− 0.8	− 0.6
3-CHO	10.8	11.6	− 1.5	3.0
3-COMe	8.7	13.3	− 0.7	1.6
$3\text{-}CO_2Et$	8.2	2.6	− 0.6	− 0.1
$3\text{-}CH_2CO_2R$	− 1.9	8.0	0.9	− 0.7
$3\text{-}CH_2CH_2CO_2R$	− 2.8	14.0	0.0	− 0.6
$3\text{-}NO_2$[b]	1.8	29.4	− 3.9	1.2

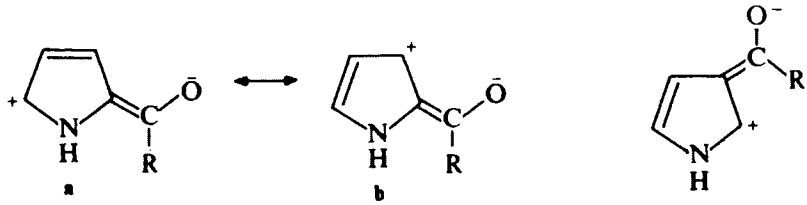
[a] Data from Ref. 102. Parameters from solutions in $CDCl_3$ containing TMS are in ppm, a positive sign denoting a downfield shift from pyrrole.
[b] Data from Refs. 305 and 306.

TABLE 1.18. STERIC COMPRESSION AND GROUP INTERACTION EFFECTS ON ^{13}C CHEMICAL SHIFTS OF PYRROLE DERIVATIVES FROM REF. 102

Substituents	C-2	C-3	C-4	C-5
2-Me, 3-Me	− 0.7	− 3.8	− 0.1	0.2
2-Me, 3-CH_2–	− 0.2	− 2.8	− 0.1	0.1
3-Me, 4-Me	− 0.1	− 2.8	− 2.8	− 0.1
3-Me, 4-CH_2–	− 0.7	− 2.0	− 2.1	0.4
3-CH_2–, 4-CH_2–	− 0.1	− 1.4	− 1.4	− 0.1
2-CO_2–, 5-CO–	− 5.1	− 2.7	− 5.2	− 4.6
2-CO_2–, 4-CO–	− 1.1	2.0	− 0.6	− 3.4

withdrawal (Table 1.18). (This effect has already been noted in Section 1.1 in relation to anodic oxidation potentials, where only 60–80% of the double substituent influence is apparent when two directly conjugated electron-withdrawing groups are present in the pyrrole α positions.)

For substitution at C-2, the C-4 resonance is least affected, whereas the C-4 and C-5 resonances are not very sensitive to substitution at C-3. These effects are consonant with the results of INDO calculations and with the charge distributions predictable from resonance considerations; important canonical forms for conjugation between the ring and a carbonyl group are **39a,b** and **40**. In addition, the prediction follows that this conjugation should be less effective



overall in electron withdrawal from the ring when the substituent is β rather than α, and this is supported by the substituent chemical-shift parameters.[102] More recent data are available on a wide range of 2-alkyl-, 2,3-dialkyl-, and 2,3-dialkyl-1-vinyl pyrroles[282] (see also Refs. 307–309). The shifts for the N–H pyrroles are generally unexceptional, lying in the ranges 121–133 (C-2), 106–126 (C-3), 106–111 (C-4), and 113–116 (C-5) ppm, although the shifts for the 2-*t*-butyl derivative are well outside these ranges at C-2 (141.1) and C-3 (102.5). In the 1-vinylpyrroles, alkyl substituents affect the electronic structure through steric inhibition of p,π-conjugation and π-induction; a correlation between the atomic charge densities as estimated by the CNDO/2 approximation and the carbon chemical shifts has been established.[282] Additional ^{13}C NMR data on substituted pyrroles are available in Refs. 310–312.

Conversion of pyrrole into its lithium salt results in an approximately 9 ppm downfield shift in the position of the α-carbons' resonance and a smaller (ca.

TABLE 1.19. ^{13}C CHEMICAL SHIFTS IN THF OF 1-METHYL AND 1-DIMETHYLAMINOPYRROLE AND THEIR α-LITHIO DERIVATIVES

1-Substituent	2-Substituent	C-2	C-3	C-4	C-5	1-Alkyl
Me	H	122.7	109.5	109.5	122.7	36.6
Me	Li	173.7	121.8	109.0	123.1	41.1
NMe_2	H	117.3	107.1	107.1	117.3	49.3
NMe_2	Li	157.6	112.3	109.2	117.1	49.9

2 ppm) upfield shift for the β-carbons.[306] The ^{13}C NMR signals in 2-lithio-1-methyl- and -1-dimethylamino-pyrrole show profound low-field shifts at C-2 and smaller shifts at C-3, as expected (Table 1.19). By direct ^{13}C NMR observation, it is possible to measure the relative concentrations at equilibrium of the α-deprotonated and nondeprotonated pyrroles in the presence of appropriate lithiated amine bases and hence derive pK values (see Section 1.1).[33] Carbon-13 NMR data are available for a number of η^5-transition-metal complexes of pyrrole [e.g., azaferrocene (**36**)] and its 2-methyl and 2,5-dimethyl derivatives. As already noted in Section 1.4.1, ready reaction of **36** with π-acidic ligands yields η^1-N-pyrrolyl complexes; the characteristic low-field ^1H NMR shifts on change of structure are mirrored by ^{13}C NMR shifts from δ 90.0 (α-C) and 72.6 (β-C) in (**36**) to δ 135–136 (α-C) and 107–109.2 (β-C) in the η^1-complexes, that is, to regions characteristic of N-metalated pyrroles.[278] 1-Pyrrolyl-phosphorus compounds containing P(III) or P(V) have been exhaustively studied by multinuclear NMR spectroscopy, and ^{13}C chemical shifts and heteronuclear coupling constants are available. The ^{13}C chemical shifts are unexceptional and similar in the P(III) and P(V) series, ranging between δ 121.8–123.8 (α-C) and 110.3–113.5 (β-C), indicating the small π-acceptor strength of both P(III) and P(V). As expected from the greater electronegativity of P(V), the magnitude of the coupling constants $^1J(^{13}C_{(2,5)}{}^1H_{pyrrole})$ is greater by 4–6 Hz than in the P(III) compounds, and there are also significant changes in the $^nJ(^{31}P^{13}C_{pyrrole})$ coupling constants in the two series of compounds.[279] 1-Pyrrolyl derivatives of the type $E(NC_6H_4)_n$, $E = Me_2B$, Et_2B, $(CH_2S)_2B$, $EtB(NC_5H_5)$, $n = 1$; EtB, $n = 2$; B, $n = 3$; Me_3Si, Me_3Sn, Me_3Pb, $n = 1$; and Me_2Sn, $n = 2$ have been studied by multinuclear NMR; the ^{13}C chemical shifts for the pyrrole nucleus are listed in Table 1.20. Compared with pyrrole, there is significant deshielding of C(3) in a number of the tabulated derivatives consonant with π-acceptor character in the N-substituents.[313]

^{13}C NMR spectroscopy has been widely used (along with other nuclei) in studies of porphyrin and corrin biosynthesis (see, e.g., Refs. 295, 296, 314, and 315 and references cited therein). The assignment of ^{13}C resonances for the important biogenetic precursor porphobilinogen **2** is given in Table 1.21.[295]

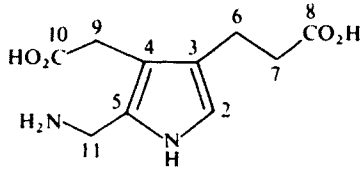
Cross-polarization, magic-angle-spinning ^{13}C NMR has been used in structural studies of polypyrrole and its doped congeners (see e.g., Refs. 262, 300, and 316 and references cited therein). Neutral polypyrrole shows a double-peak structure with signals at 125.2 and 105.2 ppm assignable to the α- and β-carbons,

TABLE 1.20. ^{13}C CHEMICAL SHIFTS FOR N-B, Si, Sn, Pb, AND P DERIVATIVES OF PYRROLE IN $CDCl_3$

1-Substituent	δ(C-2)	δ(C-3)	$^1J_{C2,C3}$ (Hz)
Me_2B	124.6	114.2	68.0
Et_2B	124.1	113.6	67.5
EtB	125.2	113.4	67.5
B	126.6	113.6	—
$(CH_2S)_2B$	125.6	113.7	68.0
$EtB(NC_5H_5)$	123.0	108.5	—
Me_3Si	127.7	114.4	67.5[a]
Me_3Sn	124.4	109.8	65.0[a]
Me_2Sn	124.1	110.1	—
Me_3Pb	125.4	108.8	63.5[a]
Me_3P[b]	123.1	111.3	—[a]
$Me_2P(S)$[b]	122.0	113.0	—[a]

[a] C_6D_6 solvent.
[b] Data from Ref. 279.

TABLE 1.21. ^{13}C NMR ASSIGNMENT OF PORPHOBILINOGEN AT pH 8.0 IN 0.1 M PYROPHOSPHATE WITH 10% v/v D_2O INTERNALLY REFERENCED TO *p*-DIOXAN (δ = 66.5 ppm)



Carbon:	2	3	4	5	6	7	8	9	10	11
(ppm):	115.62	119.26	109.55	119.26	21.35	38.10	182.84	28.02	174.30	40.05

respectively, whereas the spectrum of polypyrrole doped with BF_4^- does not show any structure; the C-α and C-β resonances are almost coincident at 123–126 ppm. [316]

1.4.3. Nitrogen NMR Spectra

Pyrrole and its derivatives may be studied by both ^{14}N and ^{15}N NMR spectroscopy, but the problems of quadrupolar broadening in the former (nuclear spin = 1, electric quadrupole moment = $2.0e \times 10^{-26}$ cm^2), of the low natural abundance in the latter (0.365%), and of the low sensitivity in both (0.00101 for ^{14}N, 0.00104 for ^{15}N relative to ^1H = 1) have discouraged widespread studies of these nuclei. Additionally, spin-lattice relaxation times for the ^{15}N nucleus can be very long (typical literature values range from 40 to 60 s for pyrrole ^{15}N, compared with ca. 10–13 s for the ring carbons), and the negative

magnetic moment can lead to loss of signal intensity (a negative nuclear Overhauser enhancement factor) when broadband proton decoupling is employed. The ^{15}N–^{1}H Overhauser effect can be quenched and the spin-lattice relaxation rate greatly shortened by the addition of paramagnetic compounds such as the acetylacetonato or dipivaloylmethanato complexes of Cr(III) or Gd(III).[317,318] Alternatively, the selective population transfer method, which allows sampling of the ^{15}N NMR spectrum at a pulse repetition rate determined by the rate of relaxation of the perturbed ^{1}H nuclei, may be applied. In this way, a ^{15}N signal-to-noise ratio (S/N) for a natural-abundance pyrrole sample about 1.5 times that for a 96% ^{15}N-enriched sample studied in the conventional manner has been achieved.[319] Useful comments on the mechanics of ^{15}N NMR data collection with particular reference to 1-pyrrolylphosphorus compounds[279] and verdinoid bile pigments and their partial structures[320] are also available.

The conclusion from a study of ^{14}N chemical shifts of a number of *N*-heterocycles, including pyrrole and 1-methylpyrrole (Table 1.22), is that the chemical shifts correlate in roughly linear fashion with π-charge densities estimated by the SCF–PPP–MO approximation and cluster in groups characteristic of the type of heterocyclic ring system. The effects of *N*-methylation on the *N*-chemical shift is minimal.[321]

TABLE 1.22. ^{14}N CHEMICAL SHIFTS FOR PYRROLE AND 1-METHYLPYRROLE[a]

1-Substituent	Solvent	$\delta(^{14}N)$ ppm	Width at Half Height (Hz)
H	Neat	-235 ± 2	172 ± 5
	Dioxan (1–1)	-232 ± 2	50 ± 5[b]
	Methanol (1–1)	-233 ± 3	40 ± 5[b]
Me	Neat	-231 ± 2	104 ± 5
	Methanol (1–1)	-233 ± 1	90 ± 3

[a] Data from Ref. 321 with respect to internal $MeNO_2$; the values given correspond to an increase in nitrogen shielding.

[b] These resonances appear as doublets, $J(^{14}N\text{–}H) = 58 \pm 1$ Hz.

Nitrogen NMR data have been measured for a range of *N*-pyrrolyl derivatives and are presented in Table 1.23.[313] Additional data on 1-pyrrolylphosphorus compounds containing P(III) or P(V) are available in Ref. 279; ^{11}B, ^{29}Si, ^{31}P, ^{119}Sn, and ^{207}Pb NMR data are also given in these papers. Data on some 1-vinylpyrroles are available in Ref. 323. A deuterium isotope effect $\delta N(^{1}H)$–$\delta N(^{2}H)$ of 0.24 ppm has been observed when the pyrrolyl imino proton is replaced by deuterium.[324] Transformation of pyrrole into its lithium salt leads to an approximately 25 ppm downfield shift in the position of the ^{14}N resonance.[306]

The results of a study of ^{15}N-labeled pyrroles show no significant correlation between nitrogen chemical shift and any Hammett substituent constant. However, the value of the ^{15}N–H coupling constant increases with the addition of

TABLE 1.23. NITROGEN CHEMICAL SHIFTS FOR PYRROLE AND SOME 1-SUBSTITUTED DERIVATIVES[a]

1-Substituent	N-Isotope	δ ppm	Solvent
H[b]	15	− 232.7	$CDCl_3$
H[b]	15	− 224.6	Me_2SO
Me[b]	15	− 230.9	$CDCl_3$
Me[b]	15	− 230.2	Me_2SO
Me[c]	15	− 230.1	Me_2SO (0.5 M)
Me_2B	15	− 187	$CDCl_3$
Et_2B	14	− 185	$CDCl_3$
EtB<	14	− 195	$CDCl_3$
B<	14	− 207	$CDCl_3$
$(CH_2S)_2B$	14	− 201	$CDCl_3$
Me_3Si	15	− 216.0	C_6D_6
Me_3Sn	15	− 216.2	C_6D_6
Me_3Pb	15	− 206.7	C_6D_6
Me_3P	15	− 219.3	C_6D_6
$Me_2P(S)$	15	− 212.6	C_6D_6

[a] Data from Ref. 313 unless stated otherwise and refer to external $MeNO_2$; solutions 10–30% w/v in $CDCl_3$ or C_6D_6 except where stated.
[b] Data from Ref. 322.
[c] Data from Ref. 318.

electron-withdrawing groups, seemingly reflecting the extent of resonance interaction between the pyrrole ring and a substituent; the value does not depend significantly on solvent, temperature, or solute concentration. The values of the long-range coupling constants are not obviously related to the nature of substituents (Table 1.24).[325]

Indirect measurements of solvent effects on the positions of the ^{14}N resonances in pyrrole and its 2-acetyl and 2,5-diacetyl derivatives have been made through observation of the variation in intensity of the NH proton resonance with change of frequency of irradiation over the expected ^{14}N chemical-shift range (Table 1.25). The ^{14}N shifts are displaced upfield on dilution of pyrrole

TABLE 1.24. ^{15}N NMR DATA FOR PYRROLE AND DERIVATIVES[a]

Substituent	$\Delta\delta(^{15}N)$ ppm	J_{N-H}	$J_{N-H(3)}$	$J_{N-H(4)}$	$J_{N-H(5)}$
None	0	96	5.39[b]	5.39[b]	4.52[b]
2-CHO	+ 0.89	98	4.15	5.00	4.05
2-COMe	+ 4.24	98	4.60	5.10	4.00
2-NO_2	+ 0.55	—	—	—	—
3-NO_2	+ 4.84	—	—	—	—
2-CO_2Me	+ 5.53	98	4.31	4.95	4.10
4-NO_2, 2-CO_2Me	+ 7.60	100.3	5.05	—	3.45
5-NO_2, 2-CO_2Me	− 0.20	101.5	3.05	3.63	—

[a] From Ref. 325, positive $\Delta\delta$ indicates a downfield shift from pyrrole, solvent $CDCl_3$ unless stated otherwise, J values in hertz.
[b] Values are for neat pyrrole.

TABLE 1.25. VARIATION OF ^{14}N CHEMICAL SHIFTS FOR PYRROLE AND ITS 2-ACETYL AND 2,5-DIACETYL DERIVATIVES WITH SOLVENT[a]

Solvent	δ(Pyrrole)	δ(2-Acetylpyrrole)	δ(2,5-Diacetylpyrrole)
CCl_4	+ 120.7 ± 0.4	+ 126.8 ± 0.7	
$CDCl_3$		+ 127.5 ± 0.4	+ 121.3 ± 0.4
$C_6{}^2H_6$	+ 122.0 ± 0.4	+ 127.6 ± 0.4	+ 122.0 ± 0.6
None	+ 125.7 ± 0.4	—	—
CH_3CO_2H	+ 125.7 ± 0.4	—	+ 125.6 ± 0.4
Dioxan	+ 126.5 ± 0.4	+ 131.2 ± 0.4	+ 128.0 ± 0.4
Acetone	+ 127.5 ± 0.4	+ 130.5 ± 0.4	+ 124.4 ± 0.4
MeCN	+ 128.6 ± 0.4	+ 130.1 ± 0.4	+ 124.9 ± 0.4
^2H_7DMF	+ 131.2 ± 0.4	+ 133.4 ± 0.5	
Et_3N	+ 132.6 ± 0.4	+ 132.8 ± 1.0	—
H_2O	+ 132.8 ± 1.4	—	—
DMSO	+ 134.8 ± 0.4	+ 137.9 ± 0.5	+ 133.0 ± 1.5

[a] Taken from Ref. 326, shifts in ppm downfield from NH_4^+.

with carbon tetrachloride in consonance with NMR studies on other nuclei, indicating a breaking down of the pyrrole self-association. In solvents such as DMSO, triethylamine, DMF, acetonitrile, acetone, and dioxan, the ^{14}N shift is downfield compared with the neat state. This is also accompanied by downfield shifts of the NH proton signals and is a consequence of solute–solvent hydrogen-bonding; the largest ^{14}N shift is observed in DMSO, the strongest proton acceptor among the solvents. Downfield shifts are also observed on dilution with protic solvents such as water or acetic acid.[326] ^{14}N Relaxation times at several temperatures for pyrrole dissolved in cyclohexane, carbon tetrachloride, 1,4-dioxan, pyridine, 3,5-lutidine, 2-fluoropyridine, and pentafluoropyridine have also been measured indirectly by ^1H NMR line-shape analysis of the pyrrole N–H signal and the results related to solvent effects on the pyrrole association equilibrium.[272,273]

Reference has already been made in Section 1.2 to the results of ab initio calculations on ^{14}N nuclear quadrupole coupling in pyrrole and 1-methylpyrrole (calculated and experimental values for the coupling constants and asymmetry parameters are listed in Table 1.6[145]) and in Section 1.4.1, to the study of the pyrrole–pyridine complex by ^2H and ^{14}N nuclear quadrupole resonance.[274] The latter results are not entirely consistent with the previously reported ^{14}N nuclear quadrupolar resonance (NQR) spectrum of the complex.[327] Hydrogen-bond formation in the complex reduces the ^{14}N quadrupole coupling constants by approximately 10% and increases the asymmetry parameter by about 100%.

1.4.4. Ultraviolet Spectroscopy

The electronic spectroscopy of pyrrole and its derivatives is reviewed extensively in Ref. 13. Tabulations of transition energies calculated by various

SCF–MO methods are available therein and in Ref. 14. References cited in Section 1.2 and Ref. 12 are also relevant. Tables of experimental data for monosubstituted[328] and polysubstituted[329] pyrroles (see also Ref. 13) are available, with annual supplementation by *Organic Electronic Spectral Data.*[342]

The results of a detailed experimental study of the electronic spectrum of pyrrole in the vapor phase over the entire absorption region down to about 140 nm are reported in Ref. 330. The four Rydberg-like series below approximately 256 nm converge to a lowest ionization potential of 8.215 eV. Above the intense and relatively sharp peak at 211 nm are several broad and overlapped bands; a featureless and very weak continuum extends from 221 to 256 nm with weak inflections near 233 and 248 nm. Several diffuse vibronic components overlapped with a continuum occur below 211 nm, becoming weaker until the next system begins with an intense absorption at 183 nm. At even shorter wavelengths, the spectrum is complex with many bands down to 152 nm, where a continuous absorption leading to the lowest ionization limit begins. The electronic spectrum of crystalline pyrrole has been interpreted in terms of an orthorhombic crystal lattice containing four molecules in the unit cell.[330] References to earlier experimental work on pyrrole can be found in Ref. 136 and in the books cited above. Recent ab initio and semiempirical MO calculations are discussed in Refs. 82, 111, 136, and 144. A new minimum basis set, developed for use in the computation of excitation energies of large molecules such as porphyrins, has been tested on pyrrole.[136] The results of this calculation are compared with those of other recent treatments in Table 1.26; an important conclusion is that the commonly used minimal-basis-set contractions developed to produce low ground-state energies or to fit Slater atomic orbitals are not very suitable for the calculation of excited-state energies or properties. The symmetry-adapted cluster (SAC) expansion and SAC–CI theory have been applied to the calculation of the valence and Rydberg excitations and ionizations of pyrrole (Table 1.26[144]). For almost all the singlet excitations the results agree to within 0.1 eV with the experimental values. For the excitations below 7.0 eV, the assignments agree with those suggested experimentally. However, assignments differ above 7.0 eV. The peak oberved at 7.22 eV (calculated 7.20 eV) is assigned to the 4^1A_1 state and the peaks at 7.43 and 7.54 eV, to the 2^1B_2 and 3^1B_2 states, respectively. The peak at 6.23 eV is assigned as Rydberg $\pi \rightarrow 3s$, in agreement with some,[336] but not other,[330] experimentalists and with other calculations. The peak at 6.78 eV is assigned to the Rydberg $^1A_1$ state produced by the excitation from the $1a_2$ MO to the $3d_{xy}$ MO, in agreement with Ref. 336. Optically forbidden transitions in the electronic spectrum of pyrrole have been studied by low-energy, variable-angle, electron-impact spectroscopy; the low-lying feature at 4.21 eV is assigned as a singlet to triplet transition analogous to the lowest $\pi \rightarrow \pi^*$ transition in benzene and the weak transition at 5.22 eV possibly to singlet–singlet excitation.[337–339]

Resonantly enhanced multiphoton ionization (MPI) spectra of pyrrole and 1-methylpyrrole have been measured in the wavelength region from 355 to 680 nm; the data generally support earlier spectral assignments for the one

TABLE 1.26. PYRROLE TRANSITION ENERGIES EVALUATED BY ab initio MO METHODS[a]

State	[b]	[c]	[d]	[e]	[f]	Experimental[g]
			CI Singlets			
$^1A_1(\pi, \pi^*)$	7.7	6.5	6.7	6.5	7.2	6.1
$(R'3p_x)$	7.1	6.9	—	—	6.9	
$(R3d_{xy})$		7.1		7.3	6.7	
$^1B_1(R3p_y)$	6.5	5.6	6.0		5.9	
$(R'3s)$	6.3	6.0	6.1	—	6.1	5.9
$(R3d_{yz})$	—	6.3	—	—		
$(R'3p_z)$	7.1	6.7	—	—	6.7	
$^1B_2(R3p_x)$	6.4	5.8	6.3	6.0	6.0	5.9
$(R3d_{xz})$	—	7.0	—	7.1		
(π, π^*)	8.9	7.9[h]	7.7		7.5	7.7
$(R'3d_{xy})$	—	8.1	—	—	7.6	
$^1A_2(R3s)$	5.7	5.2	5.2		5.2	5.2
$(R3p_z)$	6.5	6.0	—	—	6.0	
$(R3d_{z^2-y^2})$		6.6	—	—		
$(R3d_{x^2})$		6.9				
$(R'3p_y)$	7.2	7.1			6.9	
$^2A_2^+$	8.4	—	—	8.1		8.2[i]
$^2B_1^+$	9.1	—	—	—		9.2[i]
			SCF Triplets			
$^3B_2(\pi, \pi^*)$	4.3		4.4	[e]	4.7	4.3[j]
$^3A_2(R3s)$	5.4		5.3		5.2	
$^3A_1(\pi, \pi^*)$	6.0		5.7		5.8	
$^3B_1(R'3p_y)$	6.1				5.8	

[a] For assignments, see Refs. 136 and 144; energies in electron volts from the $^1A_1$ ground state. The term $(R3s)$ denotes the Rydberg state that has a hole in $1a_2$ and an electron in 3s; $(R'3s)$ denotes the state that has a hole in $2b_1$ and an electron in 3s.

[b] Ref. 136.

[c] Ref. 331.

[d] Ref. 332

[e] Ref. 333; triplet excitations are assigned as 4.27 $^3B_2(1a_2 \rightarrow 3b_1)$, 5.45 $^3A_1$ $(1a_2 \rightarrow 2a_2$, $2b_1 \rightarrow 3b_1)$, 6.37 $^3B_2$ $(1a_2 \rightarrow 4b_1)$, and 7.14 $^3A_1$ $(1a_2 \rightarrow 2a_2$, $2b_1 \rightarrow 3b_1)$.

[f] Ref. 144.

[g] Ref. 334.

[h] Predicted as Rydberg $f + (\pi, \pi^*)$.

[i] Ref. 335.

[j] Ref. 336.

photon spectrum of pyrrole. The majority of the peaks in the MPI pyrrole spectrum can be assigned to *ns*, *np*, and *nd* Rydberg series and associated vibronic structure. The main features of the MPI spectrum of 1-methylpyrrole are totally different; only one prominent Rydberg series (assigned as *ns*) is identifiable.[340]

The solution spectrum of pyrrole displays a strong band (ε ca. 4.2) at about 210 nm in ethanol; the weak band at about 240 nm reported in the older

literature is now generally accepted as arising from autoxidation products. *C*-Alkyl substitution generally leads to only small shifts of approximately 3–8 nm; for example, 3-ethyl-2,4-dimethyl pyrrole (kryptopyrrole) has a single maximum at 200 nm in ethanol and 3,4-dimethylpyrrole at 203 nm; the effect of alkyl substitution does not appear to be additive. Conjugation of the pyrrole ring with electron-withdrawing groups leads to a bathochromic shift of about 30–60 nm and the emergence of a second, intense band at longer wavelength corresponding to electron transfer from the ring to the substituent. The position of this band moves to increasingly long wavelength as the degree of conjugation increases, that is, in the order CN < CO_2H < $CONH_2$ < CO_2R < CH=NOH < CHO< COR <CO·CO_2R < CH=CHCOR < CH=CH·COPh for monosubstitution at a given position. In addition, the band position for 3-substituted pyrroles is generally 15–20 nm to shorter wavelength compared with the corresponding 2-substituted isomer. For a range of pyrrole mono- and dicarboxylic acids and esters, the wavelength of the electron-transfer band increases in the order of substitution 3- < 3,4- < 2- < 2.3- and 2,4- < 2,5-.[341] Representative data for a selection of mono- and disubstituted pyrroles are listed in Tables 1.27 and 1.28. Further data are available in the references cited at

TABLE 1.27. UV SPECTRA FOR PYRROLE AND SELECTED MONOSUBSTITUTED DERIVATIVES

Substituent	λ_{max} (nm) (log ε)	Solvent	Ref.
None	210(4.20)	EtOH	328
1-Me	210(3.76)	H_2O	328
2-Me	208(3.85)	H_2O	13
3-Me	208(3.77)	H_2O	13
1-CHO	236(4.05), 241s(3.98), 263s(3.18)	C_6H_{14}	342
2-CHO	251(3.49), 287(4.12)	EtOH	328
3-CHO	243(3.97), 270(3.66)	EtOH	12
1-COMe	238.5(4.03), 288s(2.88)	EtOH	328
2-COMe	250s(3.64), 287(4.20)	EtOH	328
3-COMe	243(3.97), 270s(3.66)	MeOH	343
2-$COCCl_3$	312(4.13)	EtOH	342
2-$COCF_3$	260s(3.7), 303(4.21)	EtOH	342
1-COPh	220(4.1), 250(4.1)	C_6H_{14}	342
2-CH=NOH	270(4.30), 278(4.25)	dioxan	342
3-CH=NOH	243(4.03)	dioxan	342
1-CO_2H	224(3.68)	EtOH	13
2-CO_2H	228(3.66), 258(4.10)	EtOH	13
3-CO_2H	223(3.89), 245(3.71)	EtOH	13
1-CO_2Me	228(3.85)	EtOH	328
2-CO_2Me	238s(3.63), 263(4.14)	EtOH	328
3-CO_2Me	224(3.90), 247(3.73)	EtOH	328
2-COCl	288(4.23)	$CHCl_3$	342
1-Ph	253(4.13)	EtOH	13
2-Ph	228s(3.90), 287(4.31)	EtOH	13
2-NO_2	231(3.61), 335(4.23)	MeOH	343
3-NO_2	268(3.86), 315(3.73)	MeOH	343
3-Cl	246(3.18)	H_2O	342

TABLE 1.28. UV SPECTRA OF REPRESENTATIVE DISUBSTITUTED PYRROLE DERIVATIVES

R_1	R_2	R_3	R_4	R_5	Solvent	λ_{max} (nm) (log ε)
H	CHO	CN	H	H	H_2O	265(3.62), 300(4.17)
H	H	CN	H	CHO	H_2O	281(4.15)
H	CHO	Me	H	H	H_2O	295(4.21)
H	CHO	H	Me	H	H_2O	258(3.78), 300(4.13)
H	CHO	H	H	Me	H_2O	253(3.65), 306(4.32)
H	Me	CHO	H	H	H_2O	258(3.97), 283(3.81)
H	CHO	OMe	H	H	H_2O	294(4.30)
H	CHO	H	H	OMe	H_2O	251(3.38), 315(4.36)
H	Et	Me	H	H	C_6H_{12}	213(3.94)
H	CHO	Ph	H	H	H_2O	299(4.11)
H	Me	Me	H	H	C_6H_{14}	212(3.89)
H	Et	Me	H	H	C_6H_{14}	224(3.83)
H	Me	Et	H	H	C_6H_{14}	213(3.95)
H	Me	Pr	H	H	C_6H_{14}	213(3.90)
H	Pr	Et	H	H	C_6H_{14}	222(3.87)
H	Ph	Ph	H	H	C_6H_{14}	202(4.31), 242(4.08), 248(4.04), 297(3.95)
H	Ph	H	H	Ph	EtOH	208(4.13), 232(4.05), 327(4.48)
H	COMe	H	H	Me	Et_2O	290(4.27)
H	Me	COMe	H	H	EtOH	206(4.17), 243(3.96), 281(3.82), 279(3.78)
H	Me	H	COMe	H	EtOH	205(4.14), 245(4.01), 280(3.72)
H	CO_2Et	H	H	CN	EtOH	268(4.50), 275s(4.38)
H	H	Cl	Cl	H	EtOH	208(3.72)
H	CN	Me	H	H	EtOH	231s(3.94), 248(4.15)
H	CN	H	Me	H	EtOH	224(3.76), 256(4.05)
H	CN	H	H	Me	EtOH	220(3.65), 257(4.18)
H	Me	CN	H	H	EtOH	238(3.87)
H	H	COMe	Me	H	Et_2O	239(4.13), 272s(3.64)
H	COMe	H	NO_2	H	MeOH	247(4.10), 303(3.88)
H	COMe	H	H	NO_2	MeOH	241(4.08), 330(4.17)
H	NO_2	H	COMe	H	MeOH	226(4.06), 323(3.95)
H	CO_2Me	H	NO_2	H	MeOH	236(4.25), 301(3.78)
H	CO_2Me	H	H	NO_2	MeOH	228(4.10), 325(4.10)
H	H	CO_2Me	H	NO_2	MeOH	321(4.08)
Me	COMe	H	H	H	EtOH	247(3.65), 287(4.18)
H	CHO	H	Br	H	EtOH	253(3.85), 298(4.10)
H	CHO	H	Cl	H	EtOH	252(3.84), 302(4.16)
H	CHO	H	I	H	EtOH	257(3.95), 303(4.07)
CHO	$CONH_2$	H	H	H	EtOH	249(4.03), 258(3.92), 310(4.03), 335s(3.70)
Me	CHO	H	H	H	C_6H_{14}	246(3.79), 280(4.21)
Me	H	CHO	H	H	EtOH	254(4.08), 274s(3.93)
Me	H	CO_2H	H	H	EtOH	233(3.96), 246s(3.86)
Me	H	COMe	H	H	C_6H_{14}	241(3.93), 262(3.72)
H	H	CO_2H	CO_2H	H	MeOH	240(3.90), 259(3.88)
H	H	CO_2Me	CO_2H	H	EtOH	245(3.90), 260(3.87)
H	Et	H	H	Me	MeOH	216(3.80)
H	H	CO_2Me	CO_2Me	H	EtOH	253(3.90)
H	Me	CO_2Et	H	H	EtOH	255(3.87)

TABLE 1.28. (*Contd.*)

R_1	R_2	R_3	R_4	R_5	Solvent	λ_{max} (nm) (log ε)
H	H	CO_2Me	CO_2Et	H	EtOH	252(3.93)
H	H	CO_2Et	CO_2Et	H	EtOH	252(3.88)
CHO	Ph	H	H	H	EtOH	234(4.13), 282(3.95)
H	Me	H	H	Ph	EtOH	298(4.33)
H	CHO	H	H	Ph	EtOH	318(4.46)
H	CN	Cl	H	H	H_2O	248(4.15)
H	CN	CN	H	H	H_2O	233(3.84), 240(3.85), 267(4.01)
H	CN	OMe	H	H	H_2O	247(4.28)
H	CN	Ph	H	H	H_2O	265(4.18)
H	MeS	NO_2	H	H	EtOH	222(4.17), 274(3.77), 382(3.84)
H	COMe	H	COMe	H	MeOH	228(4.32), 260s(3.9), 286(4.21)
H	CO_2Et	OH	H	H	EtOH	263(4.23)

the beginning of this section and in Refs. 344 (alkylated 2-amino-3-cyanopyrroles), 285 (1-aryl-2,5-dimethylpyrroles), 345 (nitropyrroles), 346 (methylated CO derivatives), 347 (substituted 1-vinylpyrroles), 348 (carboxylic acids and esters), 349 (1-arylpyrroles), and 350 (netropsin-like polypeptides, including MCD measurements). Some information on the influence of solvent on the UV spectra of pyrrole derivatives is gathered in Table 1.29.

Protonation of alkylpyrroles leads to bathochromic shifts of the absorption maxima from the positions of those for the free bases, and, in general, the bands are of lower intensity. Shifts of between 25 and 35 nm are characteristic of α-protonation and of approximately 60 nm for β-protonation.[14] UV spectra have been recorded on a number of charge-transfer complexes of pyrrole and its derivatives with, for example, tetracyanoethene, chloranil, iodine, quinone, picric acid, and trinitrobenzene, and, in some instances, thermodynamic parameters have been evaluated.[13] From the positions of the absorption maxima, estimates of the donor IP can be made (see, e.g., Ref. 353).

A number of authors have reported UV spectroscopic data for polypyrrole and its doped congeners (see, e.g., Refs. 54, 99, 301, 354, and 355 and references cited therein). The UV absorption spectrum of polypyrrole exhibits a peak at 3.0 eV ascribable to a $\pi \rightarrow \pi^*$ transition from the bonding π-orbital band, and the electron energy loss spectroscopy shows a peak at 7.0 eV for undoped film prepared electrochemically.[99,356] At low doping levels in polypyrrole perchlorate, three absorptions are present below the gap at 0.7, 1.4, and 2.1 eV attributable to the presence of polarons. At intermediate doping, the 1.4 eV absorption associated with transitions between the polaron levels in the gap disappears. At very high doping, two wide optical absorptions peaking at 1.0 and 2.7 eV are present below the gap, in agreement with the existence of two bipolaron bands, and the band-gap transition shifts to 3.6 eV.[301]

TABLE 1.29. UV SPECTRA OF MONOSUBSTITUTED PYRROLES IN SELECTED SOLVENTS

Substituent	Solvent	λ_{max} (nm) (log ε)	Ref.
2-NO_2	C_7H_{16}	227(3.51), 313(4.07)	351
	MeOH	231(3.61), 335(4.23)	343
		230(3.53), 336(4.11)	352
	Dioxan	230(3.08), 330(3.93)	351
	C_6H_{14}	194(3.82), 231(3.49), 316(4.05)	352
	THF	230(3.53), 333(4.15)	352
	H_2O	233(3.47), 352(4.13)	352
	MeCN	231(3.47), 335(4.12)	352
3-NO_2	C_6H_{14}	199(4.10), 246(3.80), 287(3.60)	352
	C_7H_{16}	245, 287	351
	MeOH	268(3.86), 315(3.73)	343
		222(3.55), 269(3.80), 313(3.65)	352
	H_2O	198(4.03), 223s(3.53), 281(3.79), 329(3.65)	352
	Dioxan	262(3.85), 307(3.68)	351
	THF	222s(3.53), 265(3.79), 310(3.64)	352
	MeCN	202(4.04), 224(3.54), 268(3.81), 314(3.65)	352
None	C_7H_{16}	210(3.88)	351
	Dioxan	208(3.71)	351
2-CHO	C_7H_{16}	245(3.69), 279(4.17)	351
	Dioxan	294(3.69), 321(4.22)	351
	MeOH	252s(3.79), 289(4.24)	343
3-CHO	C_7H_{16}	230, 258	351
	Dioxan	237(3.70), 264(3.51)	351
2-CH_3	C_7H_{16}	212(3.89)	351
	Dioxan	214(3.86)	351
3-CH_3	C_7H_{16}	211(3.81)	351
	Dioxan	212(3.90)	351

1.4.5. Infrared Spectroscopy

The extensive literature on the IR spectra of pyrrole and its substituted derivatives is well surveyed in Refs. 12–14, 357, and 358.

The IR and Raman spectra of pyrrole and its variously deuteriated derivatives have been investigated in detail and the 24 pyrrole normal vibrational modes assigned to observed absorptions on the basis of C_{2v} symmetry. Pyrrole has also been subjected to molecular vibrational analysis, in which valence force constants are adjusted to yield a least-squares fit between calculated and observed vibration frequencies.[152,172,173,359–361] Computed and experimental frequencies for the fundamental vibrations of pyrrole are listed in Table 1.30 and for the deuteriated derivatives, in Table 1.31. Detailed discussions of the assignments in Tables 1.30 and 1.31 are available in the references already given and in the extensive publications of Navarro and Orza.[368–371] The first to the fifth overtones of the pyrrole C–H stretching vibration have been recorded, the latter

TABLE 1.30. COMPUTED AND EXPERIMENTAL VIBRATIONAL SPECTRUM AND INTENSITIES OF PYRROLE[152]

Number	Symmetry	Approximate Assignment[a]	Computed Data				Raman[c]	IR[c]	IR[d]	IR[d]	IR[e]	IR[e]	Raman[f]	Raman[g]	IR[g]	IR[h]	IR[h]	Raman[i]	IR[i]	IR[i]	
			ν^a	ν^a	I^a	ν^b	Liquid	Liquid I	Liquid	Gas	Liquid I	Gas I	Liquid	Liquid	Liquid	Liquid	Gas	Liquid	Liquid	Gas	I[j]
1	B_2	N–H wag	611	474	153.7	474	565		561	465	560vs	474s	556	556	557			568	560	474	98
2	A_2	Ring torsion	608	605	0.0	613	618							615				618			
3	B_2	Ring torsion	612	615	23.6	605	647		652		649s	601m	646		649					602	21
4	A_2	C–H wag	728	707	0.0	712	711						708	712				712			
5	B_2	C–H wag	735	716	104.6	722		768s	735	721	733vs	720vs		734				735	733	720	100
6	B_2	C–H wag	865	832	3.7	830	837	839w	841	827	840m	826m	835	842	840			838	834	826	40
7	B_1	Ring *deform.*	885	868	2.5	877		844vw		875	867s	864		870	869			868	865	863	39
8	A_2	C–H wag	897	869	0.0	840	866	869m	869				865								
9	A_1	Ring deform.	895	880	1.3	879	880	884w	882	963	880m	881m		883	882			878	877	880	45
10	A_1	C–H deform.	1029	1021	41.8	1019	1015	1015vs	1016	1018	1013vs	1016s		1015	1015			1014	1010	1018	93
11	B_1	C–H deform.	1050	1046	22.2	1066	1045	1047vs	1051	1047	1047vs	1048s	1048	1051	1049			1047	1046	1049	87
12	A_1	C–H deform.	1076	1071	4.0	1075	1076	1076vs	1076	1088	1073vs	1074m	1072	1079	1076			1076	1072	1074	87
13	B_1	N–H deform.	1156	1144	6.5		1144	1146s	1145	1140	1143s	1134w	1144						1130	1134	23
14	A_1	C–C, C–N stretch	1163	1161	4.0	1148						1148		1148	1143			1144	1140	1148	29
15	B_1	C–H *deform.*	1294	1284	0.6	1308	1237	1289m	1287	1294	1286m	1287vw	1235	1240	1285			1284	1284	1287	12
16	A_1	C–H, C–N stretch	1382	1386	11.6	1391	1379	1384m	1387		1380s	1386vw	1379	1384	1384			1380	1383	1391	45
17	B_1	C–C, C–N stretch	1428	1416	3.6	1447		1418s	1420	1416	1418vs	1422s		1415	1417			1415	1415	1424	85
18	A_1	C–C, C–N stretch	1470	1463	7.4	1474	1468	1466s	1471	1466	1467s	1460	1469	1472	1470			1460	1467	1470	?
19	B_1	C–C, C–N stretch	1549	1551	13.3	1544	1528	1531s	1532	1536	1530s	1545m	1562		1567			1545	1568	1548	85
20	B_1	C–H stretch	3131	3113	4.7	3134	3100				3104s	3129m	3045	3055	3054	3102	3118	3102	3100	3116	51
21	A_1	C–H stretch	3145	3126	5.4	3118	3111		3108				3108	3105	3102	3112	3127	3110	3109	3125	44
22	B_1	C–H stretch	3160	3142	7.4	3161					3113s	3145m	3118	3114		3130	3145		3128	3140	51
23	A_1	C–H stretch	3171	3153	0.6	3148	3133		3133	3140			3138	3137	3134			3133		3148	?
24	A_1	N–H stretch	3620	3527	85.4	3529	3400		3410	3431	3410vs	3531s	3383	3408	3408			3407	3400	3527	99

[a] From Ref. 152.
[b] Ref. 172: additional band B_1 976 cm^{-1}.
[c] Ref. 362.
[d] Ref. 363.
[e] Ref. 364.
[f] Ref. 365.
[g] Ref. 366.
[h] Ref. 367.
[i] Ref. 368.

TABLE 1.31. COMPUTED AND EXPERIMENTAL VIBRATIONAL SPECTRA FOR DEUTERIATED PYRROLES

Number	Symmetry	Approximate[a] Assignment	1-^{2}H			2,3,4,5,-^{2}H			1,2,3,4,5-^{2}H		
			Calc.[a]	Calc.[b]	Expt.[c]	Calc.[a]	Calc.[b]	Expt.[c]	Calc.[a]	Calc.[b]	Expt.[c]
1	B_2	N–H wagging	353[d]	426[d]	372[d]	469	394[d]	460	352	366	369
2	A_2	Ring torsion	605	613	607	498	521	514	498	521	516
3	B_2	Ring torsion	611	605	603	501	502	515	494	499	501
4	A_2	C–H wagging	707	712	709	557	563	562	557	563	562
5	B_2	C–H wagging	715	723	716	577	586	597	574	567	569
6	B_2	C–H wagging	831[d]	688[d]	823[d]	705[d]	824[d]	686[d]	705	682	684
7	B_1	Ring deformation	837	809	827	847	848	848	904	872[d]	910[d]
8	A_2	C–H wagging	869	840	868	744	696	729	744	696	740
9	A_1	Ring deformation	867	862	869	913	900	897	890	891	891
10	A_1	C–H deformation	1016	1020	1010	781	787	786	778	784	784
11	B_1	C–H deformation	1073	995	1072	767	774	775	765	766	778
12	A_1	C–H deformation	1071	1071	1067	734	740	738	732	737	740
13	B_1	N–H deformation	914	924	906	1159[d]	1070[d]	1162[d]	809	793	804
14	A_1	C–C and C–N stretch	1152	1145	1130	1105	1072	1085	1094	1066	1068
15	B_1	C–H deformation	1267	1283	1237	950	926	955	1022	1008	1024
16	A_1	C–C and C–N stretch	1385	1380	1397	1341	1329	1320	1325	1317	1320
17	B_1	C–C and C–N stretch	1341	1390	1359	1407	1380	1409	1340	1317	1336
18	A_1	C–C and C–N stretch	1459	1474	1461	1361	1392	1399	1356	1390	1392
19	B_1	C–C and C–N stretch	1526[d]	1467[d]	1538[d]	1487	1537	1468	1456	1436	1456
20	B_1	C–H stretch	3113	3122	3115	2297	2308	2305	2297	2291	2305
21	A_1	C–H stretch	3127	3118	3126	2314	2330	2315	2314	2329	2325
22	B_1	C–H stretch	3142	3161	3142	2339	2333	2340	2339	2330	2347
23	A_1	C–H stretch	3154	3148	3148	2359	2376	2375	2358	2375	2376
24	A_1	N–H stretch	2591	2605	2606	3527	3529	3531	2592	2605	2607

[a] From Ref. 152.
[b] From Ref. 172.
[c] From Refs. 362 and 368.
[d] Inconsistencies between Refs. 152 and 172.

by the thermal lens technique. The vibrational line shapes exhibit a transformation from normal mode to local mode character with increasing level of excitation, the fifth overtone more closely reflecting properties of isolated bonds.[372] The acoustic relaxation of a range of molecules including pyrrole has been studied by monitoring of 10-GHz hypersound absorption,[373] and centrifugal distortion constants have been calculated for pyrrole and a number of isotopically labeled derivatives.[374]

The literature on the NH vibration of pyrrole (at ca. 3496 cm^{-1} in CCl_4 solution) continues to burgeon. Because of pyrrole's propensity to form intermolecular hydrogen bonds, it is not surprising that the position and intensity of its N–H stretching absorption varies widely with change of solvent. The band shifts and intensities have been used for the estimation of association data, and there have been many attempts to relate the solvatochromic shift to medium parameters (see, e.g., Refs. 375–377 and references cited therein). In a study aimed at the exploration of the nature of liquid CO_2, the displacement of the N–H stretching absorption of pyrrole dissolved in liquid CO_2 from its position in the vapor phase was found to be 130 cm^{-1} at 23°C, lying between the values for ethyl ethanoate (118 cm^{-1}) and diethyl ether (174 cm^{-1}) and much greater than those for hexane (24 cm^{-1}) and toluene (76 cm^{-1}) as solvents. Generally, liquid CO_2 behaves like a hydrocarbon solvent; the inconsistency between the pyrrole shift and other parameters is ascribed to specific H-bonding interactions.[378] A selection of frequency shifts for the pyrrole N–H stretching absorption measured for pyrrole and a range of donors in CCl_4 and extrapolated to infinite dilution is given in Table 1.32. Much additional information on the thermodynamics of interactions between pyrrole and other molecules measured spectroscopically and calorimetrically is available. Recent references to the latter include Refs. 380–387.

The pyrrole–pyridine system (see Ref. 14 for a review of earlier work in this area) has been intensively investigated; recent studies[388,389] have concentrated

TABLE 1.32. N–H STRETCHING FREQUENCY SHIFTS FOR PYRROLE AND A SELECTION OF DONORS AT INFINITE DILUTION MEASURED IN CCl_4[379]

Donor	$\Delta\nu$ (N–H) (cm^{-1})
Et_3N	331 ± 5
C_5H_5N	252 ± 3
Me_2SO	184 ± 3
DMA	170 ± 3
THF	153 ± 3
Et_2O	150 ± 3
Dioxan	127 ± 3
Me_2CO	92 ± 5
EtOAc	80 ± 3
MeCN	77 ± 3
Xylene	49 ± 3
Benzene	30 ± 3

on the effects of solvent on the H-bonded equilibrium. Values reported for the association enthalpy are (in kJ M^{-1}) in C_6H_{12} -18.0 ± 2.1, in C_6H_{14} -23.0, in CCl_4 -13.4 ± 2.9 and -14.2, in C_6H_6 -14.2 ± 0.8, and in toluene -13.4. Comparable calorimetric data are available, from which a model for solvation effects has been proposed. It has been suggested that pyrrole may simultaneously form NH . . . N and NH . . . π bonded species with pyridine. However, evidence has been presented that the steric effects obtaining for complex formation between pyrrole, 2,5-dimethyl- and 2,5-di-*t*-butyl-pyrrole, and pyridine and its 4-methyl, 2,6-dimethyl, and 2,4,6-trimethyl derivatives are similar, which argues against appreciable NH . . . π bonding.[390] These results have been disputed,[388] and more recent data measured for pyrrole and a number of pyridine derivatives in three solvents indicate a significant variation in the interaction between pyrrole and the variously alkylated pyridines (Table 1.33), suggesting the possibility of NH . . . π bonding, in agreement with other work.[391-393] Shifts in the N–H stretching absorption of pyrrole dissolved in benzene, *p*-xylene, and mesitylene indicate the formation of NH . . . π complexes and have been correlated with the ionization potentials of the proton acceptors.[394]

Pyrrole forms strong colinear hydrogen-bonded complexes with molecules containing electronegative atoms as evinced by the profound shifts in the N–H stretching frequency listed in Table 1.32. References to earlier work on the interactions between pyrrole and ethers or carbonyl compounds are available in Ref. 14. A considerable body of recent work has concentrated on H-bonding to sulfoxides, sulfones, and the corresponding sulfinamides and sulfonamides. Enthalpies of association with sulfoxides and sulfinamides are typically in the range -13 to -16 kJ M^{-1} and entropies of the order of -26 to -30 J M^{-1} K^{-1}. The H-acceptor power is found to be in the order DMSO >

TABLE 1.33. THERMODYNAMIC PARAMETERS FOR THE INTERACTION BETWEEN PYRROLE AND VARIOUS PYRIDINES, QUINOLINE, AND TRIETHYLAMINE[a,388]

	Solvent								
	n-Hexane			CCl_4			Toluene		
Acceptor	K(30°)	$-\Delta H$	$-\Delta S$	K(30°)	$-\Delta H$	$-\Delta S$	K(30°)	$-\Delta H$	$-\Delta S$
Pyridine	5.5	23.0	62	3.3	14.2	37	1.8	13.4	38
2-Methylpyridine	5.1	17.5	44	3.0	16.8	46	1.9	15.1	44
3-Methylpyridine	6.7	18.4	44	3.8	16.3	43	1.8	12.7	37
4-Methylpyridine	6.5	18.0	42	3.4	16.6	45	1.8	13.3	38
2,4-Dimethylpyridine	9.4	16.8	34	3.7	18.5	50	2.2	12.5	35
3,5-Dimethylpyridine	8.0	19.2	45	4.3	17.4	45	2.7	11.4	31
2,4,6-Trimethylpyridine	16.0	18.0	36	4.5	19.0	50	3.0	13.0	33
Quinoline				2.8	16.2	45			
Triethylamine				2.2	22.0	66	2.3	13.2	37

[a] K (L M^{-1}), ΔH (kJ M^{-1}), ΔS (J K^{-1} M^{-1}).

$MeSONMe_2$ > $(PhCH_2)_2SO$ > $PhSONMe_2$ ≈ Ph_2SO, and sulfones and sulfonamides are only weak H-bond acceptors.[395-398] The interactions between pyrrole and imino- and aminophosphanes have also been studied.[399] The weak band that appears as a shoulder about 20 cm^{-1} to low fequency of the main pyrrole NH band and of roughly one-twentieth of its intensity has been shown, by a study of the variation in the relative intensities of the two bands, to be a "hot" band, that is, one resulting from a transition from an energy state above the ground state.[400] Similar bands have been identified in substituted pyrroles.

The position of the N–H stretching vibration is sensitive to the number, type, and position of ring substituents; the effects of substituents are additive and independent provided that adjacent substituents do not experience severe mutual steric interactions. The effect of a substituent is always greater when at an α rather than a β position. Frequency shifts from 3496 cm^{-1} are listed in Table 1.34. A number of authors have used the frequency shifts of the pyrrole N–H stretch with appropriate H-bond acceptors such as THF[401] or DMF[32,402] to probe the transmission of electronic effects in substituted pyrroles. In this way, linear correlations have been established between frequency shifts (as a measure of the pK_a of a substituted pyrrole) and σ inductive constants.

TABLE 1.34. NH IR FREQUENCY SHIFTS FOR SUBSTITUTED PYRROLES[a]

Substituent	α-Substitution Δν (cm^{-1})	β-Substitution Δν (cm^{-1})
NO_2	− 49	− 29
COMe	− 45	− 18
COPh	− 42	− 18
CHO	− 36	− 18
CO_2Et	− 32 (syn)	− 13
CO_2Et	− 14 (anti)	
CN	− 22	− 12
Ph	− 12	− 7
Me	− 9	+ 2

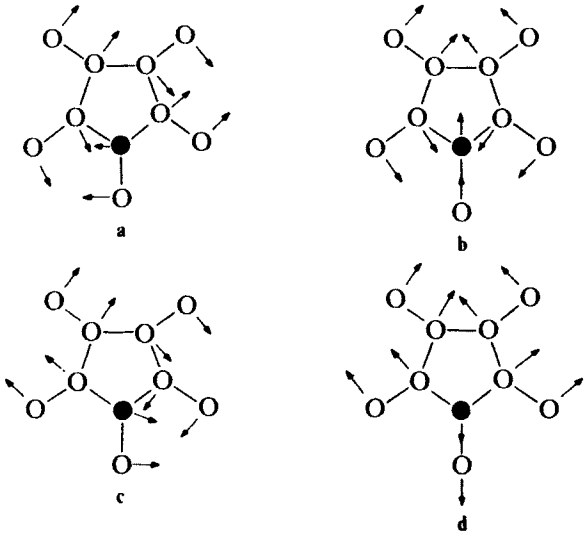
[a] From Refs. 13 and 14.

Substituted pyrroles usually have three IR absorption bands in the 1600–1375 cm^{-1} region (Table 1.35) attributable to three of the in-plane ring deformation modes **41a–d**. The absorption positions are insensitive to substituent type, whereas the band intensities are generally increased by increasing electron withdrawal by a substituent. Absorptions in the 1300–1000 cm^{-1} region (Table 1.35) are ascribable to β-CH modes corresponding to in-plane C–H deformations modified, where appropriate, by interactions with the in-plane N–H deformation at approximately 1140 cm^{-1}. The number, positions, and intensities of these bands depend on the number, location, and electronic nature of the substituents, and the pattern of absorptions can be used for structure characterization as in substituted benzenes. Thus 1-, 2-, and 3-alkylpyrroles can be distinguished by their bands at approximately 1092 and

TABLE 1.35. IR ABSORPTION BANDS OF MONOSUBSTITUTED PYRROLES[a]

Substituent	Ring Stretching				In-Plane		Out-of-Plane			Ref.
	a	**b**	**c**	**d**	β_{CH}	β_{CH}	γ_{CH}	γ_{CH}	γ_{CH}	
Position 1	1549 ± 3 (15–25)	1477 ± 7 (25–185)		1394 ± 10 (15–35)	1069 ± 6 (100–240)	1027 ± 9 (35–135)		926 ± 4 (20–140)	722 ± 2 (375–475)	403
Position 2	1558 ± 9 (20–80)	1471 ± 3 (20–70)	1415 ± 8 (20–325)		1088 ± 18 (25–450)	1033 ± 13 (40–400)	961 ± 8 (15–45)	929 ± 3 (10–75)	882 ± 4 (10–120)	404
Position 3	1549 ± 7 (20–180)	1491 ± 9 (55–195)	1427 ± 4 (60–160)		1077 ± 3 (60–100)	1041 ± 4 (30–150)	953 ± 4 (30–110)		886 ± 2 (10–20)	357, 405, 14

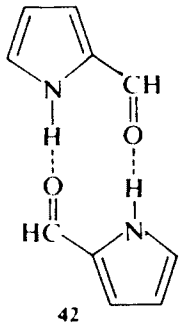
[a] Measured in $CHCl_3$. Band positions in cm^{-1}, apparent extinction coefficients in parentheses.



41

1064 cm^{-1}, 1117, 1095, and 1024 cm^{-1}, and 1066 cm^{-1}, respectively. 2,3-Dialkylpyrroles absorb near 1110 and 1070 cm^{-1} and the 2,4- and 2,5-analogs near 1120 and 1030 cm^{-1}, respectively.[270] Most of the bands in the 1000–600 cm^{-1} region can be attributed to γ-CH modes corresponding to out-of-plane C–H deformations (Table 1.35). There are large variations with substituent.

In general, the frequencies of substituent groups in pyrrole derivatives are those expected for substitution at an electron-rich aromatic system. 1-Acyl- and 1-alkoxycarbonylpyrroles have carbonyl stretching bands approximately 50–80 cm^{-1} higher than those of the corresponding 2- or 3-substituted counterparts and at much higher wavenumbers than in simple amides and urethanes [e.g., ν_{CO} for 1-acetyl- and 1-methoxycarbonylpyrrole (CCl_4 solutions) are 1732[406] and 1753[407] cm^{-1}, respectively]. This presumably reflects the balance between a reduced resonance interaction between the nitrogen lone pair (which is part of the pyrrole aromatic sextet) and the substituent carbonyl group and the opposing inductive effect of the nitrogen atom. The IR and Raman spectra of liquid and polycrystalline 2-formylpyrrole and its deuteriated derivatives have been recorded between 40 and 4000 cm^{-1}. Of the 30 expected fundamental bands, assignments have been made for 23 gas-phase and 30 condensed-phase bands.[408] Solutions in CCl_4 of 2-formylpyrrole and its 4-bromo, 5-bromo, and 4,5-dibromo derivatives exhibit N–H and C–O stretching-band doublets (Table 1.36), the lower wavenumber components of which arise from intermolecular association but not, at the concentrations cited, simply to the dimer **42**.[409] At very low concentrations, the associated form may be such a closed dimer,[410,411] and thermodynamic parameters for the association have been estimated as $-\Delta H^0 \approx 29$ kJ M^{-1}, $-\Delta S^0 \approx 64$ J K^{-1} M^{-1}.[412] The aldehydes listed in Table 1.36 are thought to exist in the *N*,*O*-syn conformation **43** (the carbonyl



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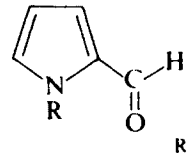


R = H, Me

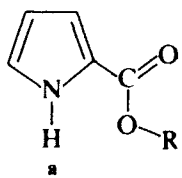
43

TABLE 1.36. N–H AND C=O STRETCHING BANDS FOR 2-FORMYLPYRROLE AND C=O STRETCHING BANDS FOR 2-FORMYL-1-METHYLPYRROLE IN CCl_4[a]

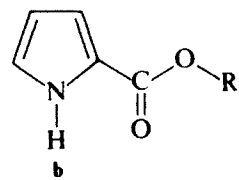
	N–H Region		C=O Region	
Substituent	ν_1	ν_2	ν_1	ν_2
None	3461 (40)	3274 (60)	1667 (55)	1656 (45)
4-Bromo	3448 (41)	3256 (59)	1672 (56)	1660 (44)
5-Bromo	3442 (50)	3200 (50)	1677 (60)	1657 (40)
4,5-Dibromo	3430 (39)	3210 (61)	1672 (53)	1658 (47)
1-Methyl	—	—	1668	
1-Methyl-4-bromo	—	—	1679 (92)	1668 (8)
1-Methyl-3,5-dibromo	—	—	1670	
1-Methyl-4,5-dibromo	—	—	1676	

[a] From Ref. 409, concentrations ca. 0.3–0.9 mg g^{-1}; band positions (cm^{-1}) are followed in parentheses by their areas expressed as percentages of the total absorption in a particular region.

band doublet observed for 4-bromo-2-formyl-1-methylpyrrole is a consequence of Fermi resonance). Pyrrole carboxylic acid esters have also been closely studied (Table 1.37). The lowest wavenumber CO bands of the N–H esters are attributed to associated forms containing more than two molecules of the esters; the remaining band doublets are assigned to anti–*s*-trans **44a** (higher wavenumber band) and syn–*s*-trans **44b** (lower wavenumber band) conformers. Approximate enthalpy differences for the anti → syn and syn → associated forms conversions are -4.8 and -21.6 kJ M^{-1}, respectively.[409] The absence of carbonyl band doubling in the 1-alkylpyrrole-2-esters suggests that they exist in solution in only one form, probably syn–*s*-trans (analogous to **44b**). 1-Alkylpyrrole



a



b

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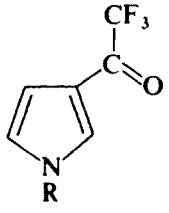
TABLE 1.37. C=O STRETCHING ABSORPTIONS FOR PYRROLE CARBOXYLATES[a]

R^1	R^2	R^3	R^4	R^5	ν_{CO} (cm^{-1}) in CCl_4		
H	CO_2Me	H	H	H	1730	1702	1678
H	CO_2Et	H	H	H	1724	1700	1686
H	CO_2t-Bu	H	H	H	1717	1694	1677
Me	CO_2Me	H	H	H		1710[b]	
Et	CO_2Me	H	H	H		1712	
n-Bu	CO_2Me	H	H	H		1709[c]	
i-Pr	CO_2Me	H	H	H		1704[c]	
t-Bu	CO_2Me	H	H	H		1713[c]	
Me	CO_2Et	H	H	H		1706	
Me	CO_2t-Bu	H	H	H		1701	
Me	CO_2Me	H	Br	H		1715	
Me	CO_2Me	H	H	Br		1712	
Me	CO_2Me	H	Br	Br		1713	
t-Bu	H	CO_2Me	H	H		1717[c]	
Me	CO_2Me	H	H	CO_2Me	1735	1712	
Et	CO_2Me	H	H	CO_2Me	1733	1710	
n-Bu	CO_2Me	H	H	CO_2Me	1733	1709	
i-Pr	CO_2Me	H	H	CO_2Me	1734	1710	
t-Bu	CO_2Me	H	H	CO_2Me	1731	1715	
1-Adamantyl	CO_2Me	H	H	CO_2Me	1735	1716	
Me	H	CO_2Me	H	CO_2Me	1726[d]	1715	
Et	H	CO_2Me	H	CO_2Me	1728[d]	1712	
n-Bu	H	CO_2Me	H	CO_2Me	1725[d]	1712	
i-Pr	H	CO_2Me	H	CO_2Me	1726[d]	1711	
t-Bu	H	CO_2Me	H	CO_2Me	1724[d]	1715	
1-Adamantyl	H	CO_2Me	H	CO_2Me	1726[d]	1713	
t-Bu	CO_2Me	CO_2Me	H	H	1737	1722	

[a] From Refs. 409 and 413; further data on MeCN solutions, N–H stretching bands, and CO overtones are available therein.
[b] 1713 cm^{-1} in Ref. 413.
[c] Broadened to high wavenumber.
[d] Estimated shoulder position.

diesters, however, display carbonyl band multiplicity, which may reflect conformational heterogeneity.[413] 3-Trifluoroacetylpyrroles are known from ^{19}F NMR studies to exist in solution as mixtures of syn (**45a**) and anti (**45b**) forms, but they do not display carbonyl band doubling presumably because the field effects



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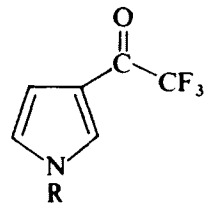

b

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experienced by the ketone carbonyl group are not sufficiently different in the two forms.[414]

The γ_{CN} band for several cyanopyrroles is split by Fermi resonance but in general, 3-cyanopyrroles absorb about 10 cm^{-1} higher than the 2-substituted analogs, which is a reflection of reduced resonance interaction through the β position.[415] This effect is also apparent in comparisons between 2- and 3-substituted carbonyl derivatives (see, e.g., Refs. 407, 416, and 417).

Infrared spectra of polypyrrole in its neutral and oxidized forms were first reported in the early 1980s,[418,419] since when numerous reports on experimental and theoretical aspects of IR and Raman spectra have appeared (see, e.g., Refs. 52, 53, 258, 261, 262, 354, 356, 420, and 421 and references cited therein). The spectrum of polypyrrole perchlorate shows a featureless decrease in absorption from 4000 to approximately 1600 cm^{-1}, below which are the pyrrole ring vibrations and the perchlorate anion vibrations. The ring vibrations in the oxidized and neutral polymers are similar, as expected, since they contain the same pyrrole moiety.[258] Maxima in the IR spectrum of polypyrrole are reported at 1644, 1543, 1453, 1305, 1167, 1040, and 895 cm^{-1} [261] and in the region of 1500, 1300, 1180, 920, and 775 cm^{-1}.[418] Infrared measurements of polypyrrole nitrate are argued as demonstrating that the processes involved in electrochemical oxidation ("doping") and reduction ("dedoping") are actually intercalation and deintercalation of counterions between polypyrrole chains.[53] The intensity of the Raman-scattered radiation is weak for all excitation wavelengths. As in the case of IR spectra, no appreciable difference can be detected as being induced by change of counterion[354] (see also Refs. 422 and 423). High-resolution electron energy loss spectroscopy (HREELS) and Auger spectroscopy have been used to explore the surface characteristics of polypyrrole films; [356,424] the HREELS spectra show broad bands corresponding to known polypyrrole vibrational modes.[356]

1.4.6. Mass Spectrometry

The mass spectrometry of heterocyclic compounds is well reviewed in a valuable book.[425] Useful accounts may also be found elsewhere.[12,13,405] Details of the mass spectrometry of the pyrrole pigments are to be found in Refs. 426 and 427. The technique has been applied to pyrrole polymers.[428] Recent developments are more concerned with studies of the ion physics involved in activation and decomposition than with "traditional" elucidation of fragmentation pathways.

The electron-impact mass spectrum of pyrrole yields a base peak molecular ion (m/z 67) and significant fragment ions at 41, 40, 39, and 28 mass units, which have been rationalized in terms of the fragmentation pathways shown in Figure 1.4. The most abundant fragment (m/e 39) is the cyclopropenyl ion accompanied by less than 1% of C_2HN^+; next in intensity is the 2-azirine ion (m/e 41) resulting from loss of acetylene; a third peak (m/e 40), only slightly weaker than

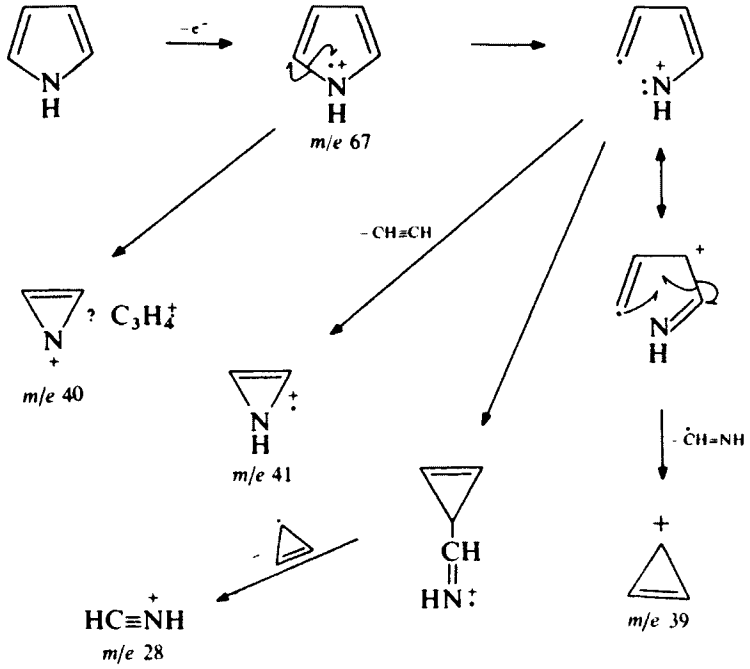


Figure 1.4. Principal mass spectrometric fragmentations for pyrrole.

its neighbors, consists of two fragments $C_3H_4^+$ (corresponding to loss of HCN) and (perhaps) the azacyclopropenyl ion in the ratio 4.5:1.[429,430] Charge-exchange mass spectrometry has been used to determine the appearance potentials of the pyrrole molecular ion and the fragment ions at *m/e* 41, 40, and 28 as 8.4 ± 0.1, 12.2 ± 0.1, 12.5 ± 0.2, and 12.05 ± 0.2 eV, respectively; the appearance potential of the molecular ion is in reasonable agreement with the approximate value of 8.2 eV from PES studies. The ion at *m/e* 41 is clearly associated with ejection of the $6a_1$ electron, as perhaps also are the ions at *m/e* 40 and 28; this is based on the MO PES assignments quoted in Ref. 137.[431] Mass-analyzed ion kinetic energy–collision-induced dissociation mass spectrometry (MIKE/CID) has been used for detailed analyses of the decompositions of ions produced on chemical ionization. It has been shown, for example, that the ion at *m/z* 96 generated by ethylation of pyrrole or protonation of 1-ethylpyrrole has a different structure depending on its origin[432] (see also Refs. 433–435). Methane and isobutane mass spectra of pyrrole are reported in Ref. 436. Ion beam techniques have been used extensively to study the nature of the $[C_4H_5N]^+$ ion derived from a variety of sources.[437–440] Photoemissions in the region 200–600 nm from electronically excited fragments such as CH and NH radicals resulting from pyrrole by electron impact and dissociation have been studied and appearance potentials measured.[441] Most of the ion currents in the electron-impact mass spectra of η^5-pyrrolyl and η^1-*N*-pyrrolyl transition-metal

complexes arise from metal-containing ions with intact pyrrole ligands as befits the stability of the ligand.[278] Mass spectrometric measurements of the ion–molecule equilibrium pyrrole + $Cl^- \rightleftarrows$ pyrrole·Cl^- yield a binding free energy of chloride ion to pyrrole at 300 K of about 58.6 kJ M^{-1} [442] (see also Ref. 443) and pulsed high-pressure mass spectrometric studies of the clustering of $CH_3NH_3^+$ with pyrrole give estimates of the enthalpy and entropy of dissociation as 77.9 ± 4.2 kJ M^{-1} and 87.9 ± 8.4 J K^{-1} M^{-1}, respectively.[444] Ion cyclotron resonance equilibrium and bracketing experiments have been used to demonstrate the preference for pyrrole α-protonation by 0–12.1 kJ M^{-1}; the proton affinity at the α position is found to be 875 kJ M^{-1}. MNDO calculations support these findings, the proton affinities at the 1, 2, and 3 positions being estimated as 783, 846, and 837 kJ M^{-1}, respectively.[25] Bond lengths and polarizabilities of a range of molecules and their molecular ions, including pyrrole, have been calculated by the MNDO method with addition of isotropic atomic polarizability contributions to the molecular polarizability components; the value obtained for pyrrole (7.94×10^{-24} cm^3) is in perfect agreement with experiment, and the polarizability of the molecular ion is somewhat higher (8.16×10^{-24} cm^3).[118] Resonance dissociative electron capture by pyrrole yields as base peak the $NC_4H_4^-$ ion corresponding to addition of an electron and elimination of a hydrogen atom. Additionally, peaks are observed at $(M\text{-}2H)^-$, $(M\text{-}3H)^-$ and, for ions formed by the capture of electrons with disintegration of the ring, ($NC_2H_2^-$, NC_2H^-, $C_3H_3^-$).[445]

The mass spectrum of 1-methylpyrrole is characterized by a high abundance peak at M-1 resulting from loss of a hydrogen atom from the methyl group (**46**→**47**). Studies of 1-methyl[^{13}C]pyrrole have established that the immonium ion rearranges to a *C*-protonated pyridinium ion, which can subsequently undergo hydride shift before characteristic loss of $H^{12}CN$ or $H^{13}CN$; the ratio of labeled and unlabeled fragment ions *m/e* 54 and *m/e* 53 corresponding to M-1-HCN is about 2:1 (Figure 1.5).[446] 1-Methylpyrroles additionally undergo α-

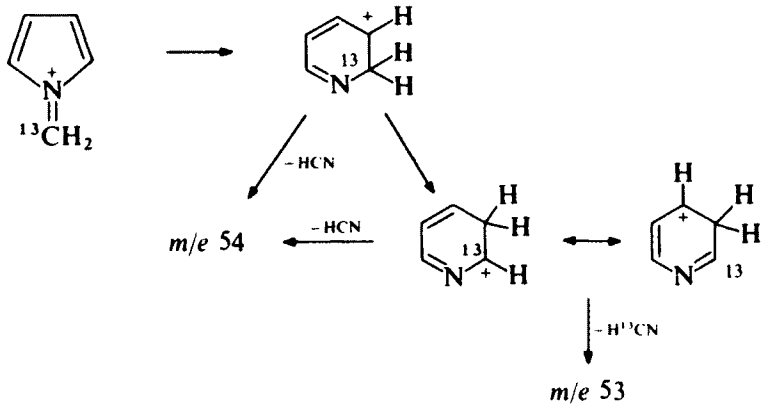
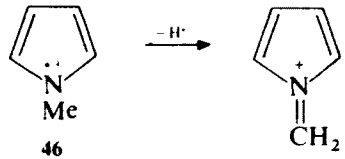


Figure 1.5. Rearrangement and fragmentation of 1-[^{13}C]methylpyrrole.



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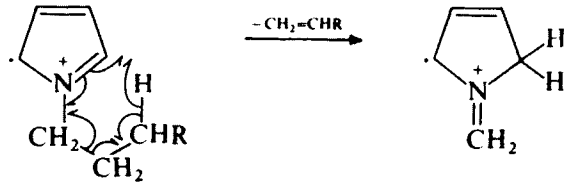
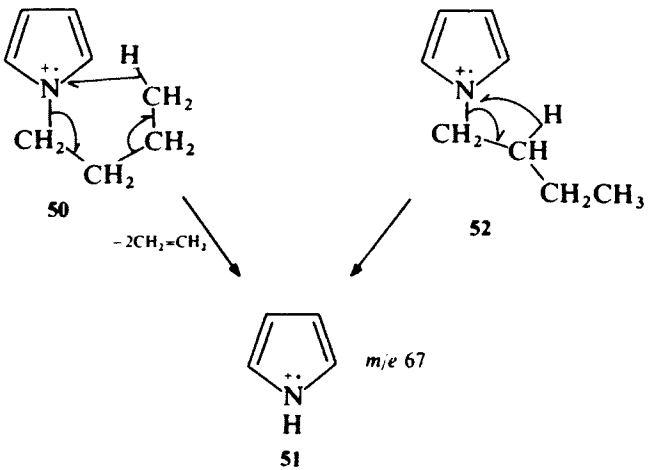


48 49

cleavage to give CH_3^+ and rearrangement of the molecular ion and subsequent loss of $CH_3N^+{\equiv}CH$. The base peak at *m/e* 81 in the spectra of 1-*n*-pentyl- and 1-*n*-butyl pyrrole has been shown, by detailed deuterium labeling experiments, to arise from the rearrangement (**48** → **49**) with the extrusion of the alkene. The ion at mass 80 in both compounds consists entirely of the $C_5H_6N^+$ species **47** arising from α-cleavage. The ion at mass 67 in these compounds is virtually homogeneous, corresponding to $C_4H_5N^+$, and is generated via two pathways, **50** → **51** and **52** → **51**.[447] 1-Benzylpyrrole has a simple mass spectrum in which



50 52 51

the tropylium ion (*m/e* 91), arising from α-cleavage of the *N*-substituent, is the base peak.[448] Information on some 1-arylpyrroles is available in Refs. 285, 429, 449, and 450.

For *C*-alkylpyrroles the predominant fragmentation involves β-cleavage of the alkyl substituent (Figure 1.6) to yield azafulvene cations. These are believed

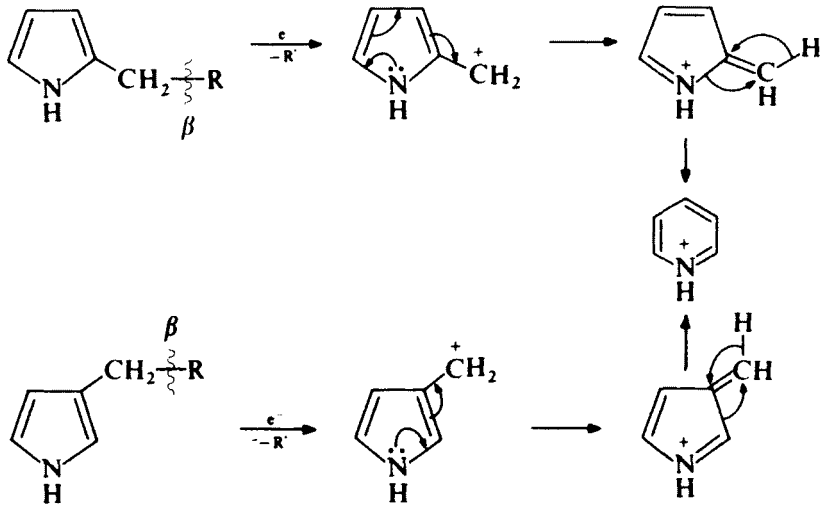


Figure 1.6. Principal mass spectrometric fragmentations for *C*-alkylpyrroles.

to rearrange to a common pyridinium ion, often the base peak, whose stability suppresses further fragmentation.

C-Formyl, *C*-acyl, and *C*-alkoxycarbonyl derivatives of pyrrole show a strong tendency to fragment to the resonance-stabilized acylium ion (Figure 1.7). α-Acylpyrroles also yield a relatively intense fragment at *m/e* 66 corresponding to complete loss of the acyl group. This mode of fragmentation is less important for the β-isomers, which supports the proposal that ejection of the 2-substituent is facilitated by a 1,2-hydrogen shift.[430] Benzoylpyrroles fragment to give both the pyrrolyl and phenyl acylium ions whose relative abundance is a function of the

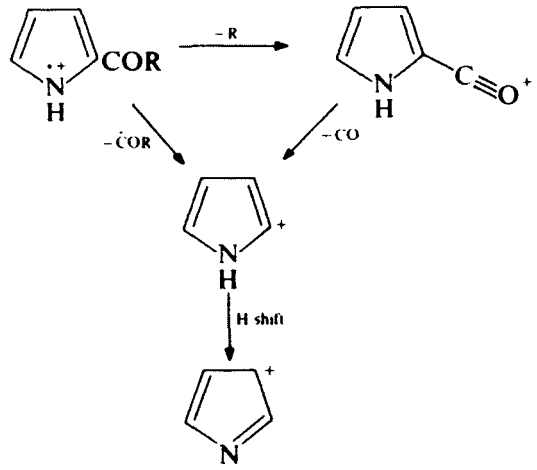


Figure 1.7. Principal mass spectrometric fragmentations for *C*-acylpyrroles.

presence of stabilizing substituents in the phenyl ring; dipyrrolylketones fragment similarly.[451-453] Thioketone analogs also fragment to the corresponding thioacylium ions, but the major fragmentations generally involve loss of the SH radical.[454]

Pyrrolecarboxylic esters, while fragmenting in a manner similar to that of their benzenoid counterparts, display additional cleavage paths. The more important pathways for esters and acids are shown in Figure 1.8. A substantial

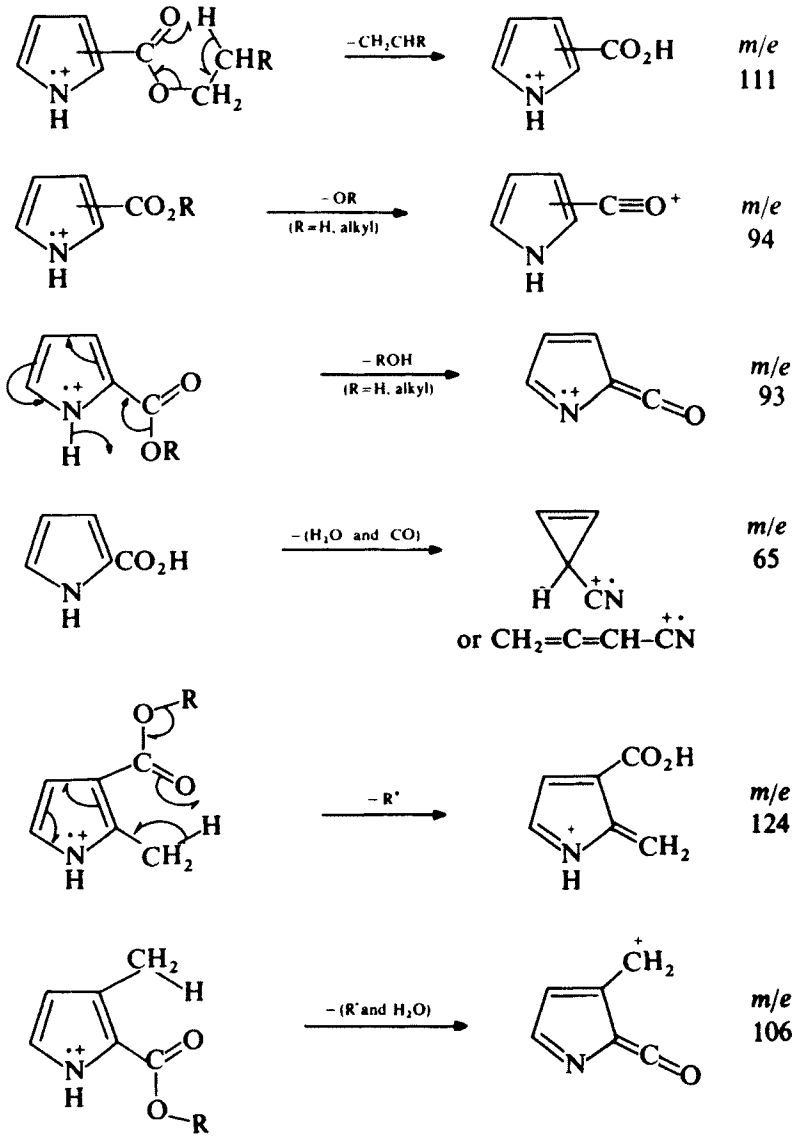


Figure 1.8. Principal mass spectrometric fragmentations for pyrrole carboxylic acids and esters.

amount of additional information on pyrrole esters and their substituted derivatives is available in Ref. 430 and on polypyrrolic compounds, in Refs. 425 and 454.

1.4.7. Photoelectron Spectroscopy

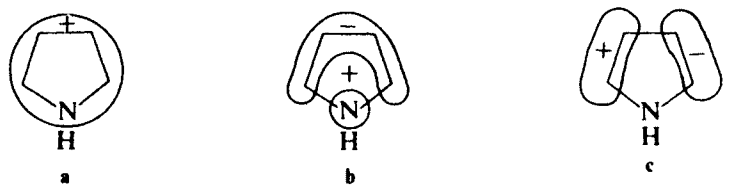
The He (I_α) photoelectron spectrum of pyrrole has been studied by several groups (see Refs. 95 and 455–457 and references cited therein); there is generally close agreement between the experimentally measured vertical ionization potentials (cf. 8.02, 9.05, 12.85, 13.57, 14.27, 14.80, 18.20, 18.90 eV;[95] 8.2, 9.2, 12.7, 13.7, 14.3, 14.8, 17.4 eV;[457] and 8.2, 9.2, 12.8, 13.5, 14.3, 14.8, 17.5 eV[458]). The first two bands have resolved vibrational structure; bands 3–6 are very broad and overlapped; band 7 is weak, extremely broad, and relatively flat.[95,457] Ionization potentials (IPs) for pyrrole and some monosubstituted derivatives have been measured by photoionization[459,460] and electron-impact methods;[461] values so

TABLE 1.38. FIRST AND SECOND IONIZATION POTENTIALS FOR SUBSTITUTED PYRROLE DERIVATIVES

Substituent							
1	2	3	4	5	1st IP (ev)	2nd IP (ev)	Ref.
Me	H	H	H	H	8.09 ± 0.01	8.83 ± 0.03	459
Me	H	H	H	H	7.95 ± 0.05	8.80 ± 0.05	462
n-Bu	H	H	H	H	7.87 ± 0.02		459
H	Me	H	H	H	7.78 ± 0.01	8.88 ± 0.03	459
H	Me	H	H	H	8.01		461
H	Et	H	H	H	7.97		461
H	*t*-Bu	H	H	H	7.95		461
H	Me	H	Me	H	7.54 ± 0.02	8.52 ± 0.03	459
H	H	Me	H	H	7.90 ± 0.02	8.62 ± 0.03	459
H	CO_2Me	H	H	H	8.65		461
H	COMe	H	H	H	8.72		461
H	CHO	H	H	H	8.93		461
H	$COCF_3$	H	H	H	9.18		461
H	NO_2	H	H	H	9.30		461
H	Me	CO_2Et	Me	H	7.95	8.83	460
H	Me	CO_2Et	Me	Me	7.82	8.90	460
H	Me	CO_2Et	Me	COMe	8.23	9.19	460
H	Me	CO_2Et	Me	CO_2Et	8.15	9.03	460
H	Me	CO_2Et	Me	Cl	7.94	9.08	460
H	Me	CO_2Et	Me	NO_2	8.78	9.62	460
H	CO_2Et	Me	H	Me	7.91	8.95	460
H	CO_2Et	Me	Me	Me	7.71	8.55	460
H	CO_2Et	Me	COMe	Me	8.26	9.13	460
H	CO_2Et	Me	CO_2Et	Me	8.15	9.03	460
H	CO_2Et	Me	Cl	Me	8.03	8.87	460
H	CO_2Et	Me	Br	Me	8.03	8.79	460
H	CO_2Et	Me	NO_2	Me	8.76	9.67	460

obtained are listed in Table 1.38. The first IPs correlate reasonably with σ_p and/or σ_p^+ constants, reflecting the extent of electronic interaction between the substituents and the pyrrole ring; alkyl substituents serve to lower the IP, whereas it is raised by electron-withdrawing groups. The first IP is affected less by *N*-methylation than *C*-methylation, because ionization is from the π_3 orbital having a node at nitrogen. The second IP is affected more by 3-methylation than 2-methylation, which reflects the electron density distribution in the π_2 MO (see later). The nitro group induces shifts of the same order of magnitude to higher IP for both the first and second IPs, confirming the important contribution of its inductive effect. The technique of multiphoton ionization has been applied to pyrrole and 1-methylpyrrole, yielding values for the ionization potentials as 8.203 ± 0.004[463] and 8.207 ± 0.003[340] eV (pyrrole) and 7.94 ± 0.02 eV[340] (1-methylpyrrole) (see also Refs. 464 and 465). Charge-exchange mass spectrometry has also been used for the measurement of the appearance potential of the $C_4H_5N^+$ ion as 8.4 ± 0.1 eV.[431]

Combination of the five pyrrole p_z atomic orbitals produces five molecular orbitals, three of which are occupied in the ground state; their shapes and nodal characteristics are shown in **53a–c**. Orbital π_1 (**53a**), which has symmetry described by the $1b_1$ irreducible representation, has no node and extends over the entire ring. Orbital π_2 (**53b**), symmetry $2b_1$, has nodes between nitrogen and the adjacent carbon atoms, and π_3 (**53c**), symmetry $1a_2$, has nodes at the



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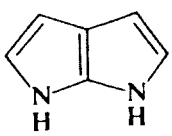
heteroatom and between the β carbon atoms. Although the three bands of lowest energy were initially assigned, on the basis of simple Hückel theory, to the ejection of electrons from the three occupied π MOs,[458] later observations and calculations suggested revised assignments. The need for such reassignment is confirmed experimentally by the determination of the asymmetry parameter β (which ranges from -1 to $+2$ and is usually 0.2–1.0 units higher for ionization from π-orbitals than from σ-orbitals) via measurements of the angular distributions in the photoelectron spectrum. High β-values (ranging from 0.76 to 1.15) are reported for only the first two bands (corresponding to ionization from π_3 and π_2, respectively); the third π-band is assumed to lie in the 12.2–15.5-eV region, overlapped with one or more σ-bands, which may explain why only relatively low β-values are observed.[457]

Numerous theoretical investigations of increasing complexity and power (far outnumbering the experimental PES studies) have been applied to the problems of the estimation of ionization energies and of orbital assignments to the

experimental data [see, e.g., Refs. 94 (CNDO, INDO, HAM/3, ab initio), 105 (INDO-CI), 113 (MINDO/3), 137 (ab initio beyond the Hartree–Fock approximation and references cited therein), 143 (ab initio multireference CI), 144 (symmetry-adapted cluster–CI), 148 (X_α multiple-scattering theory), 466 (INDO, CNDO), 467 (HAM/3), 468, and 469 (ω-technique), 470 (all bond ZDO), 471 (effective Hamiltonian), and 472 (double ζ and minimal-basis ab initio). Some of the semiempirical and ab initio predictions are listed in Table 1.4, and other recent results are compared in Refs. 95, 143, and 144. Total agreement obtains only for assignments of the first two IPs (to the $1a_2$ and $2b_1$ π MOs). Difficulties in the experimental assignment of the $1b_1$ π-orbital stem from the low purity of the $^2B_1$ configuration (only ca. 50%),[95,143] arising from mixing with shake-up configurations, that is, a breakdown of the orbital interpretation. Mixing with shake-up configurations is expected to become more important for the higher ionization peaks. This is probably the reason for the increasing discrepancy between the "3-excited" SAC–CI calculations (which include only up to three-electron excitations, including ionization) and experiment in deeper regions of the ionization potential, since the former are not well suited to the calculation of shake-up states.[144]

Ionization potentials have been calculated by MNDO and ab initio STO-3G methods (the latter utilizing MNDO-refined geometries) for pyrrole, pyrrolo-, and thieno-[2,3-*b*]pyrrole (**54** and **55**) and pyrrolo- and thieno-[3,2-*b*]pyrrole (**56** and **57**). Calculated results and experimental data (where available) are given for the fused heterocycles in Table 1.39.[117] There is some disagreement between these and previously published[473] assignments for the two highest occupied levels of **54** and **55**, which may stem from the use of different methods of calculations and/or geometries. Data have also been reported for some pyrrolotropones and orbital assignments deduced by experimental correlations and semiempirical calculations.[475]



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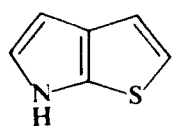

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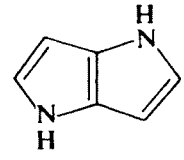

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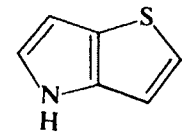

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The He(I) and He(II) photoelectron spectra of 2-formylpyrrole, of its imine derived from *t*-butylamine and of square-planar complexes of the latter with $M(CO)_2$, where M = Rh and Ir have been recorded.[476] The band at 8.77 eV for the aldehyde corresponds to ionization from the π (a_2) orbital of the pyrrole ring, about 0.5 eV higher than in pyrrole itself, and the π-ionization from b_1 is to be found at 9.75 eV overlapped with a band corresponding to oxygen lone-pair ionization. The two π-ionizations for the imine occur at 7.90 and 9.00 eV, that is, lowered by approximately 0.2–0.3 eV compared with pyrrole; these bands are further lowered to 7.39 and 8.21 eV, and 7.71 and 8.40 eV on complex formation

TABLE 1.39. THEORETICAL (MNDO AND ab initio) AND EXPERIMENTAL IONIZATION POTENTIALS (eV) FOR PYRROLO- AND THIENO-[2,3-*b*]- AND [3,2-*b*]-PYRROLES (**54**–**57**)

Compound	MNDO		ab initio		Experiment[a]
54	$3b_1$	7.96	$3b_1$	5.07	7.46
	$2a_2$	8.22	$2a_2$	5.91	7.91
	$2b_1$	10.07	$2b_1$	8.68	9.73
	$1a_2$	12.38	$8a_1$	11.51	11.47
55	$5a''$	8.56	$5a''$	5.47	7.97
	$4a''$	8.86	$4a''$	6.10	8.31
	$3a''$	10.43	$3a''$	8.51	9.89
	$2a''$	12.19	$15a'$	10.32	11.45
56	$3a_u$	7.84	$3a_u$	4.89	
	$2a_u$	8.34	$2a_u$	6.14	
	$2b_g$	9.81	$2b_g$	8.36	
	$7a_g$	12.44	$7a_g$	11.47	
57	$5a''$	8.44	$5a''$	5.39	7.70
	$4a''$	8.99	$4a''$	6.11	8.24
	$3a''$	10.29	$3a''$	8.49	9.66
	$2a'$	12.27	$15a'$	10.13	11.30

[a] From Refs. 473 and 474.

with Rh and Ir, respectively. Very little π-backbonding occurs from the metal to the imine ligand.

Photoelectron spectroscopy has been used in studies of the conformations of 2-(2-furyl)- and 2-(2-thienyl)-pyrrole,[41] 1,1′-bipyrrole and some substituted derivatives,[477] and 1-arylpyrroles.[123] Results of these investigations are discussed in a later section.

Photoelectron spectroscopy and related theoretical calculations have been applied by several groups to the study of the electronic structure of polypyrrole (see, e.g., Refs. 97, 99, 165, and references cited therein). Most of the valence-band features in the UPS of conducting doped polypyrrole films can be explained by states derived from the orbitals of the pyrrole monomer and the associated anions; the spectra are consistent with short conjugation lengths and large amounts of disorder.[478] The density of states computed from the results of band structure calculations at the Hartree–Fock ab initio level on neutral polypyrrole compares well with experimental data.[97]

The intensities and energies of satellite (shake-up) peaks in the X-ray photoelectron spectrum of gaseous pyrrole have been determined [Mg(K_α) or Al(K_α) radiation] and core ionization potentials measured as C(1*s*) 289.96(7) and 290.77(7), N(1*s*) 406.15(4) eV.[479] These differ somewhat from thin film-derived data: C(1*s*) (average) 284.8, N(1*s*) 400.4 eV[480] and C(1*s*) 285.7 and 284.8 eV, and N(1*s*) 401.2 eV,[481] but are very close to earlier gas-phase data; C(1*s*) 289.8 and 290.8, N(1*s*) 406.1 eV.[482] The C(1*s*) band is split because of the presence of nonequivalent carbon atoms. The additional small peak accompanying the main C(1*s*) line in the pyrrole spectrum has been interpreted as being

due to a shake-up phenomenon involving charge transfer from nitrogen to carbon,[480,483] a view supported, qualitatively, by the results of CNDO/2 calculations.[479] The adsorption of pyrrole on an oxidized iron surface has been studied by X-ray PES and core ionization potentials measured as 289.9 and 406.0 eV (gas phase) and 284.5 and 398.8 eV (adsorbed). The results suggest that pyrrole bonds via electron donation from the $1a_2$ π-MO to the surface.[484]

The carbon and nitrogen *K*-shell spectra of gaseous pyrrole have been recorded by electron energy-loss spectroscopy (ISEELS) under electric dipole scattering conditions, with the spectra dominated by transitions to unoccupied valence states of π and σ symmetry. Assignments have been proposed for all observed features.[485]

The self-consistent charge MO method has been used to calculate ESCA shifts and gas-phase binding energies for pyrrole. Agreement between theory and experiment is excellent.[486] The core binding energies are overestimated [by ca. 24 eV for C(1*s*) and 26 eV for N(1*s*)] by minimal (with polarization function addition or molecular scaling) and extended-basis-set ab initio calculations but the separation of the 1*s* levels (1.2–1.6 eV) is predicted reasonably well.[487]

X-Ray photoemission spectroscopy has been used extensively for the characterization of polypyrrole and its doped derivatives.[260,262,488–494] The core-level XPS spectra commonly display peaks skewed to the high-energy side.[262] These have been explained as a natural consequence of the metallic state,[495] but other authors[488] dispute this and discuss the broadening in terms of disorder in the case of the carbon peaks and electrostatic inequivalence in the case of the nitrogen peaks. Line-shape analysis with Gaussian fitting functions of the core-level spectrum of polypyrrole perchlorate reveals that the C(1*s*) peak can be decomposed into *three* lines, with those centered at 283.6 and 284.5 eV assigned to the pyrrole β and α carbon atoms respectively; in other words, $\approx$0.9-eV energy splitting of the monomer is preserved in the polymer. The third component is assigned to cross-linked, chain-terminating or non-α,α' bonded carbons and to carbons in partially saturated rings; up to one-third of all the pyrrole rings may be affected in this way. The main N(1*s*) peak, again asymmetric, is centered at 399.6 eV. In general, the results can be extended to polypyrrole doped with other counteranions. Substitution of the β hydrogens of the pyrrole ring by methyl groups ensures that the pyrrole rings are exclusively bonded via the α,α' carbons and increases the degree of order relative to the parent polymer: this is evident from the significant reduction in the C(1*s*) line width.[488,490,491,496] X-Ray photoemission spectroscopic (XPS) data for thin conducting films of poly(thieno[3,2-*b*]pyrrole) (poly **57**) doped with BF_4^- have been reported as C(1*s*) 285.2, N(1*s*) 400.5 eV.[492]

1.5. AROMATICITY

It is universally accepted that the physical and chemical properties of pyrrole are those of an aromatic molecule. In particular, the tendency of the ring system to retain its identity throughout a series of electrophilic substitution reactions

attests to this. Nonetheless, the quantification of *degree* of aromaticity, particularly vis à vis the other five-membered heteroaromatic compounds, has proved tantalisingly difficult and, at times, contentious. The wide range of criteria that have been applied to the problem is reviewed in Ref. 497. The criteria include measurements of bond alternation and bond order (see, e.g., Refs. 111, 498, and 499), the mesomeric dipole moment (which is the difference between the measured values for the heteroaromatic compound and its fully saturated derivative: utterly anomalous for pyrrole, compared with furan and thiophen), NMR chemical shifts and coupling constants,[500-504] and magnetic anisotropy (see, e.g., Refs. 49 and 505–507).

Historically, the resonance energy (RE) of an aromatic system has been a widely employed criterion for the quantitative assessment of aromaticity. The RE is defined, in general, as the difference between the total π-electron energy of an aromatic system and of some hypothetical reference structure. For the vertical (or true RE), this reference structure should have the same geometry as the aromatic system but with the π-electrons localized in the double bonds; such a species is, however, unattainable and data obtained from heats of combustion and heats of hydrogenation yields, instead, empirical resonance energies (Table 1.40). The calculations from which these numbers are derived in general neglect not only geometry differences between the reference structure and its aromatic partner but also the dependence of the carbon–heteroatom bond energy on the hybridization of the carbon atom and the energy differences between primary, secondary, tertiary, and aromatic hydrogen atoms. There is, additionally, a general lack of accurate thermodynamic information on model compounds.

TABLE 1.40. EMPIRICAL RESONANCE ENERGIES (kJ M^{-1}) FOR PYRROLE AND SOME DERIVATIVES[a]

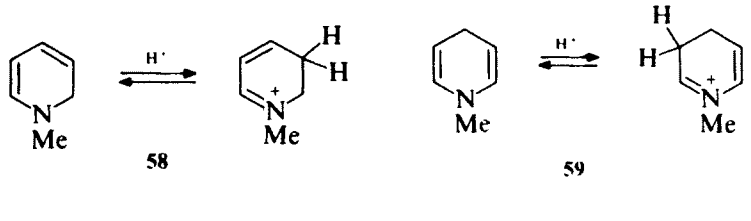
Compound	—[b]	—[c]	—[d]	—[e]	—[f]	—[g]
Pyrrole	101	85	124	79	87	31
1-Phenylpyrrole	283	303	283	252	204	122
2-Phenylpyrrole	259	282	268	241	155	96
2-Formylpyrrole	169	173	173	124	123	52

[a] Data taken from Ref. 14.
[b] Ref. 508.
[c] Ref. 509.
[d] Ref. 510.
[e] Ref. 511.
[f] Ref. 512.
[g] Ref. 513.

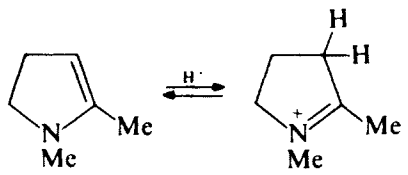
A modified definition of resonance energy has been introduced by Dewar[514] (see also Ref. 515) in which the reference point is the corresponding open-chain polyene. Dewar resonance energy (DRE) is then simply defined as the difference in heat of atomization of the aromatic compound and a corresponding acyclic polyene (e.g., benzene and 1,3,5-hexatriene); the latter is estimated as a sum of polyene bond energies. Although this overcomes, in principle, the difficulties

stemming from the requirement of an idealized, nondelocalized, molecule, in practice relatively little accurate thermochemical data on appropriate acyclic polyenes are available. Reliance on heats of formation evaluated by Hückel or PPP–MO methods has, therefore, been necessary. A value of 22.2 kJ M^{-1} has been calculated for pyrrole.[516] More recently, a graph-theoretical approach to aromaticity has been proposed that is the result of the translation of the Dewar reference structure into graph theory formalism within the framework of Hückel MO theory.[517] The approach can easily be extended to include conjugated ions and radicals.[518,519] Perturbation theory has been used to examine the effects of variations of the Hückel heteroatom parameters on the calculated topological resonance energies.[520] Ab initio calculations (but without geometry optimization) have been used to derive vertical REs for a variety of heteroaromatic systems, including pyrrole, for which a value of 149 kJ M^{-1} is given. This result is not directly comparable with the DRE since the definitions of RE are different, but trends in differences between molecules are similar.[521] It has been proposed that the concept of aromaticity should include an element of *uniformity* of π-electron delocalization through the cyclic system. On this basis (and with total electron-density maps calculated ab initio at the 4–21 level with additional *d*-functions on heteroatoms) pyrrole is found to be more aromatic than thiophene, which is, in turn, more aromatic than furan.[134]

An entirely different approach to the experimental estimation of REs utilizes equilibrium protonation data instead of thermochemical data, assuming that comparisons of the basicity of pyrrole with that of a nonaromatic system that forms a cation of π-electron structure similar to that of pyrrole should furnish a measure of the loss of RE accompanying protonation of the aromatic system.[522,523] Thus, for the α-protonation of 1-methylpyrrole, Katritzky chose the model nonaromatic system **58** since the cation formed on protonation is isoelectronic with that from 1-methylpyrrole. Combination of pK_a values for the protonation of the aromatic and nonaromatic molecules, taking into account the intrinsic resonance stabilization of the dieneamine system in **58**, gives an estimate for the total RE of 1-methylpyrrole as approximately 80 ± 21 kJ M^{-1}.



58 **59**



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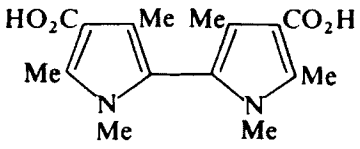
Similar treatment of the pK_a data for β-protonation of 1-methylpyrrole and for the model system **59** provides an alternative estimate for the 1-methylpyrrole RE as about 84 ± 17 kJ M^{-1}. Lloyd and Marshall,[523] using as the nonaromatic model compound the Δ^2-pyrroline **60**, estimate the RE of 1,2-dimethylpyrrole to be approximately 92 kJ M^{-1}.

1.6. CONFORMATIONAL STUDIES

The earliest reports on the conformational preferences of pyrrole derivatives stem from an extension of studies of restricted rotation in biphenyls to heterocyclic analogs, and early successful resolutions were effected on structures such as **61**,[524] **62**,[525] and **63**.[526] More recently *N*- and *C*-aryl and -heteroaryl pyrroles have been subjected to conformational study by both theoretical and experimental methods, prompted at least in part by the potential importance of polypyrrole as a conducting organic polymer.



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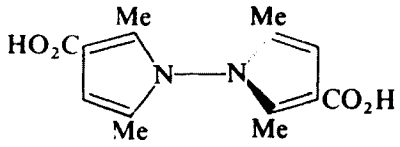

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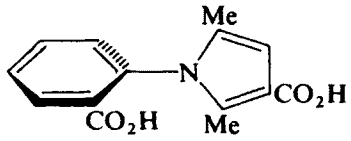

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1-Phenyl- and 1-(4-cyanophenyl)-pyrrole, along with several hindered derivatives bearing ortho- and/or pyrrole-α methyl groups, have been studied by photoelectron and fluorescence spectroscopy; the long wavelength fluorescence observed in polar solvents is assigned as arising from a twisted intramolecular charge-transfer state. The ground-state twist angles, obtained from a combination of MINDO/3 calculations and the experimentally determined MO energies, are given in Figure 1.9.[123] These figures are not unreasonable when viewed alongside the results of extended Hückel MO calculations, which indicate an angle of twist of ca. 40° for 1-phenylpyrrole, ca. 30° for the 3-phenyl isomer, and a preferred planar conformation for 2-phenylpyrrole.[65] It is of interest to compare such predictions with crystallographic data (Section 1.3), in particular with compounds **24**, **25**, **27**, **28**, **30**–**31**, **35**, and **64**. The relatively unhindered α-phenyl group in **30** deviates by only 10° from the pyrrole plane, although a large

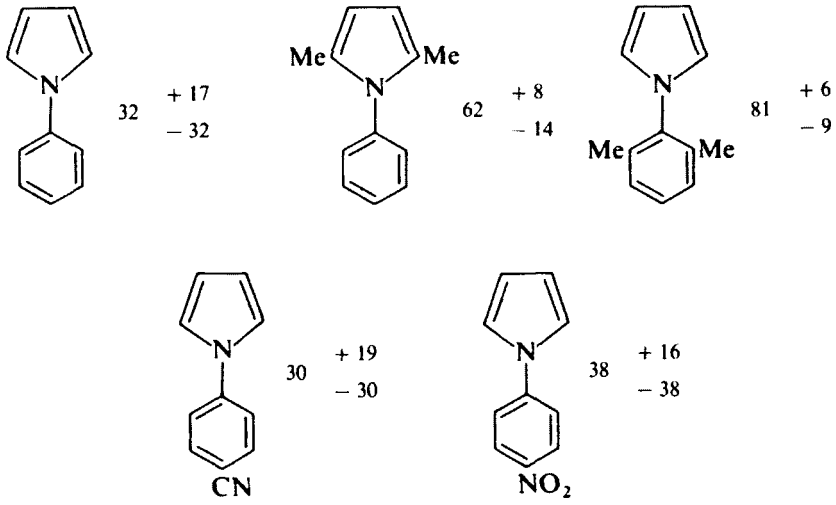
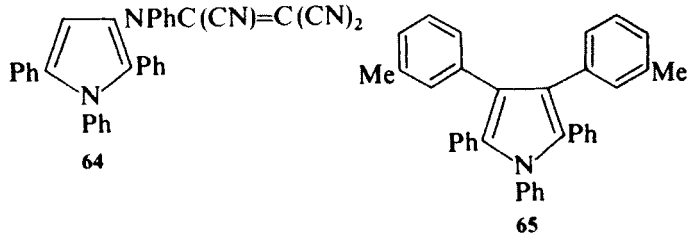
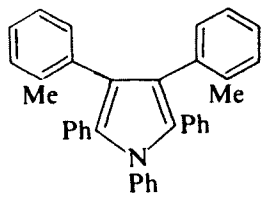


Figure 1.9. Mean spectroscopic twist angles (°) for 1-arylpyrroles.

deviation of ca. 36° is found in the similarly unhindered compound **24**. In the more congested **64**, the angles between the mean plane of the pyrrole ring and the planes of the phenyl groups are ca. 76, 62, and 36° for the 1-, 2-, and 5-phenyl substituents, respectively.[248] Presumably, observed differences in degrees of nonplanarity reflect not only differing steric environments but also the extent to which conjugation between substituents and the pyrrole ring is reinforced (or otherwise) by other substituents. To be added to these factors are environmental effects within the crystal ("packing forces"), which are difficult to quantify but no doubt important in influencing these relatively low energy rotational processes. Two pentaarylpyrroles (**65** and **66**) have been studied by dynamic ^{1}H NMR spectroscopy. It is argued that the compounds assumed a time-averaged effective conformation on the NMR time scale in which the five aryl rings are perpendicular to the plane of the pyrrole ring. However, whereas **66** exists as two rotational diastereomers ($\Delta G^{\ddagger}_{374} = 83.3\ \text{kJ M}^{-1}$) **65** shows rapid interconversion of diastereomers even at −85°C. The rotational barrier for **66** is about 75 kJ M^{-1} lower than the corresponding hexaarylbenzene mainly because of the increase in angle between adjacent peripheral rings.[527]



64 **65**



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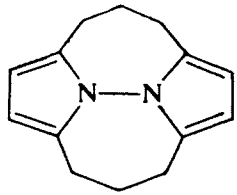

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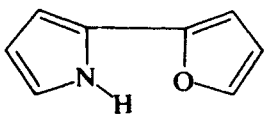
Photoelectron spectroscopy has been used for the conformational analysis of 1,1′-bipyrrole and its 2,5-di- and 2,2′,5,5′-tetramethyl derivatives, the bridged analog **67**, and 2-(2-furyl)- and 2-(2-thienyl)-pyrrole. For the bipyrroles, it is concluded from the splitting of the π_2-ionizations that, whereas **67** has coplanar pyrrole rings, the remaining systems have orthogonal rings in agreement with the results of MINDO/2 calculations on 1,1′-bipyrrole[477] and of X-ray crystallographic analysis of the substituted 1,1′-bipyrrole **34**. Similar arguments have been used to demonstrate the preference of the furyl- and thienylpyrroles for planar conformations. Dipole moment data in conjunction with the results of STO-3G ab initio calculations and the PES observations suggest that the preferred conformations are NX-cis **68** and **69**, although the ab initio calculations fail to predict correctly the direction of the dipole moment for the thiophen ring.[41]



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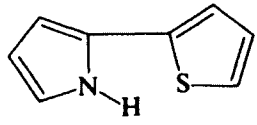

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Such systems have been studied extensively by theoretical methods. The results of ab initio STO-3G (with limited geometry optimization) and 4–31G calculations serve to predict the preferred conformation of 1,1′-bipyrrole as having a perpendicular disposition of the pyrrole rings. The two treatments yield potential energy curves for rotation about the interannular bond of similar, qualitative, shape but with energy barriers of approximaely 21 and 44 kJ M^{-1}, respectively.[158] These predictions are contrary to earlier ones from the same school based on the INDO-SCF method in which the most stable conformation corresponds to an interannular torsion angle ω of 38°, and the barrier for rotation through $\omega = 0$ or 90° is approximately 3 kJ M^{-1}.[107] Recent comparative STO-3G and 4–31G studies on all C–C′ bipyrroles and furylpyrroles yield both qualitative and quantitative differences in the potential-energy curves for interannular rotation, the conclusion being that the STO-3G calculations provide an insufficient description of the conformational behavior. At the 4–31G level, 2,2′-furylpyrrole and 3,2′-furylpyrrole exhibit twofold potential functions with minima corresponding to planar conformations and highest

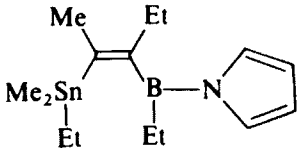
rotational barriers of about 26 and 19 kJ M^{-1}, respectively, whereas the remaining molecules are characterized by fourfold potentials with gauche minima between planar and perpendicular conformations and barriers in the range 6–13 kJ M^{-1}.[155–157,159] These results supersede earlier predictions based on an INDO treatment[108] and suggest that predictions concerning the conformational preferences of bi- and oligopyrroles in relation to the properties of polypyrrole based on INDO or STO-3G approaches need to be tested further.[98,110]

The conformational preferences of substituted pyrrole derivatives, particularly those bearing carbonyl substituents, have been widely investigated chiefly by NMR, IR, and dipole moment methods. Variable-temperature ^1H NMR has been used in the measurement of the barriers to rotation in 1-formyl- and 1-acylpyrroles (Table 1.41). The barriers decrease in the order formyl > acetyl > benzoyl, as expected from comparisons with the corresponding *N,N*-dimethylamides, but are much smaller than in the amides as a result of the lower resonance interaction between the carbonyl group and the pyrrole nitrogen. Cross-conjugation of the pyrrole and benzene rings with the carbonyl group reduces the barrier further in 1-benzoylpyrrole, but the barriers are higher in the hindered derivatives presumably as a result of steric hindrance to rotation[528,530] (see also Ref. 531). Attempts to estimate the rotamer populations in a range of 1-acetyl heterocycles based on the use of ^{13}C NMR shifts averaged between the two planar conformations were largely unsuccessful.[532] This is in accord with conclusions from an earlier study that neither ^1H nor ^{13}C NMR furnishes reliable information on the conformational preferences of 1-formyl- and 1-acetylpyrroles based on changes in the resonance frequencies of nuclei in the two rotamers.[533] Nonetheless, ^{13}C NMR chemical shifts have been used to predict the value of the phenyl–carbonyl group torsion angle in 1-benzoylpyrrole (in $CDCl_3$) as 64°[534] and in conformational analyses of 1-vinylpyrrole

TABLE 1.41. COALESCENCE TEMPERATURES (T_c K) AND ENERGY BARRIERS TO ROTATION ($\Delta G^{\ddagger}$ kJ M^{-1}) FOR 1-ACYLPYRROLES

1-Substituent	T_c (K)	$\Delta G^{\ddagger}$ (kJ M^{-1})	Ref.
	Pyrroles		
CHO	278	58.9	283, 528
COMe	245	52.2	283, 528
		50.7	529
COPh	203	≈ 42	283, 528
2,4,6-Mesitoyl	338	69.0	528, 530
Pentachlorobenzoyl	300	61.0	528
	3,4-Dimethylpyrroles		
COMe	268	56.4	283, 528
COPh	217	≈ 46.0	528

derivatives.[282] Carbon-13 coalescence temperatures for the α- and β-carbon resonances in **70** provide a value for the barrier to rotation about the B–N bond as $\Delta G^{\ddagger} = 64 \pm 1$ kJ M^{-1}, which is argued as indicating the presence of B–N π-interactions. Rotation around the B–C= bond is also restricted ($\Delta G^{\ddagger} = 58 \pm 1$ kJ M^{-1}).[535] 2-Formylpyrrole and its simple derivatives adopt the syn conformation in **71** preferentially.



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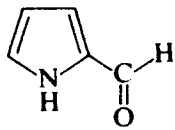

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Energy barriers separating the syn and anti forms of a range of 1-alkylated 2-formylpyrroles have been estimated from ^{1}H NMR coalescence temperatures (Table 1.42), although the results are best treated as approximate since the equilibria are biased to the extent that only signals due to the syn form can be detected at temperatures below coalescence.[536] Nonetheless, it is noteworthy that the values for the 2-formylpyrroles are significantly lower than the value for 1-formylpyrrole. Variable-temperature ^{13}C NMR spectroscopy yields similar indications. As the temperature of a solution of 2-formyl-1-methylpyrrole in a nonpolar solvent is lowered, the resonance due to C-3 broadens to a maximal value at 253 K and then sharpens to resume its original height at 223 K, but signals due to the anti (minor) form cannot be detected in the slow-exchange spectrum.[537] The low rotational barrier estimated for 1-*t*-butyl-2-formylpyrrole by ^{1}H NMR spectroscopy (Table 1.42) is in accord with the results of previous IR and UV studies on a range of 1-alkyl-2-formylpyrroles in which the prediction was made that this compound, while preferring an approximately syn conformation, would accommodate steric interactions through noncoplanarity of the carbonyl group and ring planes.[538]

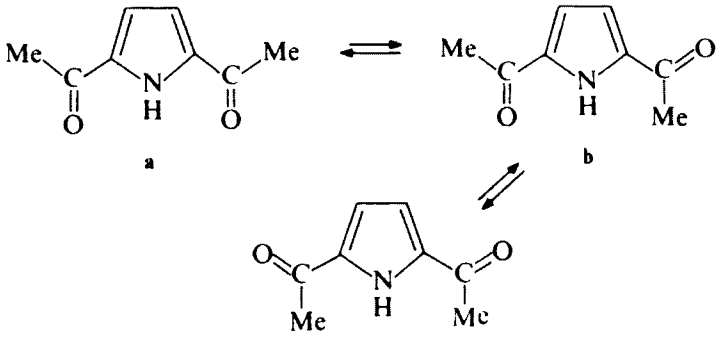
The percentage populations of the syn forms of 2-formylpyrrole and 2-formyl-1-methylpyrrole at room temperature have been estimated as 100 and 90, respectively, on the basis of the stereospecificity of the long-range coupling

TABLE 1.42. COALESCENCE TEMPERATURES AND ROTATIONAL ENERGY BARRIERS FOR 1-ALKYL-2-FORMYLPYRROLES

N-Substituent	Coalescence Temperature (K)	Energy Barrier (kJ M^{-1})
Me	222	46.8
Et	221	46.8
i-Pr	215.5	45.6
n-Bu	220	46.4
i-Bu	221.5	46.8
s-Bu	214	45.1
t-Bu	< 193	< 40.5

constants between the formyl hydrogen and the ring hydrogens at positions 4 and 5.[539] Substitutents in the ring may, however, dramatically alter the situation. Thus, it has been argued from coupling constant measurements that 5-ethoxycarbonyl- and 5-nitro-2-formylpyrroles exist as approximately 1:1 mixtures of syn and anti conformers in $[^2H]_6$-DMSO, that the 3- and 4-nitro isomers have syn/anti ratios of 4:1 and 13:1, respectively, and that whereas 3-iodopyrrole-2-carbaldehyde exists exclusively in the syn form, the 4-iodo isomer has 8% of the anti form.[540,541]

The predictions of dipole moment studies seem generally to agree with those from NMR experiments, although the details may differ at least in part because different solvents are routinely used in the two types of investigations. Thus, early dipole moment measurements on 2-formyl- and 2-acetylpyrrole indicated the predominance of the syn conformer,[542] and later results[37,39,543,544] support this conclusion. Measurements on 2-formyl-, 2-acetyl-1-methyl-, and a range of 1-alkyl-2-formylpyrroles in benzene solutions at 25°C indicate percentage populations of the syn forms to be 85, 81, and about 60, respectively.[545] The syn form for 2-formyl-1-methylpyrrole is aso indicated in CCl_4 solution, but 2-formyl-1-phenylpyrrole exists, according to dipole moment data, exclusively in the *O,N*-anti form and with the phenyl and pyrrole rings orthogonal.[546] The preference of 2-formyl- and 2-acetylpyrrole for the syn conformation in cyclohexane, benzene, and dioxan solutions has been confirmed by later dipole moment studies, but 2-acetyl-3,4,5-trialkylpyrroles appear to adopt a syn-twisted conformation with the acetyl group rotated out of the pyrrole plane by about 60°.[547] The predominant conformer for 2,5-diacetylpyrrole has been argued as being **72a** on the basis of a comparison of the observed dipole moment with values calculated for conformations **72a–c**.[548] Variable-temperature NMR measurements on 2,5-diformylpyrrole indicate a mixture of syn–syn and syn–anti (but not anti–anti) conformers analogous to **72a** and **72b** and a rotational barrier of about 39 kJ M^{-1},[549] and this is reinforced by the results of a crystal structure analysis, which revealed the presence of both structures in the crystal (Section 1.3). 2-Trifluoroacetyl- and 2-acetylpyrroles are alike in their



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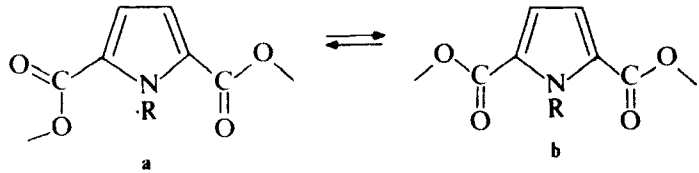
conformational propensities, and H–^{19}F nuclear Overhauser effect (nOe) experiments have established the preferred conformation of 1-methyl-2-trifluoroacetylpyrrole as syn.[414]

Less is known about the conformational preferences of pyrrole-2-carboxylic acids and their derivatives. Acids and esters lack a suitable ^{1}H NMR probe, and the observation of ^{13}C coalescence phenomena is more problematic than in aldehydes and ketones since the barrier to rotation about the ring-to-carbonyl bond is expected to be lower in the esters. As noted in Section 1.4.5, however, IR spectroscopy has been especially valuable in this area, and it may be confidently concluded that whereas 1-alkylpyrrole-2-esters exist in solution in only one form (probably syn-*s*-trans, **44b**), the diesters are conformationally heterogeneous.[409,413] 1-Alkyl-2,5-dimethoxycarbonylpyrroles display well-separated doublet carbonyl stretching bands in their IR spectra (separation typically ca. 20 cm^{-1}), which have been assigned to anti–syn and syn–syn conformers **73a,b**. The related 2,4-diesters display only single carbonyl stretching bands but having distinct shoulders to high wavenumber; the probable conclusion is that the esters exist as mixtures of 2-*syn*-4-*cisoid* and -*transoid* conformers **74a,b**. 1-*t*-



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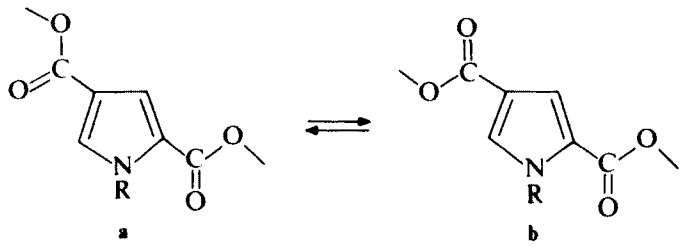

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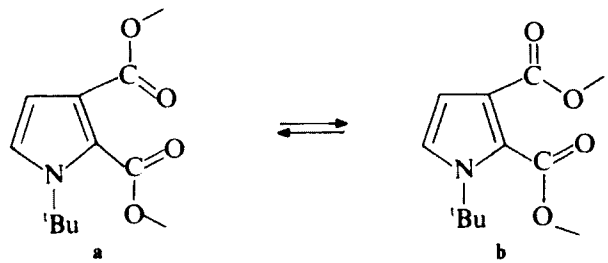

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Butyl-2,3-dimethoxycarbonylpyrrole displays a well-separated carbonyl stretching doublet tentatively assigned to anti–cisoid and anti–transoid conformations **75a** and **75b**, although steric effects may induce considerable out-of-planarity of the ester groups (cf. the crystal structure of 2,3-diester **24** in Section 1.3). 1-*t*-Butyl- and 1-adamantyl-2,5-dimethoxycarbonylpyrrole have been examined by variable-temperature ^1H and ^{13}C NMR spectrometry. Whereas little change is observed in the appearance of the ^{13}C NMR spectra on cooling of solutions in CD_2Cl_2 down to 203 K, the ^1H spectra show significant broadening of the ester–methyl and 1-alkyl signals (although not of the aromatic signals) at this temperature, from which it may be argued that hindrance to rotation about the *N*-alkyl bond is responsible for the observed effects. A very low barrier to rotation about the ring–carbonyl group bond seems likely and is consonant with results obtained for furan-2-esters in which no coalescence phenomenon in ^{13}C or ^1H NMR spectra is observed even at 183 K.[413,537,550] The barriers to rotation ($\Delta G^{\ddagger}_{298.2}$) about the N–CO bonds in pyrrole-2- and -3- *N*,*N*-dimethylcarboxamides have been measured by variable-temperature ^1H NMR spectrometry as 60.3 ± 0.4 and 61.1 ± 0.4 kJ M^{-1}.[551]

3-Substituted pyrrolylaldehydes and ketones have been studied in a similar fashion to the 2-substituted derivatives. The 3-formyl group has a lower barrier to rotation about the ring–carbonyl group bond (42.9 kJ M^{-1}) than does the 2-formyl group,[552,553] and the difference in the ground-state energies of the two conformers is smaller. Most workers are in agreement that the preferred conformation for 3-formylpyrrole and 1-alkyl-3-formylpyrroles is *N–O trans*,[540,541,545,547,549,552–554] although the position of equilibrium is sensitive to ring substitution and solvent. Variable-temperature NMR studies of 3-formylpyrrole show that the cis/trans ratio is 1 : 4 at room temperature and that the trans conformation is favored to the extent of 91% at 183 K.[552] The 2-iodo- and 2-nitro-derivatives show an even stronger preference for the trans form (ca. 95% at room temperature), and this is the favored conformation in 2-chloro-3-formyl-1-methyl-5-phenylpyrrole,[555] but the 4-iodo compound exists as an approximately 1 : 1 mixture of cis and trans conformers, and the 4-nitro analogue is seemingly all cis.[540,541] The general preference for the trans conformation tends to be reduced by substituents in position 5.[540] NMR and dipole moment measurements indicate a trans preference in 3-acetyl pyrroles,[537,547,552,556] and ^{19}F NMR studies show that 1-alkyl-3-trifluoroacetylpyrroles adopt two conformations with a ratio of approximately 3 : 1 differing little in enthalpy, although it was not established whether the more populated conformer is trans.[414]

Conformational preferences, rotational barriers, stabilities, and charge distributions of 70 monosubstituted pyrroles have been investigated by ab initio MO theory at the STO-3G level. It is predicted that the pyrrolyl group acts as a stronger π-donor than the phenyl group with the effect being more pronounced at position 2 than position 3. The 2-pyrrolyl group is found to be a stronger σ-acceptor than is phenyl, whereas the 3-pyrrolyl group can be either a stronger or a weaker σ-acceptor than phenyl depending on the nature of the substituent.

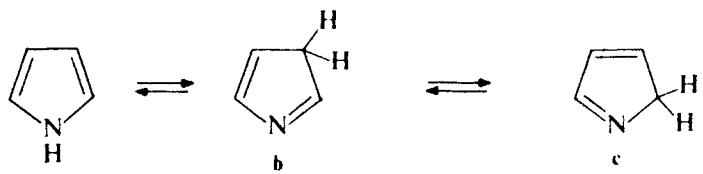
Calculations indicate that the NCCH trans conformation of 2-methylpyrrole is preferred while the C(2)CCH cis conformation is favored for the 3-isomer; in other words, both conformations have the favorable disposition in which the pyrrole C(2)–C(3) bond is eclipsed by a methyl C–H. Whereas 2- and 3-hydroxymethylpyrroles are found to adopt conformations in which NCCO and C(2)CCO are respectively cis, nonplanar conformations are indicated for 2- and 3-fluoromethyl- and 2- and 3-lithiomethylpyrroles. Aminopyrroles are predicted to be pyramidal at nitrogen and hydroxy- and vinylpyrroles, as adopting planar trans conformations and formylpyrroles planar cis(syn) conformations. For 2-formylpyrrole the syn form is calculated to be 7.3 kJ M^{-1} lower in energy than the anti form, and the barrier to anti→syn rotation is estimated as 36.3 kJ M^{-1}. For the 3-isomer, the cis conformation is favored over the trans conformation but only by 1.3 kJ M^{-1}, and the trans → cis barrier (27.7 kJ M^{-1}) is significantly lower than for the 2-isomer. The acetyl compounds are also predicted as favoring syn(cis) conformers, the 2-isomer much more so than the 3-isomer, and syn(cis) forms are also favored for amides and acids, although in the latter the balance is fine. Both 2- and 3-nitrosopyrroles are predicted to adopt planar trans conformations with large barriers to rotation to cis conformations, and the nitropyrroles are predicted to be planar.[130]

1.7. TAUTOMERISM

The tautomerism of heterocycles is reviewed extensively in Refs. 557 and 558, and additional information on pyrroles may be found in the books by Gossauer[13] and Jones and Bean.[14]

1.7.1. Tautomerism Not Involving Functional Groups

The results of MINDO/3 calculations indicate that the pyrrole–pyrrolenine interconversion **76** is highly endothermic; the tautomerization energies for the transformation of pyrrole and 2-methylpyrrole to the pyrrolenines **76c** (and the α-methyl analogue) are 78.3 and 115.3 kJ M^{-1}, respectively.[114] More recent HMO,[62] INDO, and STO-3G calculations support this general view, although the numerical results vary considerably. Thus, INDO calculations give the relative energies of **76a–c** as 0, 79.9, and 58.6 kJ M^{-1}, respectively, whereas the



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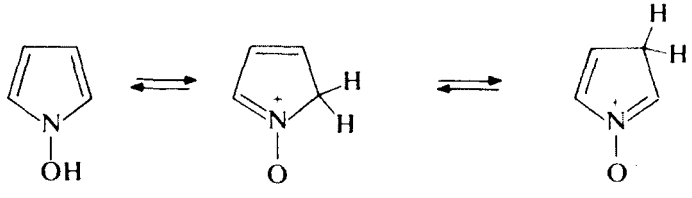
STO-3G method (on INDO-optimized geometries) predicts the values as 0, 23.0, and 19.7 kJ M^{-1}. The activation energy for proton migration from **76c** to **76b** is estimated by the INDO method to be 65.7 kJ M^{-1}.[106] Not surprisingly, then, there is no authenticated case of the pyrrolenine tautomers **76b,c** predominating when proton transfer from carbon to nitrogen can reestablish aromaticity (see Chapter 4).

1.7.2. Compounds with a Potential Hydroxy Group

Three tautomeric structures (**77a–c**) are possible for 1-hydroxypyrroles, but the zwitterionic forms **77b,c**, having lost the aromatic resonance energy, would not be expected to feature significantly. IR and NMR evidence confirm, in support of this, that 2-cyano-1-hydroxypyrrole and some substituted derivatives exist in solution in the hydroxy form (analogous to **77a**).[559]



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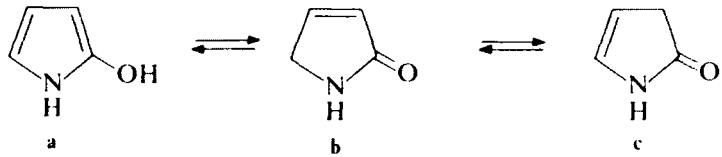
Potential *C*-hydroxy compounds usually exist as the oxo tautomers unless the hydroxy tautomer is appreciably stabilized by other substituents. Some semiempirical MO calculations support the preference for 2- and 3-hydroxypyrrole to exist as the pyrrolinones **78b** and **79b**,[560] whereas others do not.[114,126] For example, MINDO/3 calculations predict that 3-hydroxypyrrole **79a** is 18.8 kJ M^{-1} *more* stable than the pyrrolinone tautomer **79b**, although the dipole



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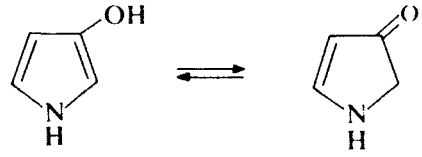

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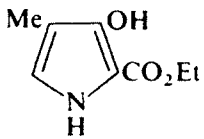
moments are very different (2.84D for the former, 5.19D for the latter), so the equilibrium position should be strongly solvent dependent.[114] MINDO/3 and MNDO calculations on a range of 2-hydroxypyrrole derivatives indicate a general preference for the Δ^4-pyrrolinone **78c** over the Δ^3-isomer **78b**, which is contrary to experiment.[126] HMO calculations with the ω-technique correctly predict the order of stabilities for the tautomers of 3-alkyl-, 3-thio-, 3-amino-, and 3-hydroxypyrroles, and also for the 2-alkyl-, 2-thio-, and 2-amino-compounds. However, like the MINDO/3 and MNDO calculations, these show the Δ^4-pyrrolinone tautomer **78c** to be more stable than the Δ^3-tautomer **78b**.[62] It seems that calculated energy differences between tautomeric forms are often so small as to make the conclusions unreliable, particularly as possible solvent effects are ignored.

Both Δ^3- and Δ^4-pyrrolin-2-one have been synthesized unambiguously.[561] The tautomers exist in equilibrium in aqueous solutions, but deuterium exchange experiments show that, in the absence of acid or base catalysis, the transformation of the Δ^4-isomer **78c** into the more stable Δ^3-isomer **78b** is slow.[562,563] Spectroscopic data for pyrrolin-2-ones substituted in the 3,4, 3,5, or 3,4,5 positions by alkyl or aryl groups indicate that the Δ^3-tautomer is preferred,[546-568] whereas an electron-withdrawing group in the 4 position[567,569,570] or an alkyl group only in the 5 position[571,572] favors theΔ^4-tautomer.

Most 3-hydroxypyrroles[573,574] exist preferentially as the oxo tautomer **79b**, although hydroxy forms occur in some instances, especially when intramolecular H-bonding is possible, as in conformations **80**,[574] **81**,[574] and **82**.[575] 4-Hydroxypyrrole-2-carboxylic acid also exists as such, rather than in the pyrrolinone form.[576]



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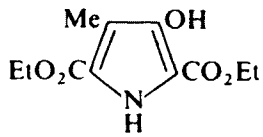

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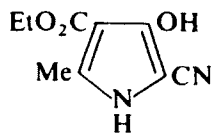

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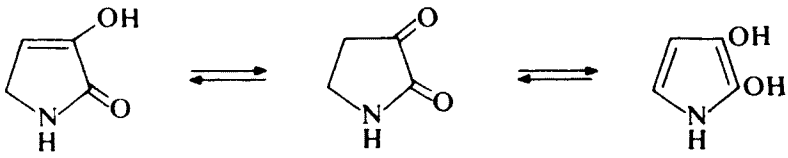
IR, UV, and ^{1}H NMR spectroscopic evidence indicates that potential 2,3-dihydroxypyrroles adopt the monoenol form **83a** in preference to the alternative dioxo **83b** or dihydroxy **83c** structures.[577,578] 2,5-Dihydroxypyrrole can exist in four tautomeric forms (**84a–d**), but only the dioxo structure **84d** (succinimide) is



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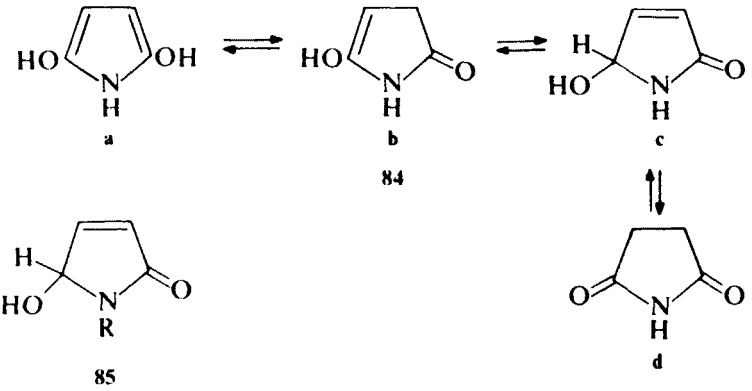
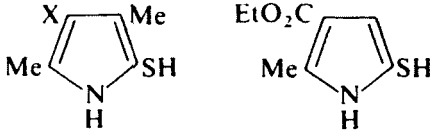


important; an X-ray crystal structure is available.[579] The tautomer **85** (R = H or Me) can, however, be prepared under kinetic conditions by photooxidation of pyrrole or 1-methylpyrrole and is sufficiently stable to allow for characterization.[580]

1.7.3. Compounds with a Potential Thiol Group

The thiol form is much more strongly favored over the thione tautomers than is the hydroxy form over the oxo analogs. The results of HMO (ω-technique) calculations on the 2- and 3-substituted systems also indicate this preference for aromatic (thiol) tautomers.[62] In agreement with this, IR and NMR data confirm thiol structures for **86** (X = CO_2Et, COMe)[581] and **87**.[582]

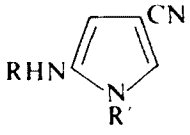


86 **87**

1.7.4. Compounds with Potential Amino Groups

Although the results of MO calculations predict that 2- and 3-aminopyrroles should prefer the amine to the imino tautomer, experimental data are very limited.[62,560] The IR spectra of substituted 2-aminopyrroles of the type **88** [R = H or Ac, R′ = Ph, Et, $CH_2CH(OEt)_2$] display bands characteristic of the

NH_2 group, and the amino tautomer is also indicated for **89**.[583] However, the latter's 1-acetyl derivative has been shown by NMR spectroscopy to have the imino structure **90**.[584]



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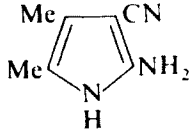

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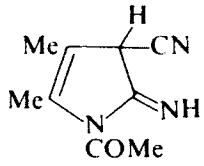

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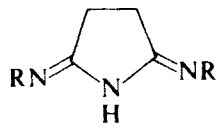
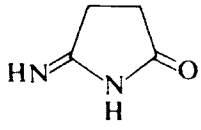
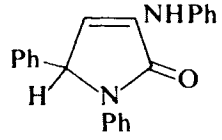
The fact that 2,5-diaminopyrrole (**91**; R = H) and the derivatives R = Ph or OH prefer diimino forms is evinced by NMR spectroscopy.[585] The structure of the product of partial hydrolysis has been established as **92** by IR, UV, and NMR methods.[585–587] The preferred tautomeric form of the 3-amino-2-hydroxy-1,5-diphenylpyrrole is the Δ^3-pyrrolin-2-one structure **93** drawn, possibly stabilized by intramolecular H-bonding.[588]



91



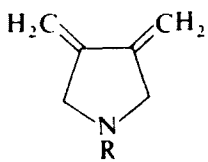
92



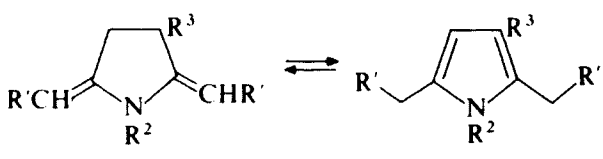
93

1.7.5. Compounds with Potential Alkyl Groups

The alkylidene tautomeric forms of simple alkylpyrroles are not populated significantly at equilibrium,[62] although compounds such as **94** (R = H or various alkyls) may be prepared under nonequilibrating conditions.[589] However, 2,5-dialkylpyrroles in which the alkyl groups bear electron-withdrawing functionality can exist in tautomeric equilibrium with alkylidene forms; the ratio of tautomers is very sensitive to the number and nature of substituents on the alkyl groups and pyrrole ring. NMR spectroscopy has been used in the study of the acid-catalyzed tautomerization, with the equilibrium position approached from both sides. At ambient temperatures, the ratio of alkyl to alkylidene forms is 8:1 for **95** (R^1 = CN, R^2 = Me, R^3 = H) and 30:1 for **95** (R^1 = CN, R^2 = Ph, R^3 = H). Pyrroles **95** ($R^1 = CO_2Et$, R^2 = Me or Ph, R^3 = H, and R^1 = CN,



94



95

$R^2 = R^3 = Me$) displayed only the alkyl forms when subjected to tautomerization.[590]

1.8. REFERENCES

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CHAPTER 2

The Synthesis of 1*H*-Pyrroles

Gerritt P. Bean*

Department of Chemistry
Western Illinois University
Macomb, Illinois

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* *Present Affiliation*: Department of Chemistry and Biochemistry, University of Colorado, Boulder, Colorado.

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2.1. INTRODUCTION

Since the discovery of pyrrole by Runge in 1834 many pyrrole compounds have been found in nature. The development of synthetic methods for pyrroles having a variety of substituents has been dominated not by the interest in the methods so much as by the need for the specific pyrroles themselves. For many years the synthesis of substituted pyrroles was directed primarily toward their use in constructing porphyrins or other polypyrroles. The synthetic methods of this period have been well described in the classic three-volume work of Fischer and Orth, *Die Chemie des Pyrrole.*[1] Corwin's chapter on pyrroles in the Elderfield series in *Heterocyclic Chemistry* has covered much of the work prior to 1950.[2]

With the discovery and subsequent commercial success of the antibiotic pyrrolnitrin [3(3-chloro-2-nitrophenyl)chloropyrrole],[3] the search for other pyrroles having pharmacological action has tended to encourage the search for new synthetic methods to construct the pyrrole system. In addition, the investigation of 1,3-dipolar cycloaddition reactions has included the preparation of a number of pyrroles. Much of this work has been included in the recent monographs by Gossauer[4] and Jones and Bean.[5] In addition, a recent review of synthetic methods for 1*H*-, 2*H*-, and 3*H*-pyrroles by Patterson has appeared.[6]

The section on 5-membered rings in the encyclopedic *Comprehensive Heterocyclic Chemistry* includes a discussion of their synthesis.[7]

The wide distribution of pyrroles in nature is indicative of the ease with which the pyrrole ring is formed. This is due in part to the favorable entropy change for 5-membered ring formation and the resonance stabilization of the resulting aromatic system.

In this chapter, the various methods of forming the pyrrole ring are organized according to carbon–carbon bonds formed in the construction of the pyrrole ring or by the transformation of other ring systems.

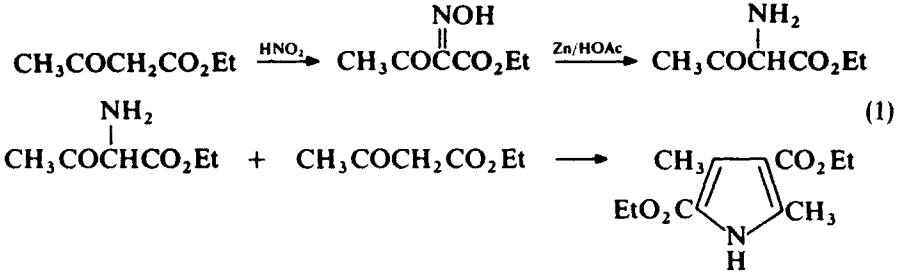
It will be noted that in a number of synthetic methods, the stoichiometry indicates that although a pyrroline (dihydropyrrole) should be formed, the isolated product is a pyrrole. This is probably due in most cases to ease of aerial oxidation leading to the aromatic compound.

2.2. FORMATION OF PYRROLES FROM TWO 2-CARBON UNITS WITH INITIAL FORMATION OF N–C_2 BOND

2.2.1. Condensation of Dicarbonyl Compounds with Nitrogen-Containing Compounds

2.2.1.1. With α-Aminoketones: The Knorr Synthesis

In 1884 Knorr reported the preparation of diethyl 3,5-dimethylpyrrole-2,4-dicarboxylate (often called *Knorr's pyrrole*) by first nitrosating ethyl acetocetate and then reducing the nitroso compound in the presence of additional ketoester:[8]

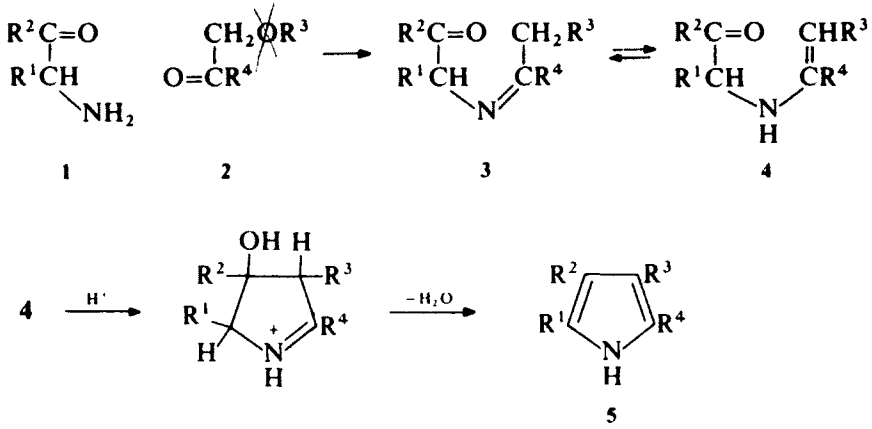


(1)

Since then the condensation of an α-aminoketone with a carbonyl compound has been referred to as the *Knorr synthesis*, and, in spite of its long history, it has continued to be widely exploited, particularly to prepare the necessary building blocks for the synthesis of tetrapyrroles. Many of the early examples of the Knorr synthesis have been discussed in the monograph by Fischer and Orth,[1] and only a few references to the earliest work will be made here. Corwin has examined the limitations on the method and found that the yield of pyrrole is

low unless there is a resonance stabilizing electron-withdrawing substituent at the α-carbon atom of the carbonyl compound (e.g., COR, CO_2R, CN, aryl).[2]

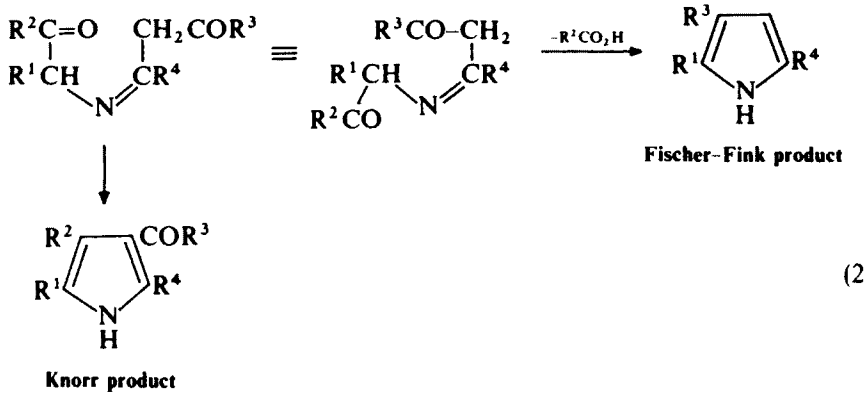
The mechanism for the reaction has been inferred by the isolation of the enamine (or aminocrotonic ester) **4** ($R^2 = H$, R^3 = 3-chloro-2-nitrophenyl, $R^4 = CO_2Et$, and $R^5 = Me$), when the reaction was buffered at a pH 4.[9] (See Scheme 1.)



Scheme 1

Molecular orbital calculations using the AM1 method indicate that, although the imine **3** is more stable than the enamine **4** when $R^4 = H$, for $R^4 = CHO$, the resonance-stabilized imine is the more stable.[10]

As discussed in Section 2.6.1, if R^4 is an alkyl group, that is, a β-diketone, ring closure may occur by the attack on the carbonyl group to give the alternate pyrrole by what is referred to as the "Fischer–Fink reaction":



Fischer–Fink product

Knorr product

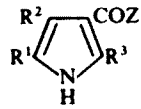
(2)

Preparation of the requisite aminoketone is often carried out in situ, for example, with zinc or sodium dithionite reduction of the nitroso compound, although they can also be prepared separately by catalytic reduction of the

nitroso compound. There may be some advantage to use lithium nitrite or hydroxylamine sulfate for the nitrosation.[11,12] Aminoacetone has been prepared by hydrolysis of the phthalimide.[13] The Neber rearrangement has also been utilized to prepare aminoketones for the Knorr synthesis.[14]

The various pyrroles prepared through the use of the Knorr synthesis are given in Tables 2.1–2.3.

TABLE 2.1. PYRROLES UNSUBSTITUTED ON NITROGEN FROM THE KNORR REACTION OF α-AMINOKETONES [$R^1CH(NH_2)COR^2$] WITH β-DICARBONYL COMPOUNDS (R^3COCH_2COZ)



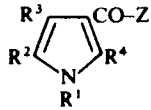
R^1	R^2	R^3	Z	Ref.
H	Me	Me	COOH	15
H	Me	COOH	Me	15
H	Ph	Me	EtO	16
H	Me	COOH	EtO	9, 17
H	H	Me	EtO	18–19
H	H	Ac	EtO	20
H	H	CH_2CO_2Et	EtO	21
H	$CH_2CH_2NH_2$	CO_2Et	EtO	22
H	Ph	Me	EtO	23
H	*p*-$NO_2C_6H_4$	Me	EtO	24
H	3-Cl-2-NO_2-C_6H_3	Me	EtO	13, 25–26
H	3-Cl-2-NO_2-C_6H_3	COOH	EtO	26
H	H	Me	Ph	18
Me	H	Ac	EtO	20
Me	Me	Me	EtO	11[d], 27[a]
Me	Et	Me	EtO	11[d]
Me	Me	*n*-Pr	EtO	27[a], 28
i-Pr	Me	Me	Me	28
Ph	Ph	Me	EtO	28
p-$MeOC_6H_4$	*p*-$MeOC_6H_4$	Ph	EtO	29
CO_2Et	Me	Me	EtO	12, 27, 30–33
CO_2Et	Me	Me	EtS	34
CO_2Et	Me	Me	*t*-BuO	35[a]
CO_2Et	Me	COOH	EtO	27[a]
CO_2Et	Ph	Me	EtO	30
CO_2Et	*m*-ClC_6H_4	Me	EtO	36
CO_2Et	*m*-ClC_6H_4	Me	*t*-BuO	36
CO_2Et	*m*-ClC_6H_4	Me	Me	36
CO_2Et	CH_2CO_2Et	Me	EtO	37
CO_2Et	$CH_2CH_2CO_2Et$	Me	Me	38
CO_2CH_2Ph	$CH_2CH_2CO_2Et$	Me	Me	38
CO_2Et	$CH_2CH_2CO_2Et$	Me	EtO	37, 39
CO_2Et	$CH_2CH_2CO_2Et$	Me	$PhCH_2O$	40
CO_2Et	CH_2CH_2Ph	CH_2CO_2Et	EtO	41
CO_2Et	CF_3	Me	EtO	42

TABLE 2.1. (*Contd.*)

R^1	R^2	R^3	Z	Ref.
CO_2Et	CF_3	Me	Me	43
CO_2t-Bu	Me	Me	Me	35[b]
CO_2t-Bu	Me	Me	EtO	35[b]
CO_2t-Bu	Me	CH_2CO_2Et	EtO	35[b]
CO_2CH_2Ph	Me	Me	Me	44
CO_2CH_2Ph	Me	Me	EtO	45
CONHPh	Me	Me	NHPh	12[c]
$CONEt_2$	Me	Me	Me	46
CH_2Ph	Me	Me	Me	44
CH_2CO_2Et	Me	Me	EtO	11[d]
Ac	Me	Me	Me	12[c]
EtCO	Et	Et	Et	12[c]
Ac	Me	Me	t-BuO	35
p-ClC_6H_4	Me	Me	EtO	47
$-(CH_2)_3-CO-$		Me	EtO	48
$-(CH_2)_3-CO-$		H	H	49[e]

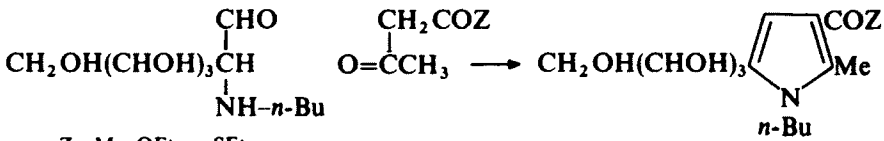
[a] Reduction with dithionite.
[b] From phthalimide derivative.
[c] Nitrosated with NH_2OSO_4H.
[d] Nitrosated with $LiNO_2$.
[e] Used acetal.

TABLE 2.2. 1-SUBSTITUTED PYRROLES PREPARED BY THE KNORR SYNTHESIS



R^1	R^2	R^3	R^4	Z	Ref.
Ph	H	p-$NO_2C_6H_4$	Me	EtO	50, 51
Ph	Me	NO_2	Me	EtO	52
3,5-$Me_2C_6H_3$	H	p-$NO_2C_6H_4$	Me	EtO	53–56

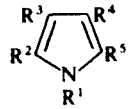
A number of 2-alkylaminosugars have been utilized as the aminoketones in the Knorr synthesis to prepare pyrroles having a sugar residue at the 2 position.[67–69]



Z = Me, OEt, or SEt

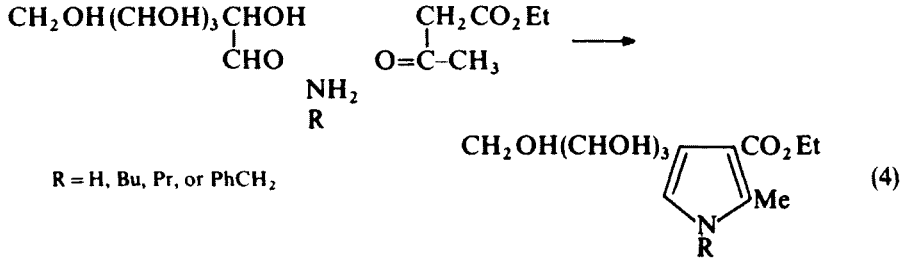
(3)

TABLE 2.3. OTHER PYRROLES FROM THE KNORR SYNTHESIS



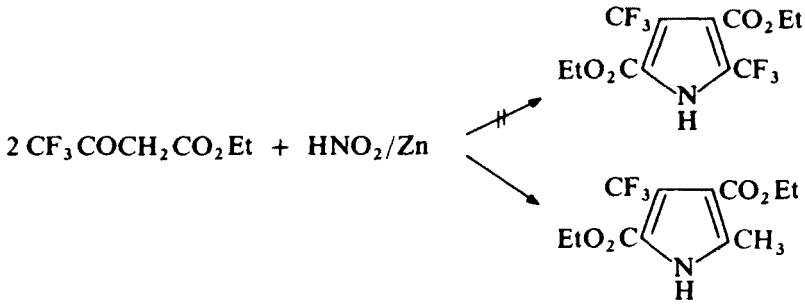
R^1	R^2	R^3	R^4	R^5	Ref.
H	Ph	Ph	Ph	Me	57
H	Ph	Ph	Ph	Ph	57
H	Ph	Ph	Ph	CH_2Ph	57
H	Me	CO_2t-Bu	CH_2CO_2Et	CO_2Et	35
H	Me	CO_2t-Bu	$CH_2CH_2CO_2Et$	CO_2Et	35
H	CO_2Et	Me	Me	Tos	58
H	Me	3-Cl-2-$NO_2C_6H_3$	H	H	59
H	COOH	3-Cl-2-$NO_2C_6H_3$	H	H	59
H	CO_2Et	3-Cl-2-$NO_2C_6H_3$	H	H	60–61
H	CO_2Et	3-Cl-2-$NO_2C_6H_3$	H	Me	59
H	Ac	3-Cl-2-$NO_2C_6H_3$	H	H	59
Ph	Ph	Ph	Ph	H	62
Ph	Ph	Ph	Me	Ph	62
Ph	Ph	Ph	Ph	Me	62
Ph	Ph	H	Ph	Ph	63
Ph	H	Ph	Ph	Ph	63
Ph	Ph	Me	Ph	Ph	63
Ph	Me	Ph	Ph	Ph	63
Ph	Ph	Ph	Ph	Ph	63
Ph	$-(CH_2)_3-$		Ph	Ph	63
Ph	$-(CH_2)_4-$		Ph	Ph	63
Ph	$-(CH_2)_5-$		Ph	Ph	63
Ph	$-(CH_2)_6-$		Ph	Ph	63
Ph	*o*-$CH_2C_6H_4CH_2-$		Ph	Ph	63
Ph	*o*-$CH_2C_6H_4CH_2-$		Ph	Ph	63
Ph	*o*-$CH_2C_6H_4CH_2-$		Ph	Ph	63
Ac	H	Me	H	CH_2NHAc	64
Ac	H	H	3-Cl-2-$NO_2C_6H_4$	Me	65–66

In the presence of an amine and diketone, hexoses give the pyrrole having the sugar residue at the 3-position.[70,71]



(4)

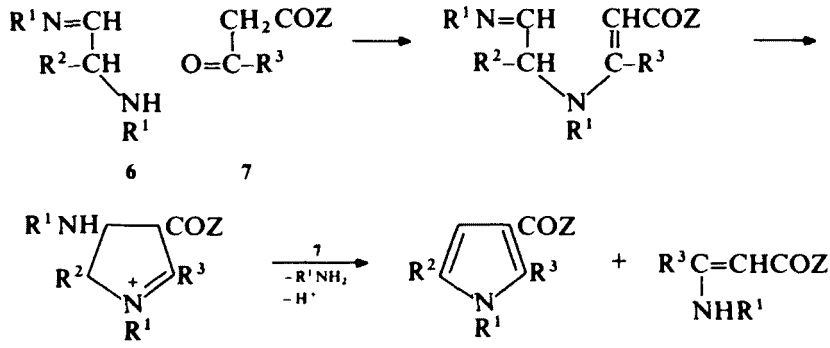
Under the conditions of the Knorr synthesis using ethyl trifluoracetoacetate, reduction of the trifluoromethyl group of the nonnitrosated ketoester also occurs, and the product is the 3-trifluoromethyl-5-methyl compound rather than the 3,5-bis(trifluoromethyl)pyrrole.[42,72,73]



(5)

2.2.1.2. *With α-Aminoimines*

Since imines are the synthetic equivalent of a carbonyl group, it is not surprising that α-aminoimines (**6**) are able to undergo a Knorr-like cyclocondensation with β-dicarbonyl compounds **7** to produce the pyrrole **8**. In this case a second molecule of **7** is required to remove the amine released in the reaction:



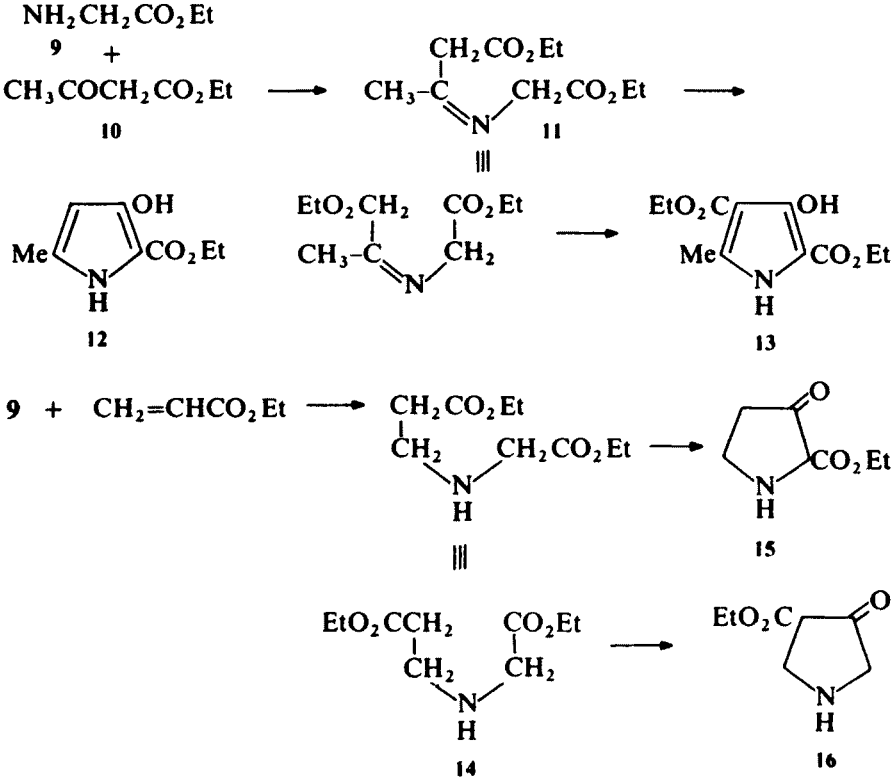
(6)

R^1	R^2	R^3	Z
H	*i*-Pr	Me	Me
H	*i*-Pr	Me	OEt
Me	*i*-Pr	Me	Me
i-Bu	*i*-Pr	Me	Me
n-Pr	*i*-Pr	Me	Me
Et	*t*-Bu	Me	Me
Me	*i*-Pr	Me	OEt
Et	*i*-Pr	Me	OEt
i-Pr	*i*-Pr	Me	OEt
Et	*t*-Bu	Me	OEt
Et	*t*-Bu	Et	OEt
Et	*i*-Pr	$-(CH_2)_3-$	

The reaction, catalyzed by the use of molecular sieve, of an α-aminoaldimine or ketimine **6** with the β-dicarbonyl compound **7** gives an excellent yield (40–80%) of the pyrrole.[74] With an unsymmetrical ketimine (**6**, $R^2 \neq H$), only one product is formed in spite of the possibility of a tautomeric equilibrium.

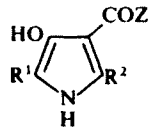
2.2.1.3. With α-Amino Acids to Give 3-Hydroxypyrroles

The imine **11** derived from an α-amino acid **9** and a β-dicarbonyl compound **10** can undergo two different Dieckmann-type condensations to give the 3-hydroxypyrroles **12** or **13**. When refluxed with base, **12** is the product, while if the reaction is carried out with cooling, a mixture of **12** and **13** is produced (Scheme 4).[75] A similar situation is found for the imine **14** formed by the Michael addition of **9** to ethyl acrylate (see Section 2.2.5.4). Under equilibrium conditions, that is, refluxing **14** with an alcoholic solution of the alkoxide, only the more stable **15** is formed, while at 0°C, with alkoxide in toluene, equal amounts of **15** and **16** are produced. If **16** is refluxed with alkoxide, it is completely converted into **15**[76] (see Scheme 2 and Table 2.4).



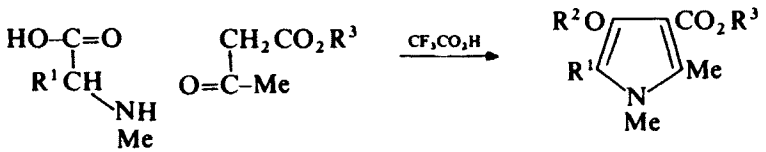
Scheme 2

TABLE 2.4. PYRROLES FROM THE CONDENSATION OF α-AMINOESTERS [$R^1CH(NH_2)CO_2R$] AND β-DICARBONYL COMPOUNDS (R^2COCH_2COZ)



R^1	R	R^2	Z	Ref.
H	Et	Me	EtO	75
H	Et	CH_2CO_2Et	EtO	75
H	Et	Ph	EtO	75
Me	Et	Me	EtO	75
s-Bu	Et	Me	EtO	75
Me	Et	Me	MeO	77
H	Me	Me	MeO	78
Ph	Me	Me	MeO	78
H	Me	Me	Me	78
H	Me	$-(CH_2)_3-$		78

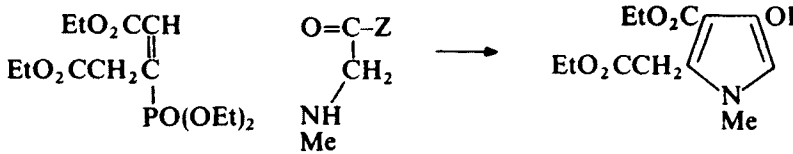
The enamine formed from the free amino acid has been cyclized with trifluoroacetic acid which also acylates the 3-hydroxyl group:[79]



(7)

R^1	R^2	R^3
Ph	H	Et
Ph	H	Me
Me	CF_3CO	Me
Ph	CF_3CO	Me

Three patents report the use of the phosphate enol ester of ethyl acetonedicarboxylate (3-ketoglutarate) **17** with either ethyl N-methylglycine or its acid chloride **18**:[80–82]



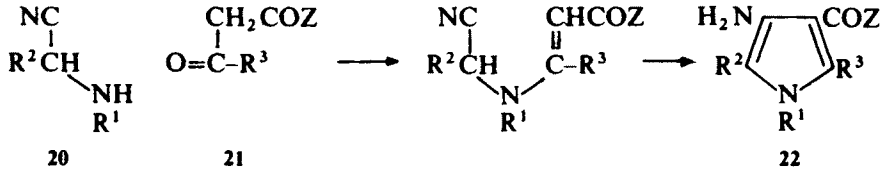
(8)

17 **18** **19**

Z = Cl or OEt

2.2.1.4. *With α-Aminonitriles to Give 3-Aminopyrroles*

Under normal conditions, a Knorr-like condensation of β-dicarbonyl compounds **21** with α-aminonitriles **20** will yield a 3-aminopyrrole **22** (see Scheme 3 and Table 2.5).



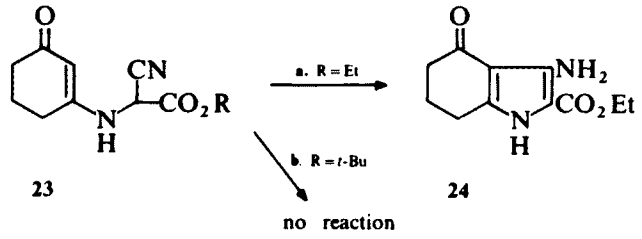
20 **21** **22**

Scheme 3

TABLE 2.5. PYRROLES (**22**, R^1 = H) FROM CONDENSATION OF AMINONITRILES WITH DICARBONYL COMPOUNDS

R^2	R^3	Z	Ref.
H	Me	MeO	78
H	Me	Me	78
H	Me	Ph	78
H	Me	NH_2	78
H	Ph	EtO	83
H	Ph	Ph	83
Me	Ph	EtO	83
Me	H	EtO	83
Me	H	Me	83
Me	Et	Me	83
Me	Ph	Me	83
Me	Ph	Ph	83
CO_2Et	Ph	Ph	83
Me	H	Ph	83
Ph	Me	MeO	84
Ph	Ph	Me	84
Ph	Ph	Ph	84
Ph	CO_2Me	MeO	84
p-C_6H_5	Me	EtO	84
$CONH_2$	Me	EtO	85
CONHMe	Me	EtO	85
Ph	Me	MeO	86
Ph	Me	EtO	87
Ph	Me	Ph	87
Ph	Me	Me	87
Ph	Me	MeO	78
Ph	CO_2Me	MeO	78
Ph	$-(CH_2)_3-$		78

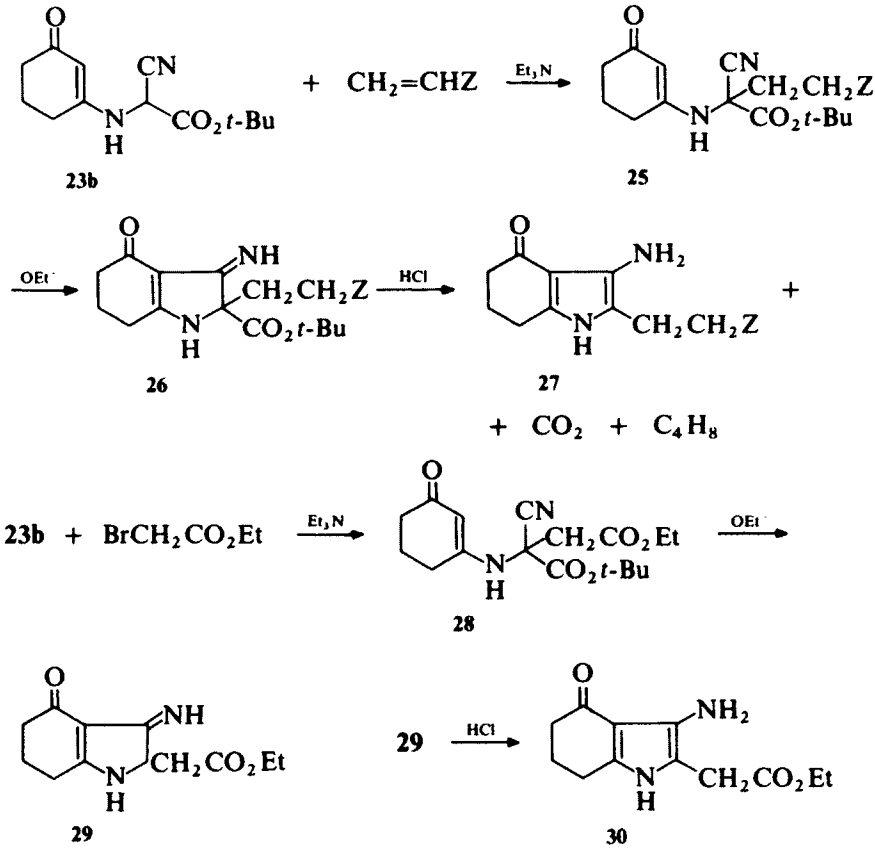
Similarly, the treatment of the enamine **23a** derived from cyclohexanedione with ethyl aminocyanoacetate with strong base will yield the expected aminopyrrole **24**[88] (see Scheme 4).



23 24

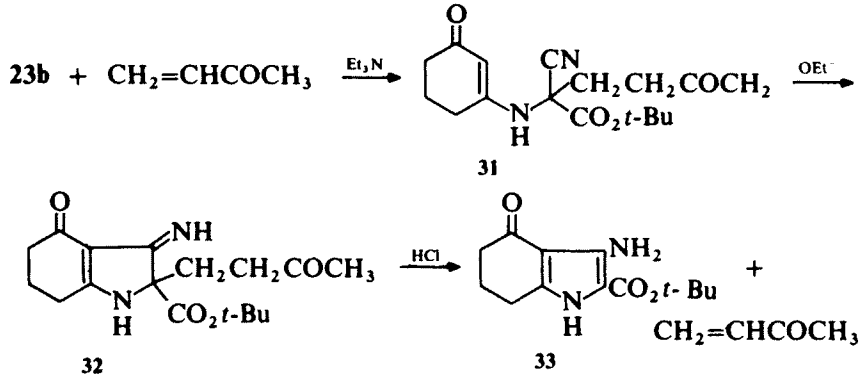
Scheme 4

However, when a *t*-butyl ester function is used, the enamine (**23b**) does not undergo ring closure, presumably as a result of steric interference. The Michael adducts **25a** or **25b**, or the alkylated species **28**, will ring-close with the formation of the imino pyrroles **26a** or **26b** or **29**. Treatment of **25** or **29** with dry HCl eliminates carbon dioxide and isobutylene from the *t*-butyl ester function to give the 3-aminopyrroles **27** or **30**[89] (Scheme 5).



23b 25 26 27 28 29 30

Scheme 5



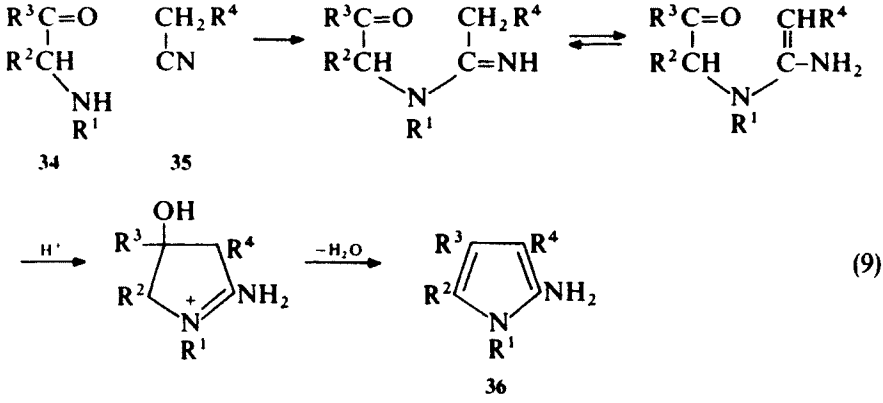
Scheme 5 (*Contd.*)

Interestingly, the Michael adduct **31**, derived from **23b** and but-1-en-3-one, undergoes ring closure to give **32** and then aromatizes via a retro-Michael reaction to give the *t*-butyl ester **33**, which could not be formed directly.

The enamines from ethyl acetoacetate gives results similar to those from use of the cyclohexanedione.

2.2.2. Condensation of α-Aminoketones with Nitriles to Give 2-Aminopyrroles

The condensation of α-aminoketones **34** with a difunctional nitrile **35** through the nucleophilic addition of the amine function to the nitrile group is somewhat analogous to the Knorr synthesis and results in a 2-aminopyrrole **36**. A number of examples using malononitrile to give the 2-amino-3-cyanopyrrole have been reported. In the case of ethyl cyanoacetate, condensation occurs only at the nitrile group; that is, no 2-hydroxypyrrole is produced:



(9)

The aminoketones can often be formed in situ from the reaction of acyloins with ammonia or amines (see Eq. 10 and Table 2.6).

$$R^1NH_2 + R^2CHOHCOR^3 \longrightarrow R^1NHCHR^2COR^3 + H_2O \quad (10)$$

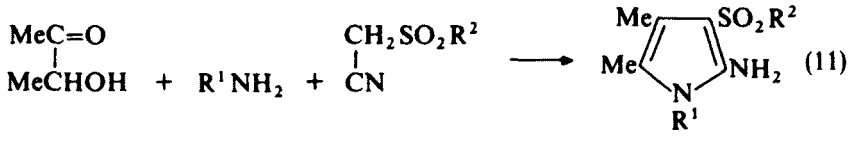
TABLE 2.6. 2-AMINOPYRROLES (36) FROM CONDENSATION OF AMINOKETONES WITH NITRILES

R^1	R^2	R^3	R^4	Ref.
H	Me	Me	CN	90
H	H	Me	CN	90
H	H	Ph	CN	90
H	Me	Ph	CN	90
H	H	Ph	Ph	91
H	H	Ph	CN	91
H	Me	Me	CN	92[a]
H	Me	Et	CN	92[a]
H	Et	Me	CN	92[a]
H	Pr	Me	CN	92[a]
H	Et	Pr	CN	92[a]
H	H	Ph	CN	92[a]
H	H	Me	CN	93[a]
H	H	Me	CO_2t-Bu	93[a]
H	CH_2Ph	Me	CN	94[a]
H	Ph	Me	CN	94[a]
Ph	Me	Me	CN	95[b]
$PhCH_2$	Me	Me	CN	95
PhC_2H_4	Me	Me	CN	95
cyclo-C_6H_{11}	Me	Me	CN	95
n-C_6H_{13}	Me	Me	CN	95
$Me_2NC_2H_4$	Me	Me	CN	95
C_2H_4HO	Me	Me	CN	95
Ph	Ph	Ph	CN	95
$PhCH_2$	Ph	Ph	CN	95
n-C_6H_{13}	Ph	Ph	CN	95
cyclo-C_6H_{11}	Ph	Ph	CN	95
$Me_2NC_2H_4$	Ph	Ph	CN	95
C_2H_4HO	Ph	Ph	CN	95
Ph	Me	Me	CN	95
$PhCH_2$	Me	Me	CN	95
PhC_2H_4	Me	Me	CN	95
n-C_6H_{13}	Me	Me	CN	95
cyclo-C_6H_{11}	Me	Me	CN	95
$(CH_2)_3NMe_2$	Me	Me	CN	95
C_2H_4OH	Me	Me	CN	95
Ph	Ph	Ph	CN	95
$PhCH_2$	Ph	Ph	CN	95
n-C_6H_{13}	Ph	Ph	CN	95
cyclo-C_6H_{11}	Ph	Ph	CN	95
$(CH_2)_3NMe_2$	Ph	Ph	CN	95
C_2H_4OH	Ph	Ph	CN	95
$PhCH_2$	Me	Me	CO_2Me	96[b]
CO_2t-Bu	Me	Me	CO_2Me	96[b]

[a] *N*-Acetyl group hydrolyzed during reaction.

[b] From acyloin.

With alkylsulfonylacetonitriles (**37**) the corresponding alkylsulfonylpyrroles (**38**) are formed:[97]



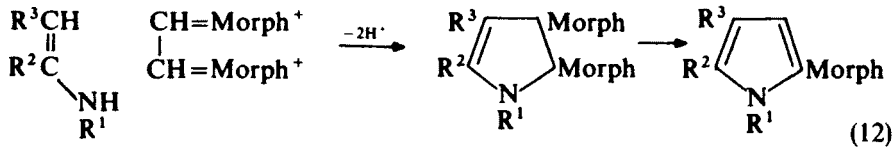
(11)

37 **38**

R^1	R^2
n-Bu	Me
n-Bu	Ph
n-Bu	*p*-Tol
n-Bu	*p*-ClC_6H_4
cyclo-C_6H_{11}	Me
cyclo-C_6H_{11}	CH_2CN
cyclo-C_6H_{11}	Ph
cyclo-C_6H_{11}	*p*-Tol
cyclo-C_6H_{11}	*p*-ClC_6H_4
$PhCH_2$	Me
$PhCH_2$	CH_2CN
$PhCH_2$	Ph
$PhCH_2$	*p*-Tol

2.2.3. Condensation of Enamines with Diimines

Pyrroles carrying a secondary amino group at position 5 (**42**) can be prepared by the condensation of an enamine **39** with a diimmonium salt **40**.The reaction presumably involves the formation of the 2,3-diaminopyrroline intermediate **41** by the initial addition of the enamine to the imine through, either the carbon–carbon or nitrogen–carbon bond formation:[98]



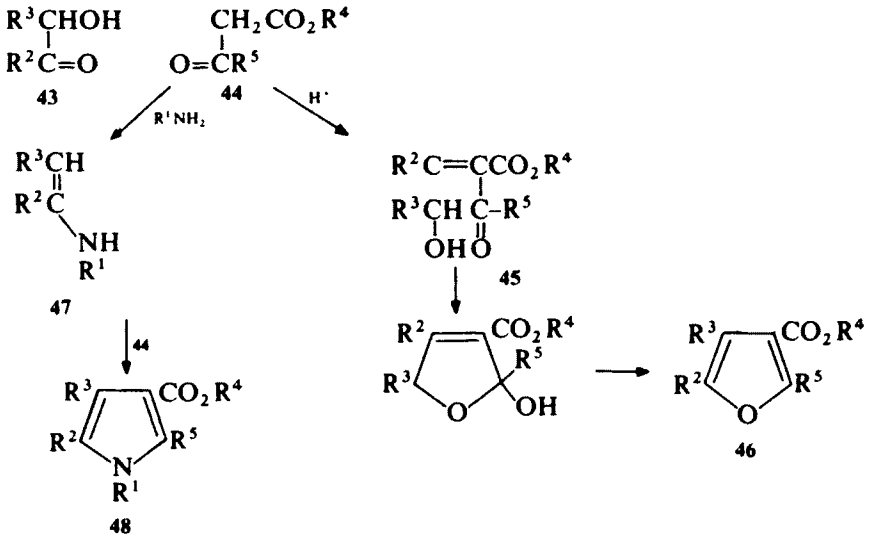
(12)

39 **40** **41** **42**

R^1	R^2	R^3
Me	Me	CO_2Et
$PhCH_2$	Me	CO_2Et
Me	Me	CO_2i-Pr
Ph	Me	CO_2Et
n-Bu	Ph	Ph
n-Bu	Ph	Me
H	Me	CO_2Et
$PhCMeCH_2$	Me	CO_2Et
t-Bu	Me	CO_2Et

2.2.4. Condensation of Enamines with Acyloins: The Feist Synthesis

Under acidic conditions, heating an unsymmetrical acyloin **43** and a ketoester **44** results in the formation of a furan **46**. The addition of an amine or ammonia to the reaction system produces a pyrrole **48** (Scheme 6). Both reactions are referred to as *Feist synthesis*. However, the resulting pyrrole and furan have the opposite orientation of the acyloin moiety. The furan can result by an acid-catalyzed aldol condensation with the initial formation of the C_3–C_4 bond to give **45**, followed by ring closure via a hemiacetal and subsequent dehydration. However, the pyrrole probably results from the initial formation of an enamine **47**, which then undergoes a Knorr-type condensation. Thus, the opposite orientation results (Scheme 6).



Scheme 6

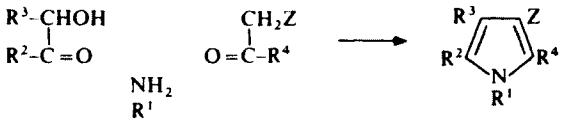
A large number of pyrroles, particularly 2,3-diarylpyrroles, have been prepared by this method, which gives yields of approximately 50% (see Tables 2.7–2.9).

2.2.5. Michael Addition to Alkenes and Alkynes

2.2.5.1. Of α-Aminoketones

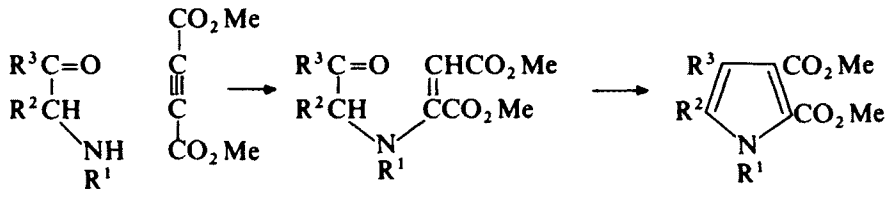
The enamines **51**, which are the product of Michael addition of aminoketones **49** to acetylenic esters **50**, undergo ring closure to the pyrrole **52**. NMR studies

TABLE 2.7. PYRROLES PREPARED BY THE FEIST SYNTHESIS



R^1	R^2	R^3	R^4	Z	Ref.
H	Ph	Ph	Me	CO_2Et	99
H	Ph	H	Me	CO_2Et	99
H	Me	Me	Me	CO_2Et	99
H	Ph	Ph	Me	CO_2Et	100
H	*p*-$MeOC_6H_4$	Ph	Ph	*p*-$MeOC_6H_4$	101
H	*p*-$MeOC_6H_4$	Ph	Ph	*p*-$EtOC_6H_4$	101
H	*p*-$EtOC_6H_4$	Ph	Ph	*p*-$EtOC_6H_4$	101
H	*p*-Tol	Ph	Ph	*p*-$EtOC_6H_4$	101
H	*p*-Tol	Ph	Ph	*p*-Tol	101
H	*p*-$MeOC_6H_4$	Ph	Ph	*p*-ClC_6H_4	101
H	*p*-BrC_6H_4	Ph	Ph	*p*-Tol	101
H	*p*-Tol	Ph	Ph	*p*-ClC_6H_4	101
H	*p*-BrC_6H_4	Ph	Ph	*p*-ClC_6H_4	101
H	Ph	Ph	Ph	Ph	102–103
H	Ph	Ph	2-naphthyl	Ph	104
H	Ph	Ph	Me	CO_2Et	105
Ph	Ph	Ph	Me	CO_2Et	99
o-Tol	Ph	Ph	Me	CO_2Et	99
p-Tol	Ph	Ph	Me	CO_2Et	99
$PhCH_2$	Ph	Ph	Me	CO_2Et	99
Ph	Ph	H	Me	CO_2Et	99
o-Tol	Ph	H	Me	CO_2Et	99
p-Tol	Ph	H	Me	CO_2Et	99
$PhCH_2$	Ph	H	Me	CO_2Et	99
o-$NMe_2C_6H_4$	Ph	H	Me	CO_2Et	99
Me	Ph	H	Me	CO_2Et	99
Ph	Me	Me	Me	CO_2Et	99
Me	Me	Me	Me	CO_2Et	99
Ph	Ph	Ph	Ph	CO_2Et	99

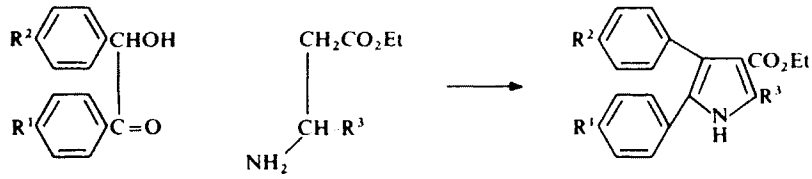
of the enamines show that they have the maleate rather than fumarate stereochemistry, favorable for ring closure[106] (see Eq. 13 and Table 2.10).



49 **50** **51** **52**

(13)

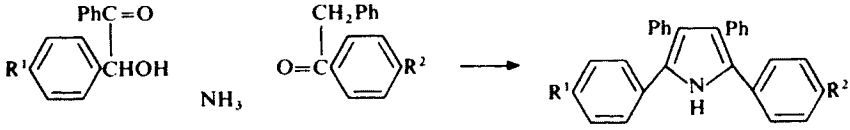
TABLE 2.8. 2,3-DIARYLPYRROLES FORMED BY THE FEIST SYNTHESIS[a]



R^1	R^2	R^3
MeO	MeO	Me
MeO	MeO	Et
MeO	Cl	Me
Cl	MeO	Me
MeO	MeO	*n*-Bu
MeO	MeO	*i*-Bu
MeO	MeO	*n*-Pr
Me	Me	Me
MeO	Me_2N	Me
Me_2N	Me_2N	Me
Cl	Cl	Me
Cl	H	Me

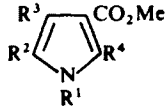
[a] Ref. 100.

TABLE 2.9. TETRAARYLPYRROLES FORMED BY THE FEIST SYNTHESIS



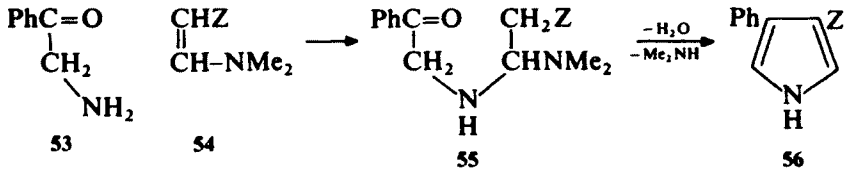
R^1	R^2	Ref.
MeO	MeO	101
MeO	EtO	101
EtO	Et	101
Me	EtO	101
Me	Me	101
MeO	Cl	101
Br	Me	101
Me	Cl	101
Br	Cl	101
Ph	H	102
Ph	MeO	102
Ph	EtO	102
Ph	Me	102
Ph	Cl	102
H	2-Naphthyl	104
MeO	2-Naphthyl	104
EtO	2-Naphthyl	104
Cl	2-Naphthyl	104
Br	2-Naphthyl	104

TABLE 2.10. PYRROLES FORMED BY ADDITION OF α-AMINOKETONES [$R^2CH(NHR^1)COR^3$] TO ALKYNIC ESTERS ($R^4C{\equiv}CCO_2Me$)



R^1	R^2	R^3	R^4	Ref.
H	Ac	Me	CO_2Me	105
H	Ph	Ph	CO_2Me	108–109
H	*p*-$MeOC_6H_4$	*p*-$MeOC_6H_4$	CO_2Me	110
cyclo-C_6H_{11}	H	Ph	CO_2Me	106
Ph	Ph	Ph	CO_2Me	111
Ph	Ph	Ph	H	111
Et	H	Ph	H	112
Et	H	Ph	CO_2Me	112
Ph	H	Ph	CO_2Me	113
o-Tol	H	Ph	CO_2Me	106, 113
p-Tol	H	Ph	CO_2Me	106
p-$MeOC_6H_4$	H	Ph	CO_2Me	106
o-EtC_6H_4	H	Ph	CO_2Me	106, 113
p-ClC_6H_4	H	Ph	CO_2Me	106,113
2-Naphthyl	H	Ph	CO_2Me	106
Ph	H	Ph	CO_2Me	106, 114

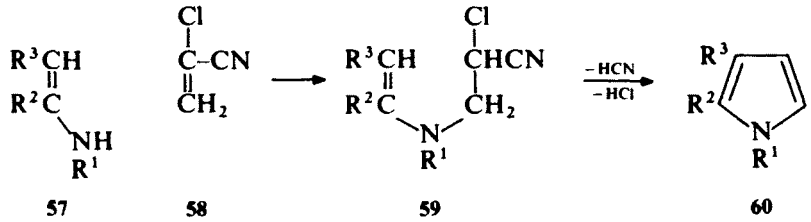
Loss of the amine from the product (**55**) of the Michael addition of aminoetones **53** to aminovinyl compounds **54** (Z = CN, CHO, CO_2R) leads to the formation of the pyrrole **56**:[115]



(14)

2.2.5.2. *Of Enamines*

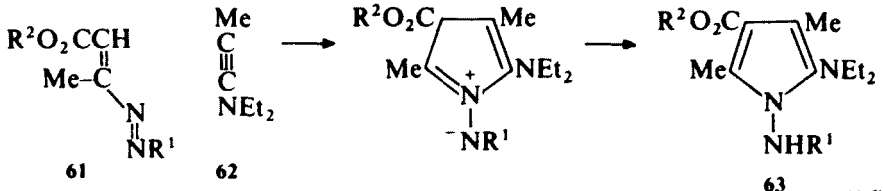
The Michael adduct **59** of an enamine **57** with chloroacrylonitrile (**58**) losses HCl and HCN to give the pyrrole unsubstituted at positions 4 and 5 (**60**) (Eq. 15). The yields range from 21 to 69%.[116]



57 58 59 60 (15)

R^1	R^2	R^3
Ph	Me	Me
n-Bu	Me	*n*-Pr
Ph	$-(CH_2)_3-$	
Ph	$-(CH_2)_4-$	
o-$MeOC_6H_4$	$-(CH_2)_4-$	
p-$MeOC_6H_4$	$-(CH_2)_4-$	
o-ClC_6H_4	$-(CH_2)_4-$	
p-ClC_6H_4	$-(CH_2)_4-$	
$PhCH_2$	$-(CH_2)_4-$	
Ph	$-(CH_2)_5-$	

The azoalkenes (or hydrazones of acetoacetic ester) **61** add to 1-(*N*,*N*-dimethylamino)propyne **62** to give the 1,2-diaminopyrroles **63**:[117]



61 62 63 (16)

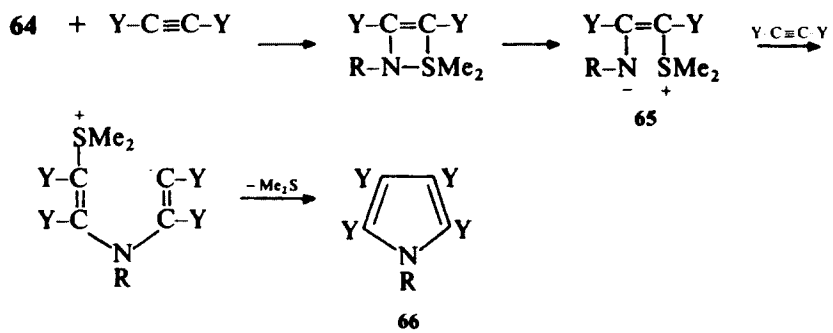
R^1	R^2
p-Tos	Me
p-Tos	Et
TBOC	Me
TBOC	Et

2.2.5.3. Of Betaines

The reaction of an arylamine with dimethylsulfide produces a sulfimide **64**, which can react with activated alkynes. The cycloadduct immediately opens to give the betaine **65**, which in turn, may add a second molecule of the alkyne to give the pyrrole **66**:[118]

$$RNH_2 + Me_2S \xrightarrow{NCS} RN{=}SMe_2 \qquad (17)$$

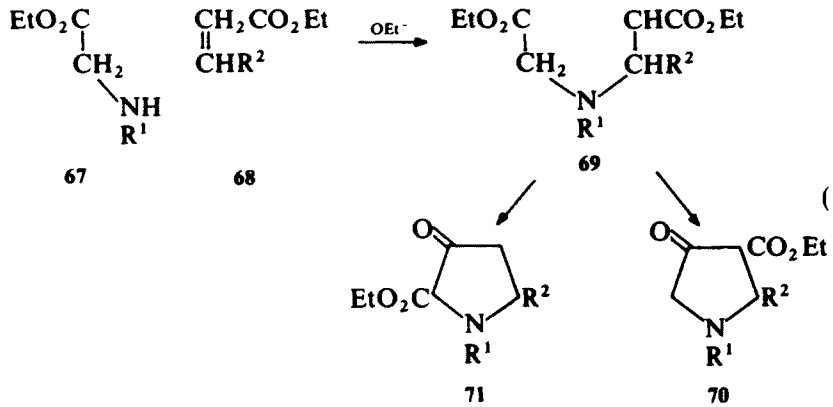
64



R	Y
p-ClC$_6$H$_4$	CO$_2$Me
p-ClC$_6$H$_4$	COPh
p-ClC$_6$H$_4$	COPh
m-ClC$_6$H$_4$	COPh

2.2.5.4. *Of α-Amino Acids to Give 3-Hydroxypyrroles*

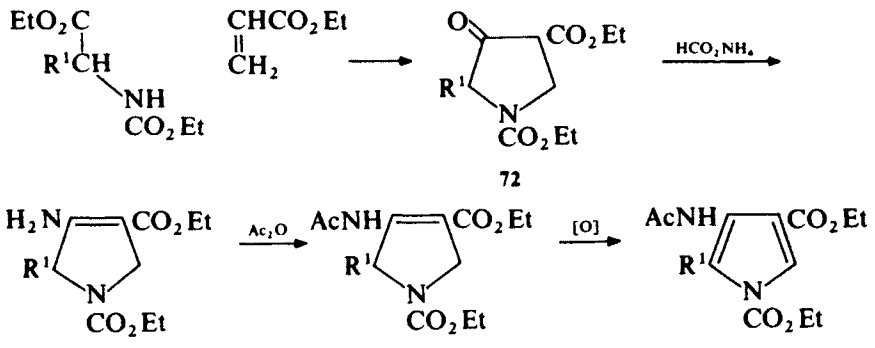
As mentioned in Section 2.2.1.3, the products **69** of the addition of aminoacids **67** to acrylates **68** can undergo a Dieckmann ring closure to either give the pyrrolidones **70** or **71**:[119]



(18)

R^1 = Me or CO_2Et; R^2 = H, Me, Ph, or CO_2Et

Rapoport has shown that, although **70** is the more stable product and is formed exclusively under equilibrium conditions with refluxing sodium *t*-butoxide in ethanol, **70** and **71** are formed in roughly equal amounts in toluene and sodium *t*-butoxide at 0°C. Similarly, **71** is completely converted into **70** in refluxing sodium *t*-butoxide–ethanol.[76] The product **72** from the addition of substituted amino acids to ethyl acrylate can be converted into the 3-acetamidopyrrole **74** by aerial oxidation of the *N*-acetyl enamine **73**:[120]

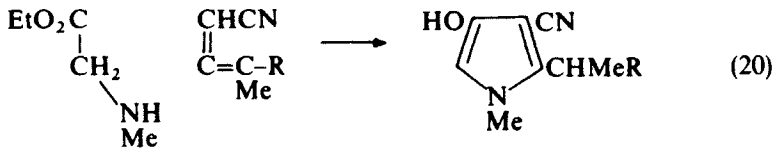


72

73 74 (19)

R = Et, *i*-Bu, $PhCH_2$, $-(CH_2)_4OH$, or $-(CH_2)_2SMe$

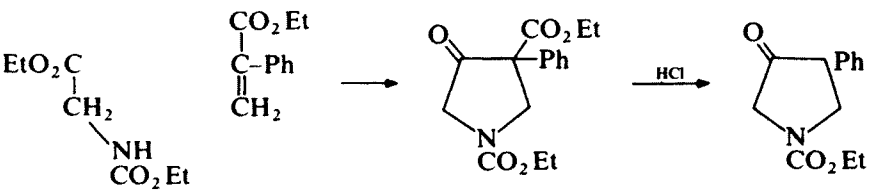
The addition of ethyl *N*-methylglycinate (**75**) to the allenic nitrile **76** produces the hydroxypyrrole **77** (actually in the keto form) (Eq. 20). With ethyl glycinate itself, however, the product is an enaminonitrile, which does not cyclize.[121]



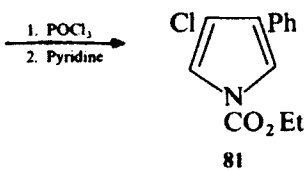
75 76 77 (20)

R = Me or Et

The pyrrolidone **80** resulting from the addition of *N*-carbethoxyglycinate (**78**) to the acrylate **79** can be converted into the *β*-chloropyrrole **81** by decarboxylation followed by treatment with $POCl_3$:[122–123]

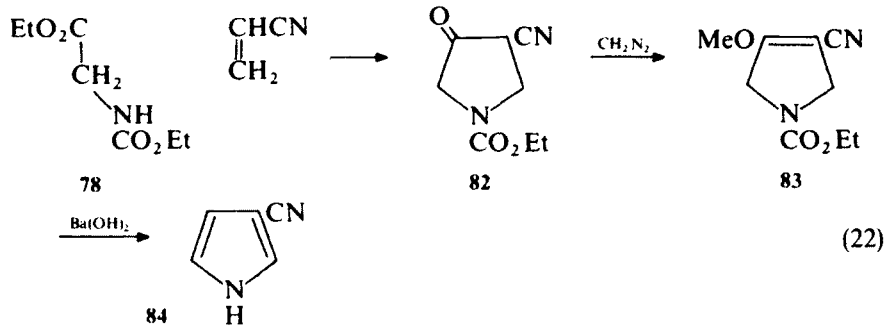


78 79 80



81 (21)

Similarly, **78** adds to acrylonitrile and to yield the pyrrolidone **82**, which produces 3-cyanopyrrole (**84**) via the initial formation of the enol ether **83** and subsequent treatment with barium hydroxide:[18]

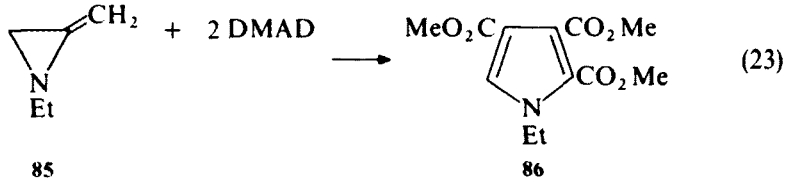


(22)

2.2.6. Ring Opening of 3-Membered Ring Compounds

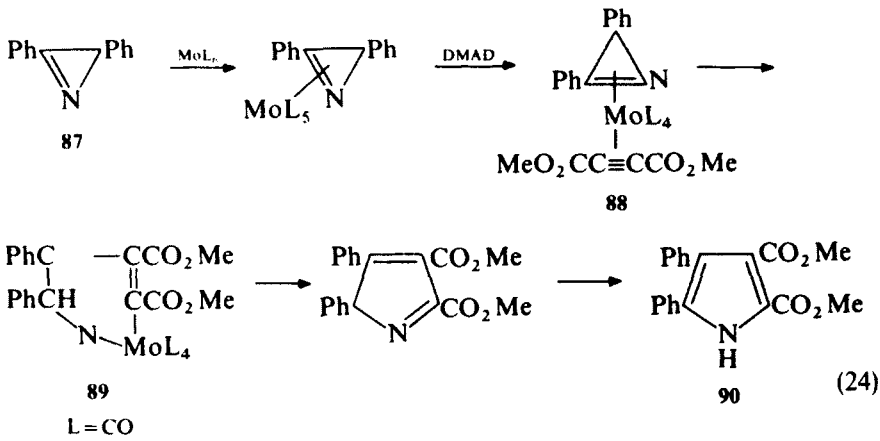
2.2.6.1. From Azirines and Aziridines

The formation of the pyrroletricarboxylate **86** from the aziridine **85** requires two molecules of DMAD, but the mechanism is unclear:[124]



(23)

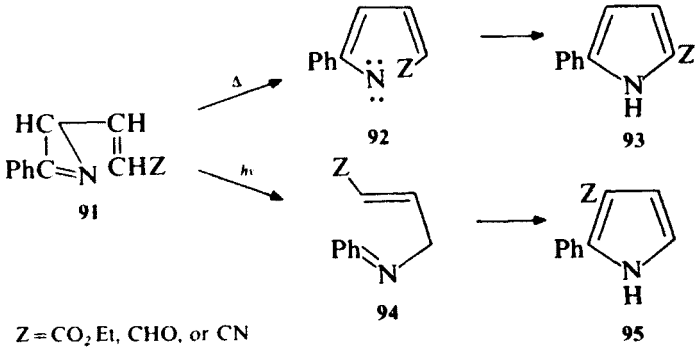
It is suggested that the reaction of diphenylazirine (**87**) with DMAD, catalyzed by molybdenum(0) hexacarbonyl, involves the initial formation of a π-complex **88**, which then is transformed into the σ-complex **89**; thence to the pyrrole **90** (20%):[125]



(24)

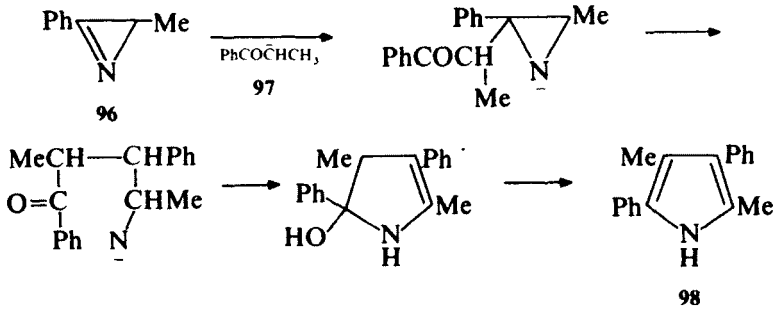
Thermolysis of 3-acrylazirines **91** produces the 5-substituted pyrroles **93** via cleavage of the C=N bond to form the nitrene, while photolysis of **91** gives the

alternate product **95** through the formation of a nitrile ylide **94**, followed by an electrocyclic ring closure:[126]



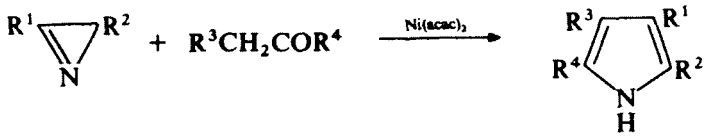
$Z = CO_2Et$, CHO, or CN (25)

Addition of carbanions to azirines, followed by ring enlargement, produce pyrroles (Eq. 26). For example, the carbanion of propiophenone (**97**) reacts with phenylmethylazirine (**96**) to give 2,4-diphenyl-3,5-dimethylpyrrole (**98**) (90%).[127]



(26)

The nickel-catalyzed reaction of azirines and ketones produces, in excellent yields, analogous pyrroles:[128]

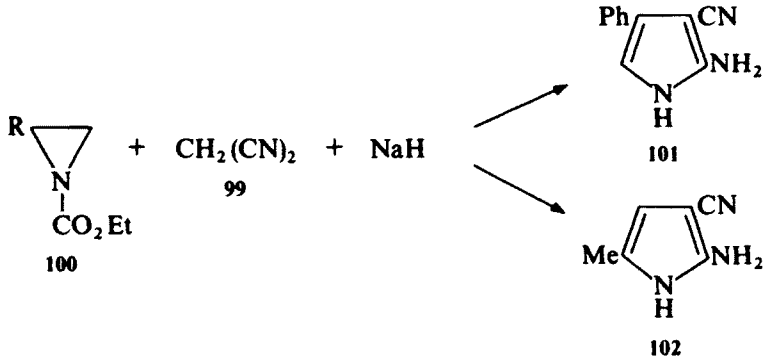


(27)

R^1	R^2	R^3	R^4
Ph	H	Ac	Me
Ph	Me	Ac	Me
Ph	Ph	Ac	Me
Ph	H	CO_2Et	Me
Ph	H[a]	Ac	Ph
Ph	H	CN	Ph
Ph	Ph	CN	Ph
Ph	H	CO_2Et	Ph

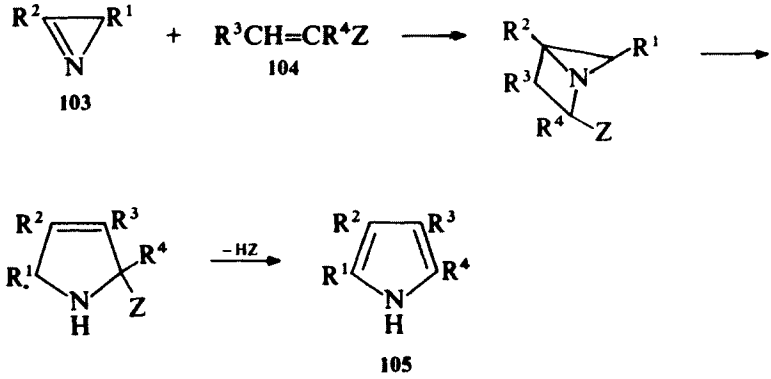
[a] Mixture of isomers

The direction of attack by the carbanion of malononitrile (**99**) on the monosubstituted carbon-substituted *N*-carbethoxyaziridine **100** depends on the substituent. In the case of the phenyl compound, attack occurs on the substituted carbon atom so as to produce **101**, but, with a methyl group, attack is at the unsubstituted position to yield **102**:[129]



(28)

The reaction of azirines **103** with enamines **104** gives excellent yields of pyrroles **105**; presumably through addition across the carbon–nitrogen double bond followed by expansion to the 5-membered ring:



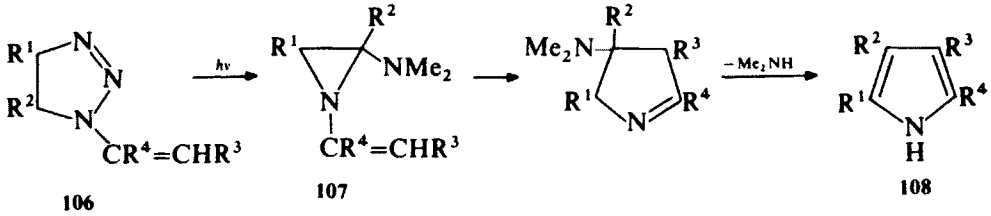
(29)

R^1	R^2	R^3	R^4	Z	Ref.
CO_2Me	CO_2Me	H	Ph	NMe_2	130
CO_2Me	CO_2Me	Ph	Me	NMe_2	130
CO_2Me	CO_2Me	Ph	Me	NMe_2	131
CO_2Me	CO_2Me	Ph	Ph	NMe_2	131
CO_2Me	Ph	Me	Et	Pyr	132
CO_2Me	Ph	Ph	Et	Pyr	132
CO_2Me	Ph	H	Ph	Pyr	132
CO_2Me	Ph	$-(CH_2)_3-$		Pyr	132

Pyr = Pyrrolidino.

2.2.6.2. *From N-Vinylaziridines*

Photolysis of *N*-vinyltriazoles **106** produce the *N*-vinylaziridines **107**, which undergo ring expansion to give surprising good yields (up to 83%) of the pyrroles **108**:[133,134]



106 **107** **108**

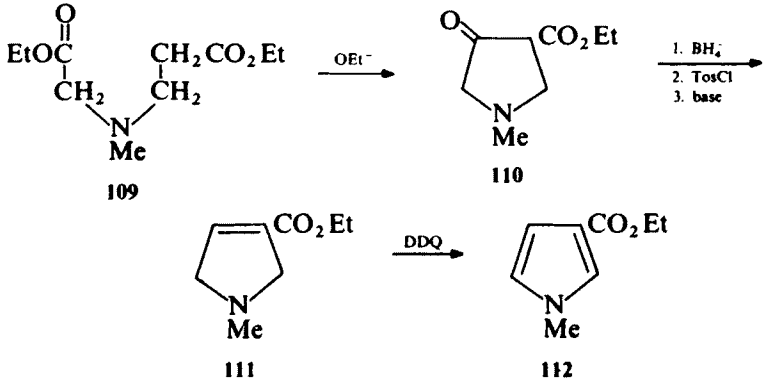
(30)

R^1	R^2	R^3	R^4	Z
H	Me	H	Ph	a
H	Et	H	Ph	a
	$-(CH_2)_4-$	H	Ph	a
H	Me	H	Ph	b
H	Me	Ph	H	b
Ph	H	Ph	H	c

a = pyrrolidino; b = piperidino; c = morpholino.

2.2.7. Miscellaneous Reactions

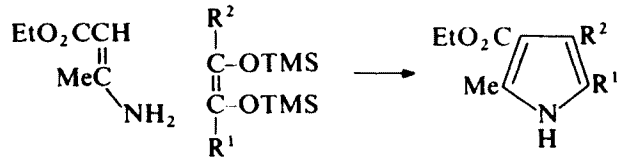
Dieckmann ring closure of **109**, which is produced by the Michael addition of methylamine to an acrylate followed by alkylation with ethyl bromoacetate, gives the pyrrolidone **110**. Conversion into the Δ^3-pyrroline **111** and oxidative aromatization produces the ethyl 1-methylpyrrole-2-carboxylate **112**:[135]



109 **110** **111** **112**

(31)

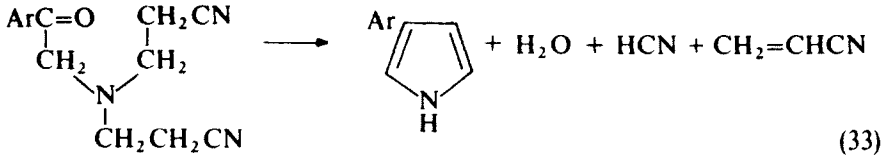
The enamine from ethyl acetoacetate and ammonia **113** adds to bis(trimethylsiloxy)alkenes **114** to give the pyrrole **115**:[136]



113 114 115 (32)

R^1	R^2
n-Pr	*n*-Pr
	$(CH_2)_4$
	$(CH_2)_5$
	$(CH_2)_7$

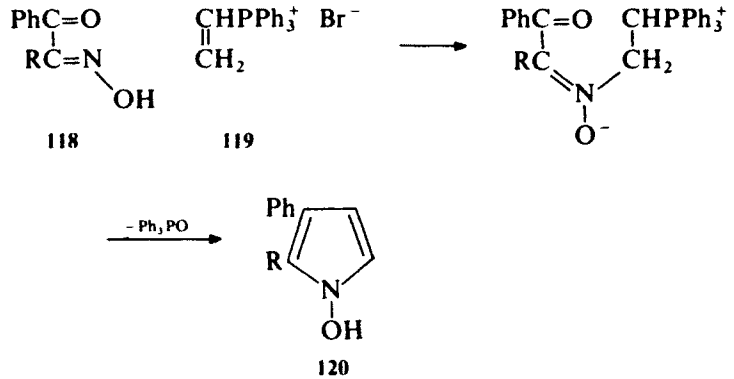
Two patents describe the preparation of **117** by the cyclization of the *N*,*N*-dicyanoethyl aminoketone **116** with the loss of water and HCN with acrylonitrile:[137,138]



116 117 (33)

Ar = *m*-$CF_3C_6H_4$

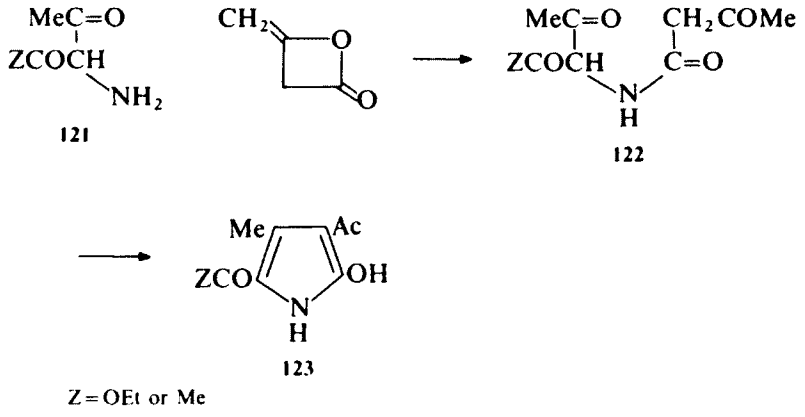
The *E*-stereoisomer of the monooxime of the α-dicarbonyl compounds **118** presumably add to the vinyl Wittig reagent **119** by attack on nitrogen rather than oxygen, since the product is a 1-hydroxypyrrole **120** in preference to the alternate 1,2-oxazine:[139]



118 119 120 (34)

R = H, Ph, or CO_2Et

Cyclization of the *N*-acetoacetyl compound **122** produced by the reaction of the aminoketone **121** with diketene, gives the 2-hydroxypyrrole **123**, albeit in poor yield:[140]



121 122 123

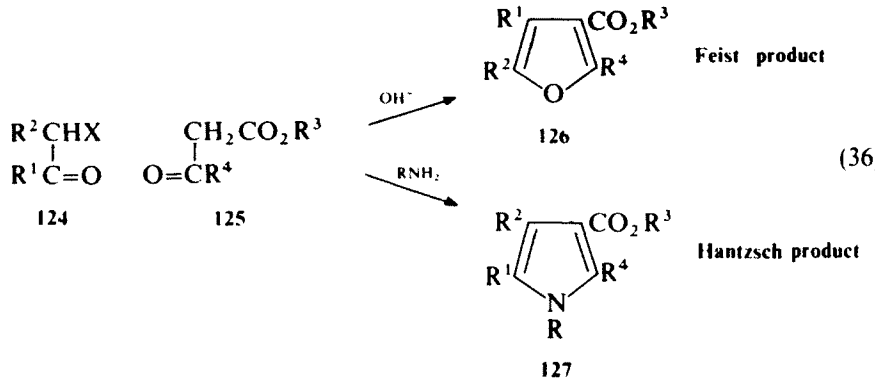
Z = OEt or Me

(35)

2.3. FORMATION OF PYRROLES FROM TWO 2-CARBON COMPOUNDS WITH INITIAL FORMATION OF C_3–C_4 BOND

2.3.1. From α-Haloketones, Amines, and Dicarbonyl Compounds or Enamines: The Hantzsch Synthesis

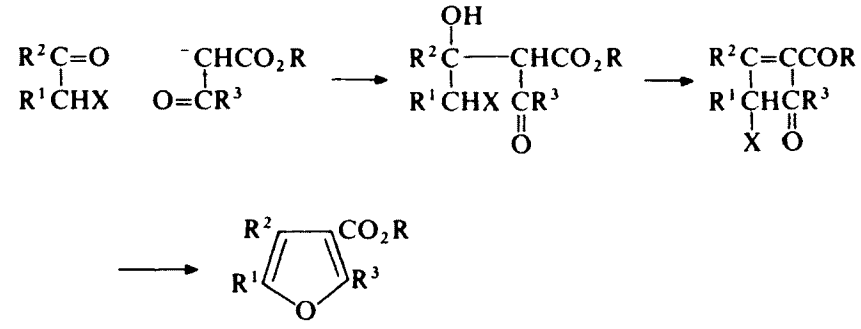
When carried out in an aqueous solution of sodium hydroxide, the condensation of an α-haloketone **124** with a β-ketoester **125** produces a furan **126** in what is termed the *Feist synthesis of furans.*[141] If the base is ammonia or a primary amine, however, the pyrrole **127** with a different orientation of the substituents is formed (Eq. 36). The reaction is known as the *Hantzsch synthesis of pyrrole.*[142]



124 125 126 127

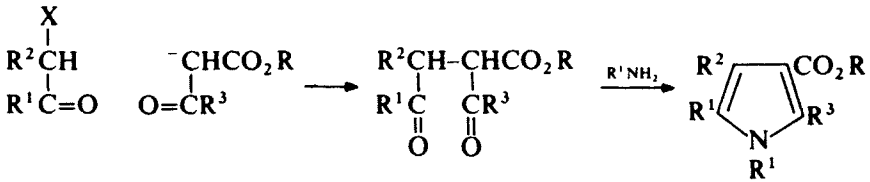
(36)

It has been suggested that, in the presence of hydroxide ion, there is an initial aldol-type condensation, which is followed by ring closure[143] (Scheme 7), whereas with ammonia or an amine, initial displacement of the halogen occurs to give a 1,4-diketone.



Scheme 7

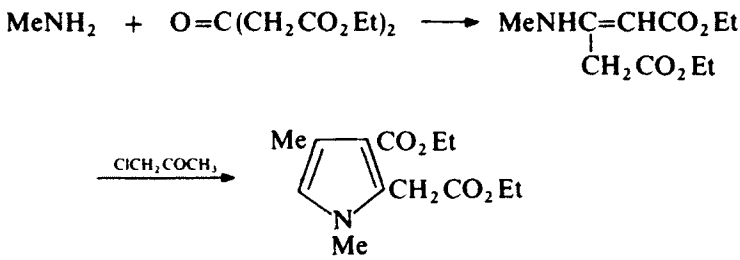
This then undergoes a typical Paal–Knorr ring closure (see Section 2.7.1) (Scheme 8).



Scheme 8

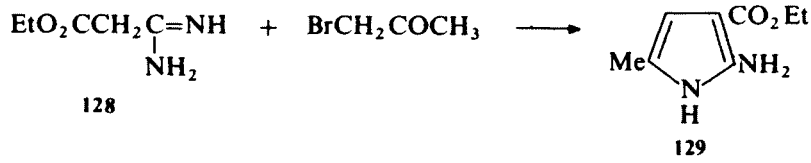
Unfortunately, from the synthetic standpoint, competition between the Feist and the Hantzsch often gives a mixture of the pyrrole and furan, although furan formation is diminished when a primary amine is used in place of the less nucleophilic ammonia.[144]

Contrary to the usual Hantzsch synthesis, a series of patents have claimed that, if the haloketone is added *after* the ketoester and amine are mixed, that is, the imine or enamine is initially formed, the resulting pyrrole has the "Feist type" of orientation:[145–149]



(37)

This finding seems to conflict with the recent reports that bromoacetone reacts with the carbethoxy amidine **128** to give the 5-methyl (Hantzsch) product **129**, rather than the 4-methyl (Feist) product:[150,151]



(38)

Roomi and MacDonald have made the most complete investigation of the utility and limitations of the Hantzsch synthesis[152] and have found that haloaldehydes, regardless of chain length, give better yields of the pyrrole than do haloketones. Although the reaction with bromoacetaldehyde, *t*-butyl, and benzyl acetoacetate gave the corresponding pyrroles, there was no reaction with chloroacetone. Table 2.11 lists the various pyrroles that have been prepared by the Hantzsch synthesis.

TABLE 2.11. PYRROLES (127) FORMED BY THE HANTZSCH SYNTHESIS

R	R^1	R^2	X	R^4	R^3	Ref.
H	Me	H	Cl	Me	Et	152
H	Me	H	Cl	Me	Me	152
H	Me	H	Cl	Me	CH_2Ph	152
H	H	Et	Cl	Me	Et	152
H	H	Et	Br	Me	Et	152
H	H	Et	Br	Me	*t*-Bu	152
H	H	Et	Br	Me	CH_2Ph	152
H	H	Et	Br	Et	Et	152
H	H	Et	Br	*n*-Pr	Et	152
H	Et	Me	Br	Me	Et	152
H	Et	C_5H_{11}	Br	Me	Et	152
H	Et	C_5H_{11}	Br	Et	Et	152
Me	Me	H	Cl	CH_2CO_2Et	Et	145–148[a]
CH_2CH_2OH	H	H	Cl	CH_2CO_2Et	Et	149[a]

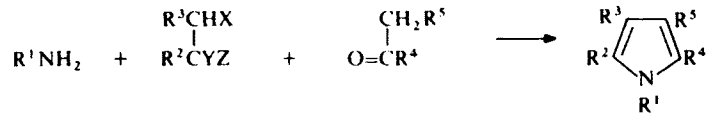
[a] Reverse addition.

Rather than use an α-haloketone, it has often been found advantageous to use either a dihaloether or a dihaloester in what is usually termed the *Feist–Benary modification* of the Hantzsch synthesis.[153,154] As can be seen in Table 2.12, the dibromoacetate has been utilized more than the dichloro ether and gives the better yield of pyrrole. It has been the method of choice to prepare pyrroles having no substituents at positions 4 and 5 ($R^2 = R^3 = H$).

2.3.2. From α-Haloketones and Schiff's Bases or Aza-Wittig Reagents

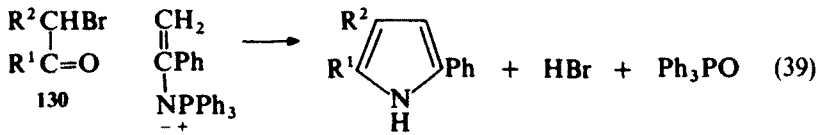
The aza-Wittig reagent **131** reacts with α-haloketones **130** to give the 2-substituted or 2,3-disubstituted 5-phenylpyrrole **132** in a manner similar to that of the Hantzsch synthesis.[159] With the exception of the reactions involving

TABLE 2.12. PYRROLES FORMED BY THE FEIST-BENARY PROCEDURE



R^1	R^2	R^3	X	Y	Z	R^4	R^5	Ref.
H	H	H	Br	Br	OAc	Me	CO_2Et	155–156
Me	H	H	Br	Br	OAc	Me	CO_2Et	144, 155
Ph	H	H	Br	Br	OAc	Me	CO_2Et	155
$PhCH_2$	H	H	Br	Br	OAc	Me	CO_2Et	155
H	H	H	Cl	Cl	OEt	Me	CO_2Et	17, 21, 152
H	H	H	Br	Br	OAc	Me	CO_2Et	144, 152
H	H	H	Br	Br	OAc	Me	CO_2t-Bu	152
H	H	H	Br	Br	OAc	Me	CO_2CH_2Ph	152
H	H	H	Br	Br	OAc	Et	CO_2Et	152
H	H	H	Br	Br	OAc	*n*-Pr	CO_2Et	152
H	H	Et	Br	Br	OAc	Me	CO_2Et	152
H	H	n-C_5H_{11}	Br	Br	OAc	Me	CO_2Et	152
H	H	H	Br	Br	OAc	Me	PhCO	144
Me	H	H	Br	Br	OAc	Me	PhCO	144
H	H	H	Br	Br	OAc	Me	Ac	144
Me	H	H	Br	Br	OAc	Me	Ac	144
H	H	H	Br	Br	OAc	$-(CH_2)_2CO-$		144
Me	H	H	Br	Br	OAc	$-(CH_2)_2CO-$		144
Me	H	H	Br	Br	OAc	CHO	CO_2Et	157
H	H	Ph	Br	Br	OAc	Me	CO_2Et	158

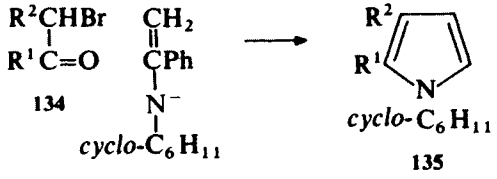
cyclic haloketones, where furans are also produced, the yields range from 22 to 66%. The best yields are obtained when $R^2 = H$.



130 131 132 (39)

R^1	R^2
Me	H
Ph	H
p-Tol	H
p-ClC_6H_4	H
p-BrC_4H_4	H
Ph	Me
Ph	Ph
$-(CH_2)_4-$	
$-(CH_2)_5-$	

The lithium salt of the ethylidenecyclohexylamine (**133**) reacts with both open chain and cyclic haloketones **134** to give **135**:[160]



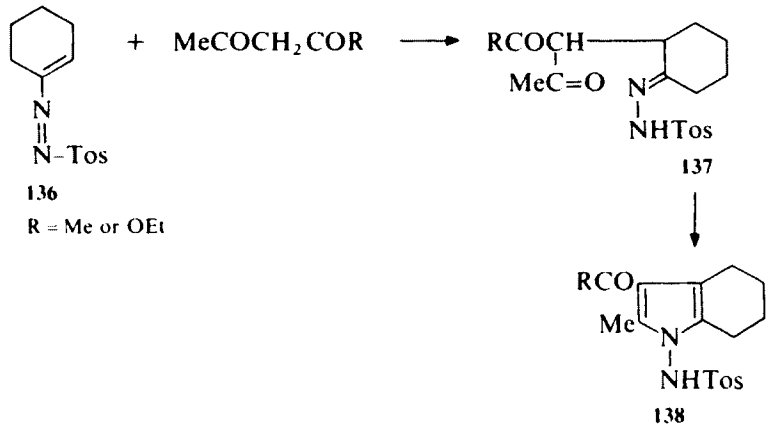
(40)

R^1	R^2
Me	H
Ph	H
	$-(CH_2)_4-$
	$-(CH_2)_5-$
	$-(CH_2)_6-$

However, since **133** is an ambident anion, substituents apparently alter the course of the reaction as mixtures of isomeric products are formed.

2.3.3. From Azo-alkenes and β-Dicarbonyl Compounds

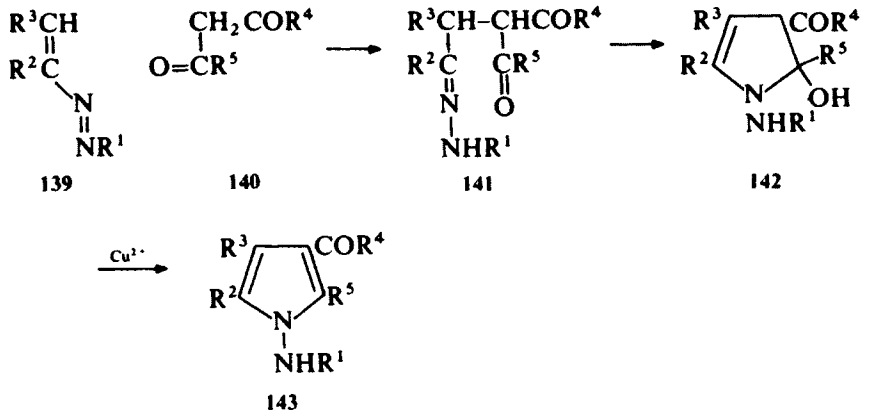
The 1,4-addition product from a β-ketoester or diketone and an azo-alkene undergoes a ring closure to yield the 1-aminopyrrole. For example, ring closure and dehydration of the addition product **137**, obtained from ethyl acetoacetate or pentanedione and tosylazacyclohexene **136**, over molecular sieve yields the pyrrole **138**:[161]



(41)

In a series of papers, Attanasi has described the preparation of a number of 1-aminopyrroles (**143**) having a wide range of groups attached to the 1-amino function. In this case the reaction is catalyzed by the copper(II) chloride ring closure of the 1,4-Michael adduct (**141**) of an aza-alkene (**139**) and a β-dicarbonyl compound **140**. It is reported that the yields range from 40 to 95%.

The copper catalyst is not involved in the ring closure step itself but rather the dehydration step since in the absence of the catalyst, the hydroxypyroline (**142**)



Scheme 9

is isolated (Scheme 9).[162] The wide variety of 1-substituted pyrroles, formed by this reaction, are listed in Table 2.13.

TABLE 2.13. 1-AMINOPYRROLES (**143**) FORMED FROM AZOALKENES

R^1	R^2	R^3	R^4	R^5	Ref.
Ph	Ph	Ph	Me	Me	163
Ph	$PhCH_2$	Ph	EtO	Me	163
Ph	$-(CH_2)_3-$		$-(CH_2)_3-$		163
Ph	Ph	Ph	Me	Me	164
Ph	Ph	Ph	Me	MeO	164
Ph	Ph	Ph	Me	EtO	164
Ph	Ph	Ph	Ph	Ph	164
Ph	Ph	Ph	$-(CH_2)_3-$		164
Ph	$PhCH_2$	Ph	Me	Me	164
Ph	$PhCH_2$	Ph	Me	MeO	164
Ph	$PhCH_2$	Ph	Me	EtO	164
Ph	$PhCH_2$	Ph	Me	Ph	164
p-$NO_2C_6H_4$	$-(CH_2)_3-$		Me	MeO	164
p-$NO_2C_6H_4$	$-(CH_2)_3-$		Me	EtO	164
p-$NO_2C_6H_4$	$-(CH_2)_3-$		Me	Ph	164
p-$NO_2C_6H_4$	$-(CH_2)_3-$		Ph	Ph	164
Ph	Ph	Ph	Me	NH_2	165
Ph	Ph	Ph	Me	NEt_2	165
Ph	Ph	Ph	Me	NHPh	165
Ph	Ph	Ph	Me	*p*-$MeOC_6H_4NH$	165
Ph	Ph	Ph	Me	*p*-ClC_6H_4NH	165
p-ClC_6H_4	Ph	Ph	Me	NH_2	165
p-ClC_6H_4	Ph	Ph	Me	NHPh	165
p-ClC_6H_4	Ph	Ph	Me	*p*-$MeOC_6H_4NH$	165
p-ClC_6H_4	Ph	Ph	Me	*p*-ClC_6H_4NH	165
p-$NO_2C_6H_4$	$PhCH_2$	Ph	Me	NH_2	165

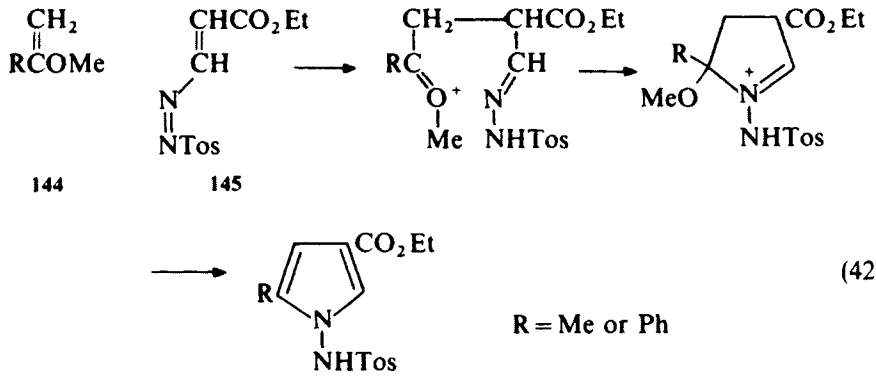
TABLE 2.13. (*Contd.*)

R^1	R^2	R^3	R^4	R^5	Ref.
p-$NO_2C_6H_4$	$PhCH_2$	Ph	Me	*p*-$MeOC_6H_4NH$	165
p-$NO_2C_6H_4$	$PhCH_2$	Ph	Me	NHPh	165
p-$NO_2C_6H_4$	$PhCH_2$	Ph	Me	*p*-$MeOC_6H_4NH$	165
p-$NO_2C_6H_4$	$-(CH_2)_3-$		Me	NEt_2	165
p-$NO_2C_6H_4$	$-(CH_2)_3-$		Me	NHPh	165
p-$NO_2C_6H_4$	$-(CH_2)_3-$		Me	*p*-$MeOC_6H_4NH$	165
p-$NO_2C_6H_4$	$-(CH_2)_3-$		Me	*p*-ClC_6H_4NH	165
p-$ClC_6H_4SO_2$	Me	CO_2Me	Me	MeO	166
p-$ClC_6H_4SO_2$	Me	CO_2Et	Me	EtO	166
p-$MeOC_6H_4SO_2$	Me	CO_2Me	Me	*t*-BuO	166
p-$MeOC_6H_4SO_2$	Me	CO_2Et	Me	$PhCH_2O$	166
p-Tos	Me	CO_2Me	Ph	EtO	167
CO_2Me	Me	CO_2Me	Me	Me	168
CO_2Me	Me	CO_2Me	Me	Ph	168
CO_2Me	Me	CO_2Me	Me	MeO	168
CO_2Me	Me	CO_2Et	Me	Me	168
CO_2Me	Me	CO_2Et	*t*-Bu	*t*-Bu	168
CO_2Me	Me	CO_2Et	Me	Ph	168
CO_2Me	Me	CO_2Et	Me	MeO	168
CO_2Et	Me	CO_2Me	Me	Me	168
CO_2Et	Me	CO_2Me	Me	Ph	168
CO_2Et	Me	CO_2Me	Me	MeO	168
CO_2Et	Me	CO_2Et	Me	Ph	168
CO_2t-Bu	Me	CO_2Me	Me	Me	168
CO_2t-Bu	Me	CO_2Me	Me	Ph	168
CO_2t-Bu	Me	CO_2Me	Me	MeO	168
CO_2t-Bu	Me	CO_2Et	Me	Ph	168
CO_2t-Bu	Me	CO_2Et	Me	MeO	168
PhCO	Me	CO_2Me	Me	Me	162
PhCO	Me	CO_2Et	Me	Me	162
PhCO	Me	CO_2Et	Ph	Ph	162
PhCO	Me	CO_2Et	EtO	Ph	162
PhCO	Me	CO_2Et	EtO	*p*-$NO_2C_6H_4$	162
PhCO	Me	CO_2Me	NH_2	Me	169
PhCO	Me	CO_2Me	NEt_2	Me	169
PhCO	Me	CO_2Me	NHPh	Me	169
PhCO	Me	CO_2Me	NHPh	Ph	169
$PhCH_2CO$	Me	CO_2Me	NH_2	Me	169
m-TolCO	Me	CO_2Me	Ph	Me	162
m-TolCO	Me	CO_2Me	Ph	Ph	162
m-TolCO	Me	CO_2Et	EtO	Me	162
m-ClC_6H_4CO	Me	CO_2Et	Ph	Me	162
$PhCH_2CO$	Me	CO_2Me	EtO	*p*-$NO_2C_6H_4$	162
3-NO_2–2-pyridyl	Me	CO_2Me	Me	Me	170
3-NO_2–2-pyridyl	Me	CO_2Me	Ph	Ph	170
3-NO_2–2-pyridyl	Me	CO_2Me	Me	MeO	170
3-NO_2–2-pyridyl	Me	CO_2Me	Me	EtO	170
3-NO_2–2-pyridyl	Me	CO_2Me	Ph	EtO	170
3-NO_2–2-pyridyl	*p*-$NO_2C_6H_4$	CO_2Et	Me	MeO	170
3-NO_2–2-pyridyl	*p*-$NO_2C_6H_4$	CO_2Et	*p*-$NO_2C_6H_4$	EtO	170
2-Pyridinyl	Me	CO_2Me	Me	MeO	170

TABLE 2.13. (*Contd.*)

R^1	R^2	R^3	R^4	R^5	Ref.
2-Pyridinyl	Me	CO_2CH_2Ph	Me	MeO	170
2-Pyridinyl	Me	CO_2CH_2Ph	Me	$PhCH_2O$	170
2-Benzothiazolyl	Me	CO_2Me	Me	MeO	170
CO_2Me	Me	CO_2Me	Me	SO_2Me	171
CO_2Me	Me	CO_2Me	Me	*p*-Tos	171
CO_2Me	Me	CO_2Me	Me	SO_2Ph	171
CO_2Me	Me	CO_2Et	Me	SO_2Me	171
p-Tos	$-(CH_2)_4-$		Me	EtO	161
p-Tos	$-(CH_2)_4-$		Me	Me	161
CO_2Me	Me	CO_2Et	Me	EtO	172–173
2-Pyridyl	Me	CO_2Et	Me	NHPh	174
2-Pyridyl	Me	CO_2Et	Me	*p*-$MeOC_6H_4NH$	174
2-Pyridyl	Me	CO_2Et	Me	*p*-ClC_6H_4NH	174
2-Pyridyl	Me	CO_2Et	Ph	NHPh	174
2-Pyridyl	Me	CO_2CH_2Ph	Me	NHPh	174
2-Pyridyl	Me	CO_2CH_2Ph	Ph	NHPh	174
2-NO_2-2-pyridyl	Me	CO_2Me	Me	NHPh	174
2-NO_2-2-pyridyl	Me	CO_2Me	Me	*p*-$MeOC_6H_4NH$	174
3-NO_2-2-pyridyl	Me	CO_2CH_2Ph	Me	NHPh	174
3-NO_2-2-pyridyl	Me	CO_2CH_2Ph	Me	*p*-ClC_6H_4NH	174
2-Benzothiazolyl	Me	CO_2Me	Me	NHPh	174
2-Benzothiazolyl	Me	CO_2Me	Me	*p*-$MeOC_6H_4NH$	174
$CONH_2$	Me	CO_2Me	NH_2	Me	175
$CONH_2$	Me	CO_2Me	NEt_2	Me	175
$CONH_2$	Me	CO_2Me	NHPh	Me	175
$CONH_2$	Me	CO_2Me	NHPh	Ph	175
CONHPh	Me	CO_2Me	NH_2	Me	175
CONHPh	Me	CO_2Me	NHPh	Ph	175
CONHPh	Me	CO_2Et	NEt_2	Me	175
CONHPh	Me	CO_2Et	NHPh	Me	175

Azo-alkenes **145** can add to enol ethers **144** to form 1-aminopyrroles **146** (Eq. 42).[176]

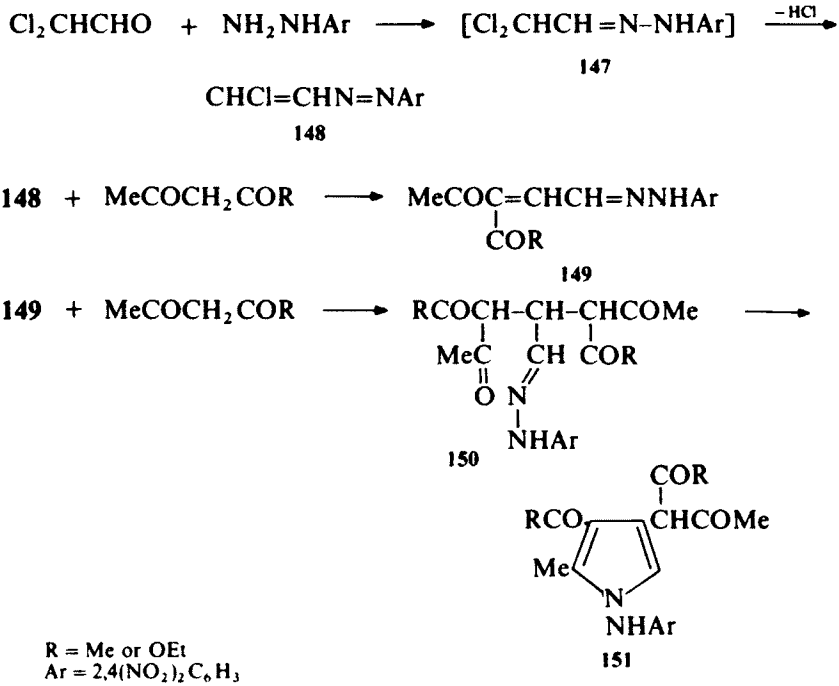


144 **145**

R = Me or Ph (42)

146

Hydrogen chloride is lost from the 2,4-dinitrophenylhydrazone of dichloroacetaldehyde (**147**) with the formation of the azoalkene **148**, which can react with two molecules of either ethyl acetoacetate or 2,4-pentanedione. Alkylation occurs in the first step, followed by addition of a second molecule to give **150**, which then ring closes to the 1-aminopyrrole **151**[173] as shown in Scheme 10.



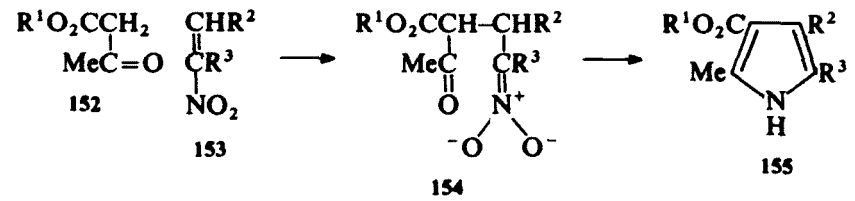
Scheme 10

2.3.4. From Nitroalkanes

2.3.4.1. With β-Dicarbonyl Compounds

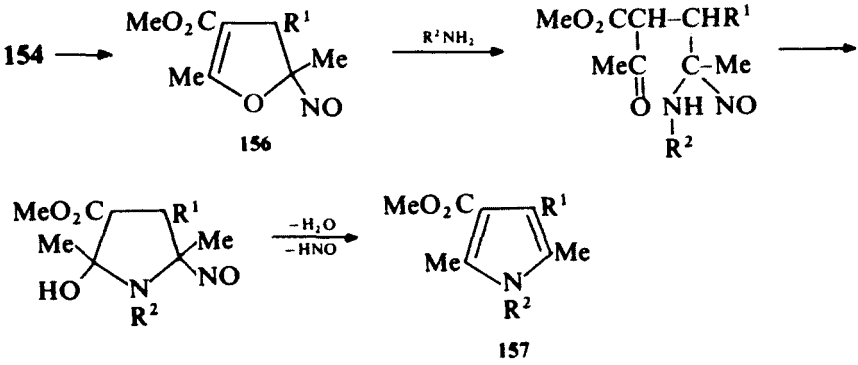
The addition of β-dicarbonyl compounds **152** to nitroalkenes **153** produces nitronic acids **154** from which pyrroles can be prepared by three different routes. The first reaction involves the reduction of the nitronic acid, as shown in Scheme 11.[177] The second route is outlined in Scheme 12. An amine furnishes the nitrogen atom in the pyrrole ring **156** via a nucleophilic attack on the intermediate 4,5-dihydro-5-nitrosofuran **157**.[178–180]

In the third reaction, condensation with a second molecule of the dicarbonyl compound leads to the formation of the 2,3-dihydro-2-methyleneaminofuran



R^1	R^2	R^3
Et	Ph	Me
Et	Ph	Et
Et	*p*-NO_2Ph_2	Me
t-Bu	*p*-$MeOPh_2$	Me
Et	2-thienyl	Me
Et	2-thienyl	Et
Et	2-thienyl	Ph
t-Bu	2-thienyl	Me
Et	2-furyl	Et
t-Bu	Ph	Me

Scheme 11

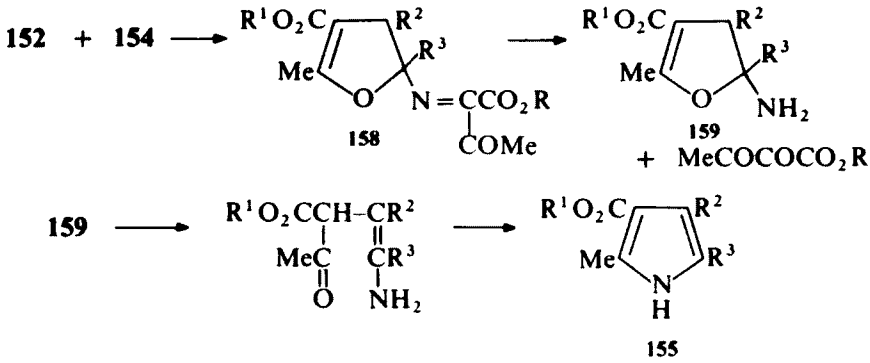


R^1	R^2
Ph	Me
4-NH_2-3-$NO_2C_6H_3$	*n*-Bu
4-NH_2-3-$NO_2C_6H_3$	$PhCH_2$

Scheme 12

158, which on hydrolytic ring opening of the 2-aminodihydrofuran **159**, leads to the pyrrole **155** (Scheme 13 and Table 2.14).[177,181]

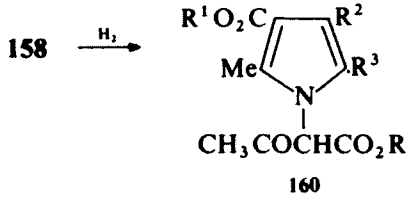
Chemical reduction of **158** gives the 1-substituted pyrrole **160**:[182,183]



Scheme 13

TABLE 2.14. PYRROLES (155) FORMED BY ADDITION OF NITROALKENES TO β-DICARBONYL COMPOUNDS

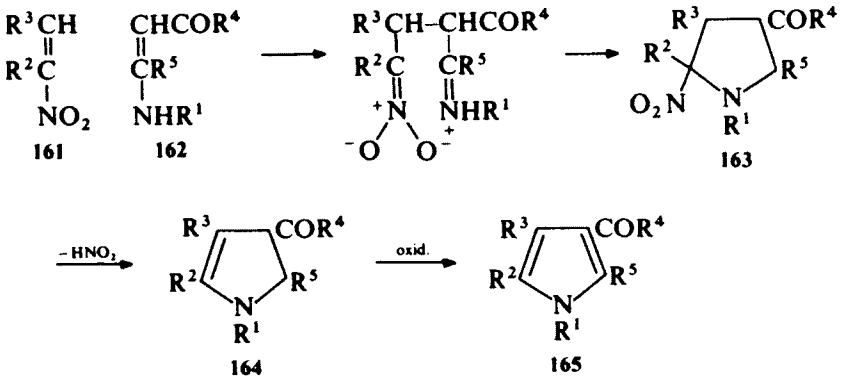
R^1	R^2	R^3	Ref.
Me	Me	Ph	177, 181
Me	Me	*m*-Tol	181
Me	Me	*p*-Tol	181
Me	Me	1-Naphthyl	177
Me	Me	*o*-$NO_2C_6H_4$	177, 181
Me	Me	*m*-$NO_2C_6H_4$	177, 181
Me	Me	*p*-$NO_2C_6H_4$	181
Me	Me	*o*-ClC_6H_4	177
Me	Me	*p*-ClC_6H_4	177, 181
Me	Me	*o*-$MeOC_6H_4$	181
Me	Me	*m*-$MeOC_6H_4$	177, 181
Me	Et	Ph	177
Me	Et	2-Pyridyl	177
Me	Et	*m*-$NO_2C_6H_4$	177
Me	Et	*p*-$NO_2C_6H_4$	177
Me	Et	*o*-ClC_6H_4	177
Me	Et	*p*-Tol	177
Me	Et	*o*-$MeOC_6H_4$	177
Me	Et	*p*-$Me_2NC_6H_4$	177
Me	*t*-Bu	Ph	177
Me	*t*-Bu	*p*-ClC_6H_4	177
Me	*t*-Bu	*p*-$MeOC_6H_4$	177
Me	Ph	Ph	181
Me	Ph	*o*-ClC_6H_4	181
Me	Ph	*o*-ClC_6H_4	181
Ph	Ph	Ph	181
Ph	Ph	*o*-Tol	181
Ph	Ph	*p*-$NO_2C_6H_4$	181
Ph	Ph	*o*-ClC_6H_4	181



(43)

2.3.4.2. *With Enamines*

The condensation of enamines with nitroalkenes leads to the formation of pyrroles **165**. As indicated in Scheme 14, a reasonable mechanism would involve the initial addition of the electron-rich enamine **162** to the electron deficient nitroalkene **161**. After loss of a proton, attack by the imino nitrogen upon the electron deficient carbon atom would ring-close to give (**163**). Loss of nitrous acid gives the pyrroline **164**, which is aromatized through oxidation by the liberated nitrous acid (see Table 2.15).



Scheme 14

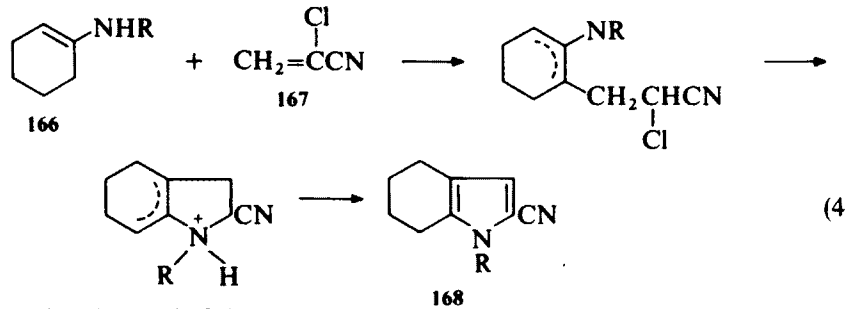
TABLE 2.15. PYRROLES (**165**) FORMED FROM NITROALKENES AND ENAMINES

R^1	R^2	R^3	R^4	R^5	Ref.
H	Me	Ph	EtO	Me	184
H	Me	Ph	*t*-BuO	Me	184
H	Me	Ph	NH_2	NH_2[a]	184
Me	H	Me	EtO	CH_2CO_2Et	185
Me	H	Me	EtO	Me	186
Ph	Me	Ph	MeO	Ph	186
$PhCH_2$	Me	Ph	Me	Ph	186
Bu	Me	Ph	Me	Ph	186
$PhCH_2$	H	Me	EtO	Me	186
cyclo-C_3H_5	Me	Ph	EtO	H	187

[a] From carbethoxyiminoamine.

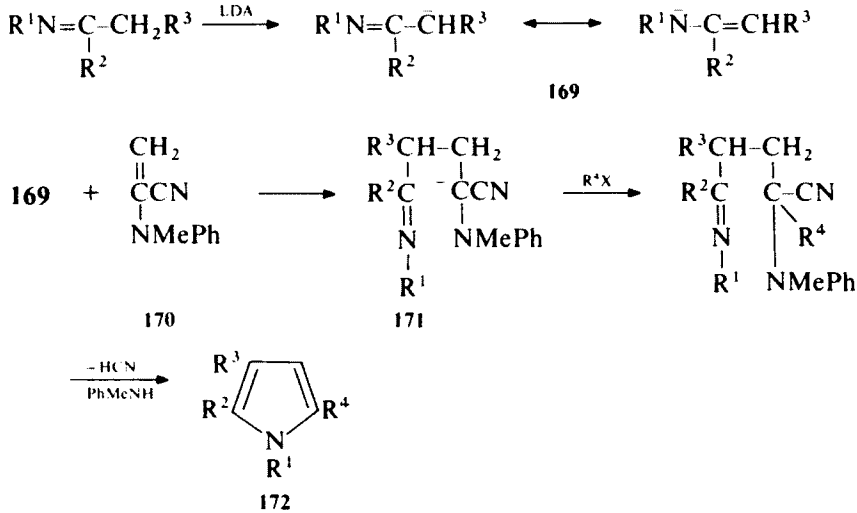
2.3.5. From Acrylonitriles and Enamines

The enamine derived from cyclohexanone, **166** adds to chloroacrylonitrile (**167**) and, after displacement of the halogen, loses hydrogen cyanide to give the tetrahydroindole **168**:[187]



R = Me or cyclo-C_6H_{11} (44)

A versatile synthesis of pyrroles (**172**), outlined in Scheme 15, makes use of the addition of an anionic enamine **169** to an aminoacrylonitrile **170**. Alkylation of



R^1	R^2	R^3	R^4
$PhCH_2$	*n*-Bu	H	H
$PhCH_2$	*n*-Bu	H	Me
i-Pr	Me	H	Me
$PhCH_2$	Et	H	Et
$PhCH_2$	Et	Me	Me
i-Pr	$-(CH_2)_3-$		Me
Ph	$-(CH_2)_4-$		Me

Scheme 15

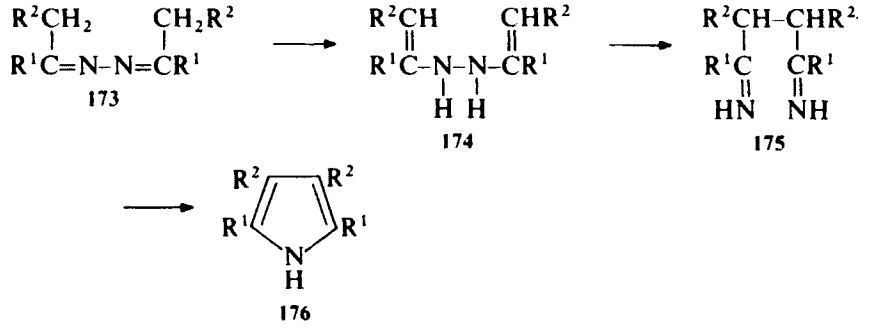
the addition product **171** provides an additional ring substituent. Yields for the reaction are in the 50–80% range.[188]

2.3.6. Via Dimerization Reactions

2.3.6.1. Of Azines: The Piloty Synthesis

2.3.6.1.1. Acid-Catalyzed

In the reaction that now bears his name, Piloty discovered that the treatment of an azine **173**, the bis-hydrazone of an aldehyde or ketone, with zinc chloride produces a symmetrical pyrrole **176**.[189] More recently, arylsulfonic acids have been used as the catalyst for the reaction. The mechanism is similar to that of the Fischer indole synthesis[190] in that a tautomeric shift gives **174**, which then undergoes a [3, 3] sigmatropic shift to form a carbon–carbon bond between the two units and simultaneously breaks the nitrogen–nitrogen bond to form the



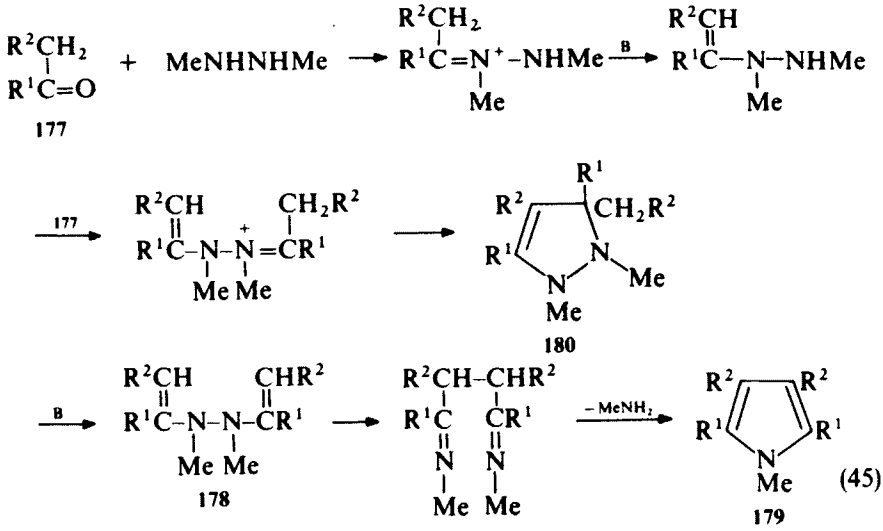
Scheme 16

bis-imine **175** (Scheme 16).[191] Table 2.16 lists pyrroles that have been prepared by this method.

TABLE 2.16. SYMMETRICAL PYRROLES (176) FROM AZINES

R^1	R^2	Ref.
Ph	H	193–194
Ph	Me	193
Ph	Ph	194–196
H	Me	197–198
H	Et	198
$-(CH_2)_4-$		193

In a number of papers, Jacquier and Elguero have investigated the reactions of the "enehydrazines" **178**, produced from either methylhydrazine or *syn*-dimethylhydrazine, which undergo the Piloty reaction to give the 1-methyl-



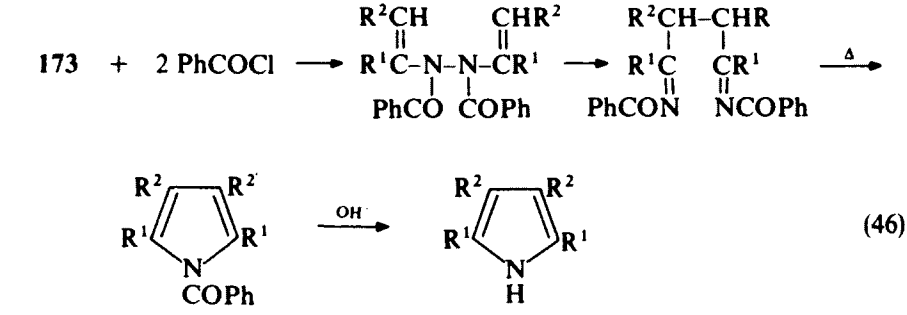
pyrrole **179**.[199,200] With dimethylhydrazine, the corresponding pyrazoline **180** may be the major product from methyl alkyl ketones.[210] Although with either the methyl or dimethyl hydrazine the methyl group is retained in the pyrrole, alkylation of **173** with two equivalents of methyl iodide gives a mixture of the 1-methyl and 1-unsubstituted pyrrole.[202] Table 2.17 lists the pyrroles produced from the enehydrazines.

TABLE 2.17. 1-METHYLPYRROLES (**179**) FROM ENEHYDRAZINES, DERIVED FROM KETONES ($R^1COCH_2R^2$) AND METHYLHYDRAZINES (MeNHNHR)

R^1	R^2	R	Ref.
Me	Ph	H	200, 203
Me	*i*-Pr	H	203
Me	*i*-Bu	H	203
Et	Ph	H	200, 203
$PhCH_2$	Ph	H	203
	$-(CH_2)_3-$	H	204
	$-(CH_2)_4-$	H	200, 203–205
	$-(CH_2)_5-$	H	205
Me	Ph	Me	199, 203, 206
H	Me	Me	206
H	Et	Me[a]	206
Ph	Ph	Me	201
$PhCH_2$	Ph	Me	201

[a] Mainly the pyrazoline.

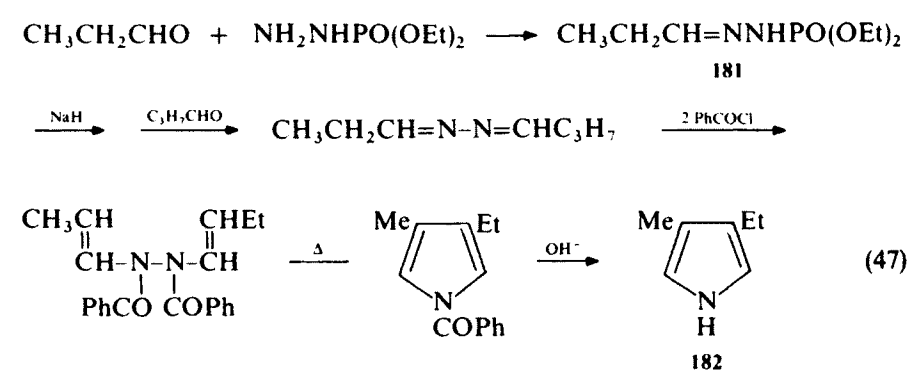
Baldwin has found that the yields of pyrrole can be improved by first benzoylating the azine, forcing it into the enehydrazine form, and then heating the dibenzoyl compound:[207]



R^1	R^2
Me	Me
H	Me
H	*n*-Pr
$-(CH_2)_4-$	

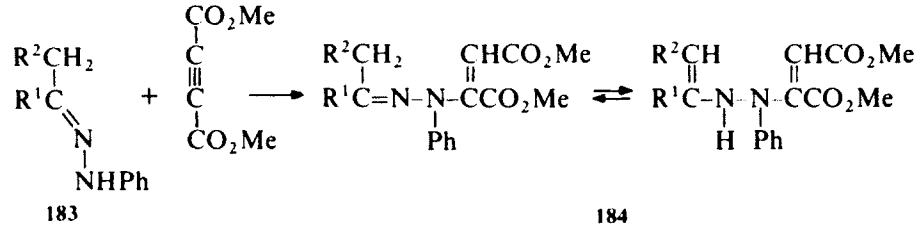
(46)

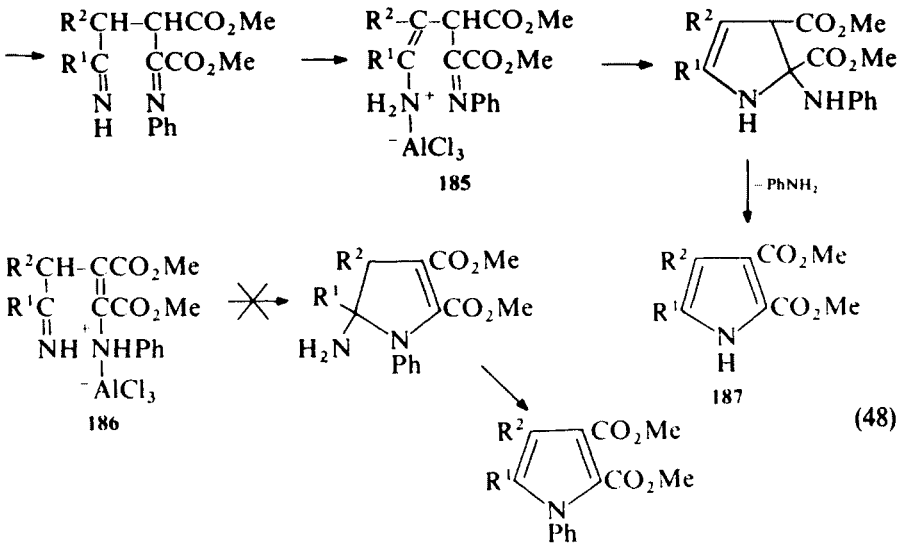
By utilizing the diethyl phosphorohydrazinoate (**181**), Baldwin was also able to prepare unsymmetrical pyrroles. Thus, propanal and butanal can be combined stepwise before cyclization to the 3-methyl-4-*n*-propylpyrrole (**182**):[207]



(47)

The addition of the hydrazone **183** to DMAD gives an azine-like system **184**, which, on treatment with aluminum chloride, undergoes a Piloty-like reaction with loss of the aniline rather than ammonia to give only **187** (70–80%). It is suggested that the aluminum chloride coordinates with the amino group of the basic tautomer **185**, rather than an anilino group of **186**:[208]

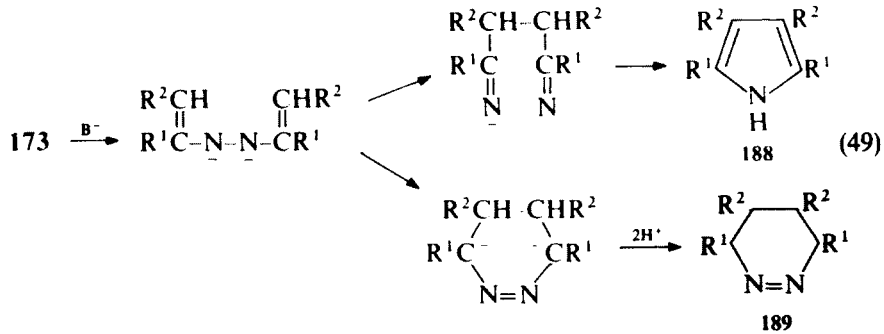




(48)

2.3.6.1.2. Base-Catalyzed

Very strong bases, such as sodium hydride or lithium dimethylamide, convert azines **173** into their dianions, which can either undergo the [3,3]-sigmatropic shift and ring closure to the pyrrole **188** or ring-close to the tetrahydropyrazine **189**:



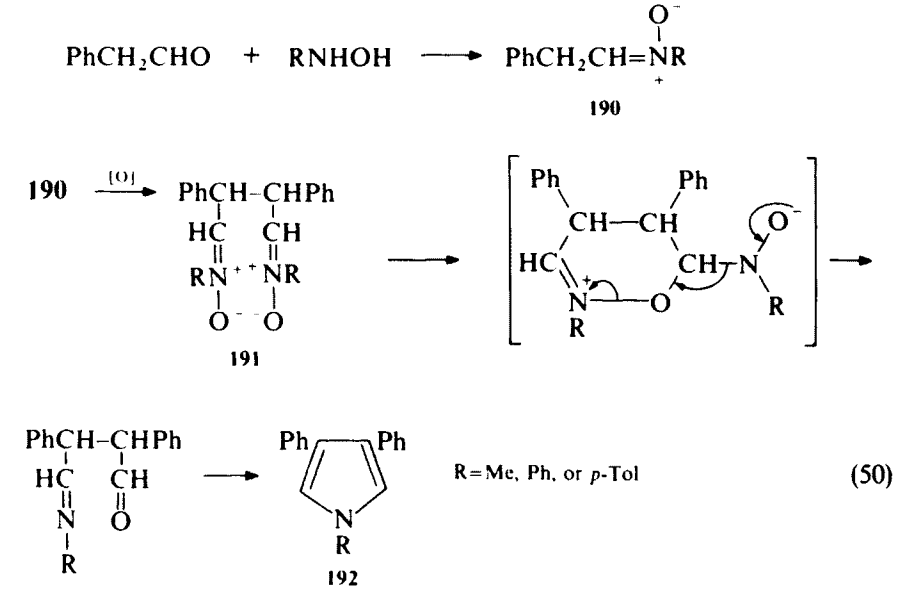
(49)

Pyrrole formation is favored when R^3 is methyl, as a result of inductive effect aiding the sigmatropic process. However larger groups seem to interfere.[209-210] Also, the formation of **189** is favored by using stoichiometric amounts of base, while catalytic amounts lead to formation of the pyrrole.[211-212]

2.3.6.2. Of Nitrones

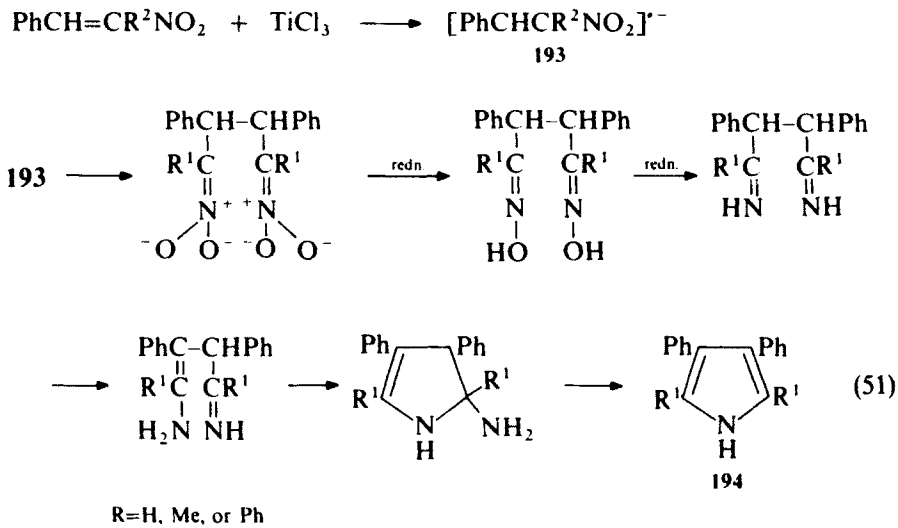
The reaction of *N*-substituted hydroxylamine with aldehydes produces nitrones **190**, which undergo oxidative dimerization to give **191**, which is

slowly converted (2 weeks at room temperature) into 1-substituted-3,4-diphenylpyrroles **192**:[213,214]



R=Me, Ph, or *p*-Tol (50)

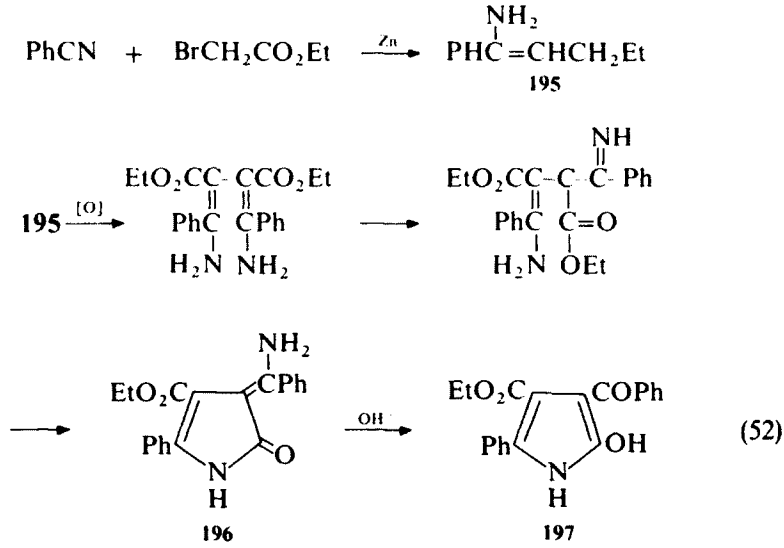
Formation of the radical anion **193** by oxidation of nitrostyrene with titanium(III) chloride, followed by dimerization, leads to the symmetrically substituted pyrrole **24**. Substituents adjacent to the nitro group decreases the amount of pyrrole:[215]



R=H, Me, or Ph (51)

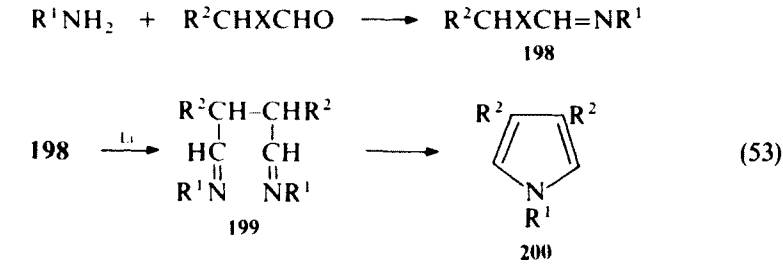
2.3.6.3. *Of Enamines*

A Reformatskii-type reaction of ethyl bromoacetate with benzonitrile yields the enamine (**195**), which oxidatively dimerizes in air and then ring-closes to the pyrrolinone **196**, which on basic hydrolysis gives the hydroxypyrrole **197**:[216]



(52)

Imines **198**, formed by the reaction of amines with α-haloaldehydes, can be dimerized by treatment with an active metal such as lithium. These dimers **199** undergo ring closure to the 3,4-disubstituted pyrroles **200**:[217–219]

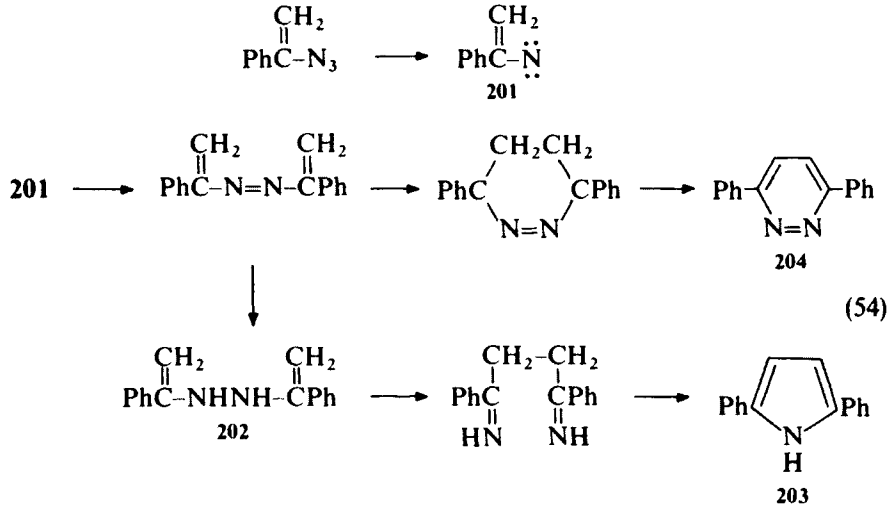


(53)

R^1	R^2	X
t-Bu	Me	Cl
t-Bu	Et	Cl
i-Pr	*i*-Pr	Br
t-Bu	*i*-Pr	Br
Et	Et	Br
$PhCH_2$	Et	Br

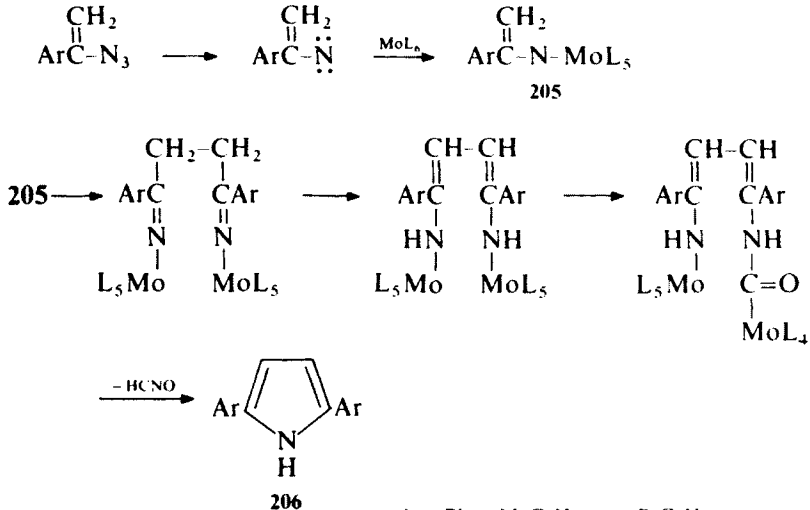
2.3.6.4. Via Nitrenes

Dimerization of the nitrene **201**, obtained from azidostyrene, gives both 2,5-diphenylpyrrole (**203**) and the pyridazine **204**, presumably via the azine **202**, which undergoes a Piloty-like rearrangement:[220]



(54)

The molybdenum carbonyl complexes of nitrenes **205**, obtained from the azidostyrene, also undergo dimerization to yield the 2,5-diarylpyrroles **206** (Eq. 55). It has been suggested that the mechanism does not involve an azine but direct carbon–carbon bond formation. This route is supported by the observation that no pyridazines are formed.[221,222]

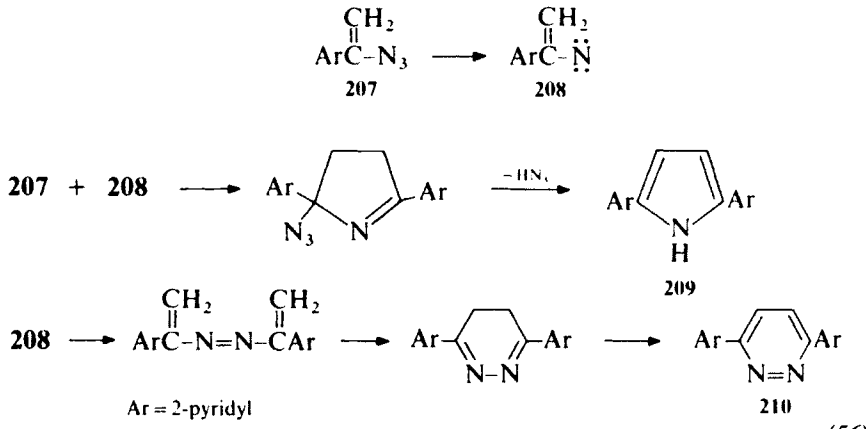


(55)

Ar = Ph, *p*-MeC_6H_4, or *p*-BrC_6H_4

L = CO

Thermolysis of the 2-pyridyl azide **207** gives a mixture of the pyrrole **209** via addition of the nitrene **208** to the azide (Eq. 56). The pyridazine **210** is also produced by dimerization of **207**.[223]



(56)

2.3.7. From Oximes

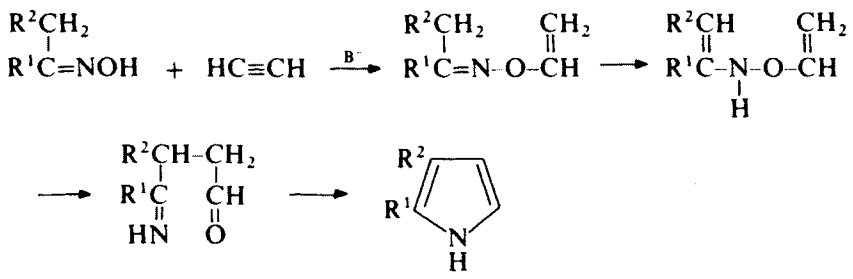
2.3.7.1. With Alkynes: The Trofimov Reaction

Trofimov and co-workers have reported the preparation of a number of 2,3-disubstituted pyrroles by the base-catalyzed reaction of oximes with acetylene or its precursors. Unfortunately, the product is often contaminated with appreciable amounts of the 1-vinylpyrrole from the Michael addition of a second molecule of acetylene. A number of basic systems have been used: alkoxides, aqueous lithium, sodium, or potassium hydroxide or metal hydroxides in DMSO. The particular cation used effects the reaction. Lithium hydroxide in DMSO will catalyze the reaction with the oximes of alkyl aryl ketones but not those from dialkylketones. The most effective general procedure appears to be with potassium hydroxide in DMSO.[224]

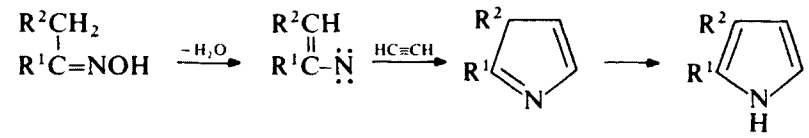
Although acetylene itself has been used in most cases, it has also been generated in situ from vinyl chloride or dichloroethane, but this seems to have little advantage.

Although a number of alternative mechanisms have been proposed, it still seems unclear as to which is the correct one. Since *O*-vinyl ethers of aryl oximes can be prepared and converted into pyrroles, this seems a plausible route (Scheme 17a), although under the conditions for the reaction it leads to lower yields of pyrrole and it is reported that the *O*-ether alkyl oximes do not yield pyrroles.[225–228] An alternative mechanism involves the generation of a nitrene intermediate (Scheme 17b).[227]

a.



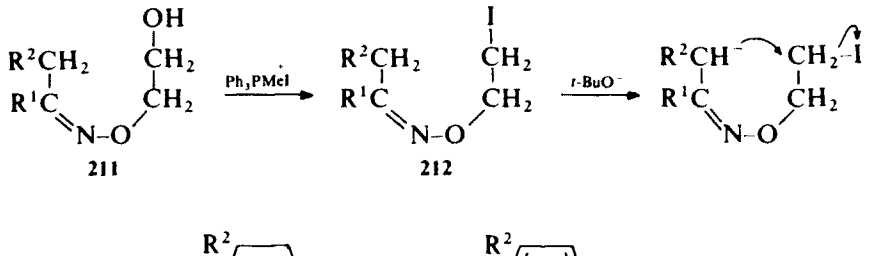
b.



Scheme 17

The reaction appears to be regiospecific. Thus for example, the methyl benzyl ketoxime gives the 2-methyl-3-phenylpyrrole at reaction temperatures below 120°C, although some 2-benzylpyrrole is formed at higher temperatures.[229] Table 2.18 lists the various pyrroles prepared by the Trofimov reaction.

In a related reaction, the *O*-hydroxyethyloximes **211** have been converted into their iodo derivatives **212**, which, on treatment with base, undergo a ring closure to the pyrroles **213**:[250]



(57)

R^1	R^2
Ph	H
n-Pr	Et
$-(CH_2)_4-$	
$-(CH_2)_5-$	
$-(CH_2)_6-$	

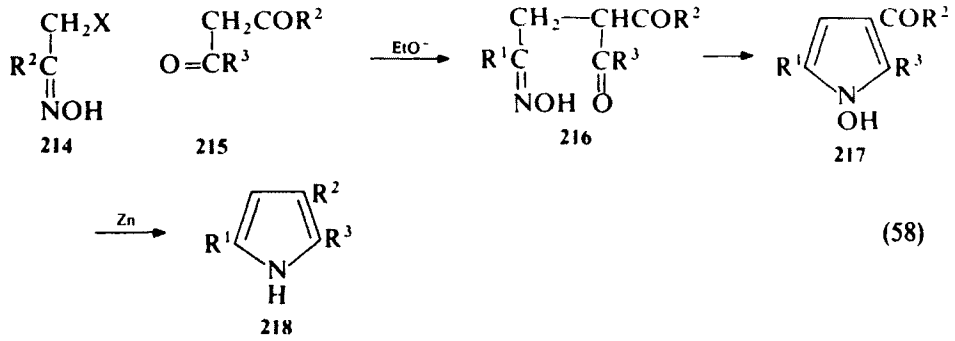
TABLE 2.18. 2,3-DISUBSTITUTED PYRROLES FROM OXIMES BY THE TROFIMOV REACTION (SCHEME 17)

2-Substituent	3-Substituent	Ref.
Me	H	230–235
Me	Me	234[a], 236
Me	allyl	237
Me	Ph	229
Et	H	232, 236
Et	Me	233[b], 234[a], 236
Et	Ph	229
n-Pr	H	231–232
n-Pr	Me	238
i-Pr	H	238
n-Bu	Me	232, 234[a]
n-Bu	*n*-Pr	236
C_5H_{11}	H	238
C_5H_{11}	Me	234[a]
$-(CH_2)_4-$		232[b], 236, 239
Ph	H	230, 231, 240, 241, 242[b], 243[a]–244
Ph	Me	231, 241, 245
Ph	Et	229, 231, 241, 245
Ph	*n*-Pr	241, 245
Ph	*n*-Bu	241, 245
Ph	*i*-Bu	245
Ph	C_5H_{11}	241, 245
Ph	Ph	231, 241
p-Tol	H	242[b], 243[a]
p-ClC_6H_4	H	235, 240, 242[a], 244
p-EtC_6H_4	H	250, 242[b]
p-*i*-PrC_6H_4	H	242[b]
p-*t*-BuC_6H_4	H	242[b]
p-$MeSC_6H_4$	H	246
1-Naphthyl	H	247
2-Naphthyl	H	247
2-Furyl	H	248
2-Furyl	Me	248
2-Furyl	Et	248
2-Furyl	*n*-Pr	248
2-Furyl	*i*-Pr	248
2-Furyl	*n*-Bu	248
2-Thienyl	H	244, 249

[a] $C_2H_4Cl_2$ used as source of acetylene.
[b] C_2H_3Cl used as source of acetylene.

2.3.7.2. *From α-Halooximes with β-Dicarbonyl Compounds*

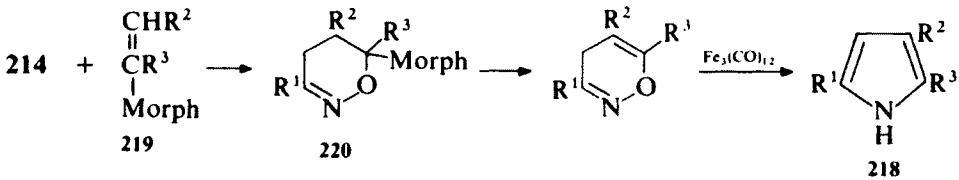
β-Dicarbonyl compounds **215** can be alkylated by α-halooximes **214**, and the resulting γ-oximinoketone **216** cyclize on treatment with acid to give the 1-hydroxypyrrole **217**. Zinc reduction of the hydroxypyrrole yields **218**:[251,252]



(58)

R^1	R^2	R^3
Me	EtO	Ph
Me	EtO	Me
Me	Me	Me
Me	Ph	Me
Me	Ph	Ph
Ph	EtO	Me
Ph	EtO	Ph

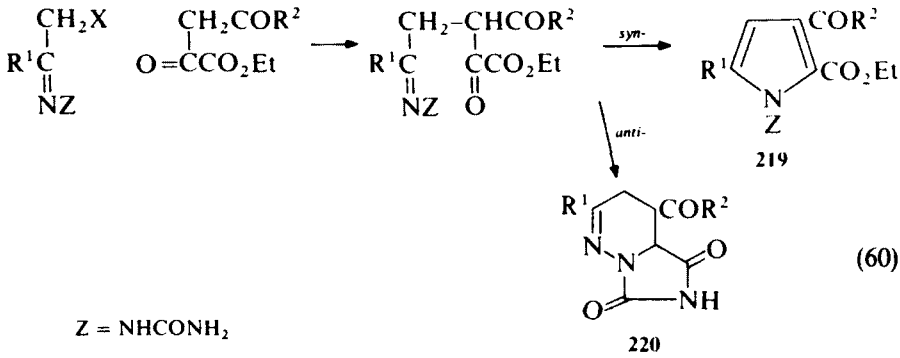
Halooximes react with enamines **219** initially to form the 1,2-oxazines **220**, which on treatment with iron(0) carbonyl give excellent yields (up to 72%) of the pyrrole **218**:[253]



(59)

R^1	R^2	R^3
Ph	$-(CH_2)_3-$	
Ph	$-(CH_2)_4-$	
Ph	$-(CH_2)_5-$	
Ph	Et	H
Ph	Me	Et
Ph	Me	Ph
CO_2Et	$-(CH_2)_4-$	

Similarly, the semicarbazone of α-haloketones alkylate dicarbonyl compounds, but the *syn*- and *anti*-isomers undergo ring closure to yield different products: the 1-ureidopyrrole **219** is obtained from the *syn*-isomer, whereas the *anti*-isomer produces the imidazo[1,5-*b*]-pyridazine **220**.[254]



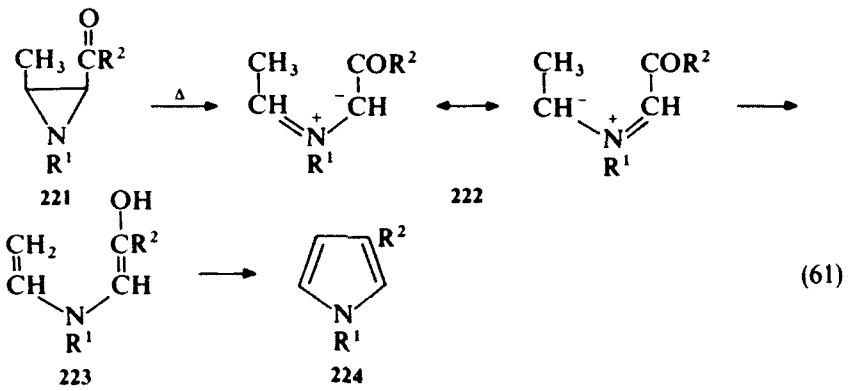
(60)

Z = $NHCONH_2$

R^1	R^2
Me	Me
Me	Ph
Me	EtO
Ph	Me
Ph	Ph
Ph	EtO

2.3.8. Ring Opening of Azirines and Aziridines

Aziridines **221**, having a methyl group and either an aldehyde or keto group on adjacent positions, are transformed thermolytically into pyrroles **224** via ring opening to an azomethine ylide **222** (Eq. 61). A transannular migration of

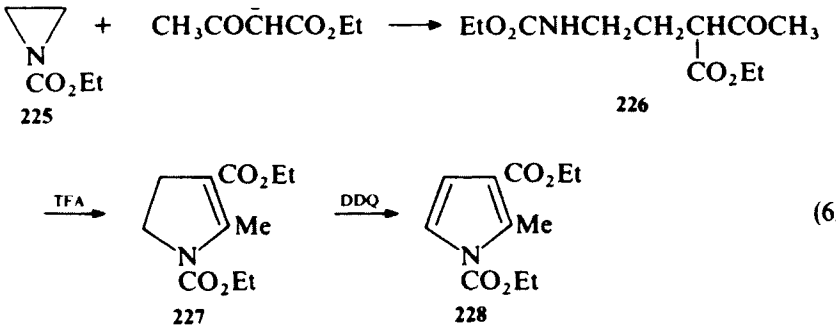


(61)

R^1	R^2
Me	H
i-Pr	H
t-Bu	H
Me	Ph
t-Bu	Ph
t-Bu	$PhCH_2$
Ph	$PhCH_2$

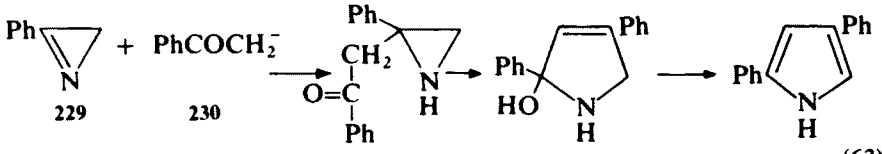
hydrogen to the carbonyl group generates the necessary divinylamine structure **223**, which is required for ring closure. As expected for the electrocyclic ring opening, the *trans*-isomer reacts more rapidly.[255] Also, the yield of pyrrole increases in the order Me < *i*-Pr < *t*-Bu for the group attached to the nitrogen atom.[256]

Attack on the aziridine **225** by the acetoacetate carbanion results in ring opening to give a γ-aminoketone **226**, which, on treatment with acid, readily undergoes ring closure to the pyrroline **227**. Oxidation with DDQ gives diethyl 2-methylpyrrole-1,3-dicarboxylate **228**:[257]



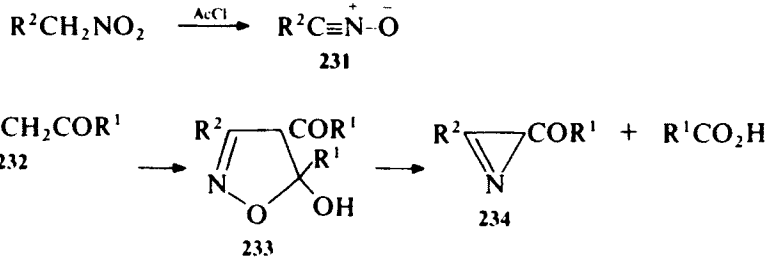
(62)

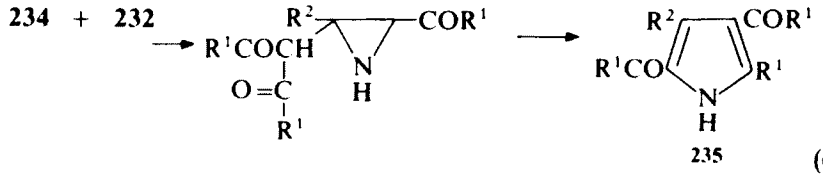
The carbanion from acetophenone (**229**) adds to 2-phenylazirine (**230**) with ring enlargement, resulting in the formation of 2,4-diphenylpyrrole:[258,259]



(63)

Zen and Harada have utilized this reaction in a "one-pot" synthesis of 2,4-diacylpyrroles, starting with an aryl β-diketone **232** and an arylnitromethane.[260] Treatment of the nitroalkane with acetyl chloride yields the nitrile oxide **231**, which reacts with the diketone to form the azirine **234** via a presumed ixoxazoline intermediate **233**. As described above, attack on **234** by the carbanion of a second molecule of the diketone leads to the pyrrole **235** in 35–85% yields.

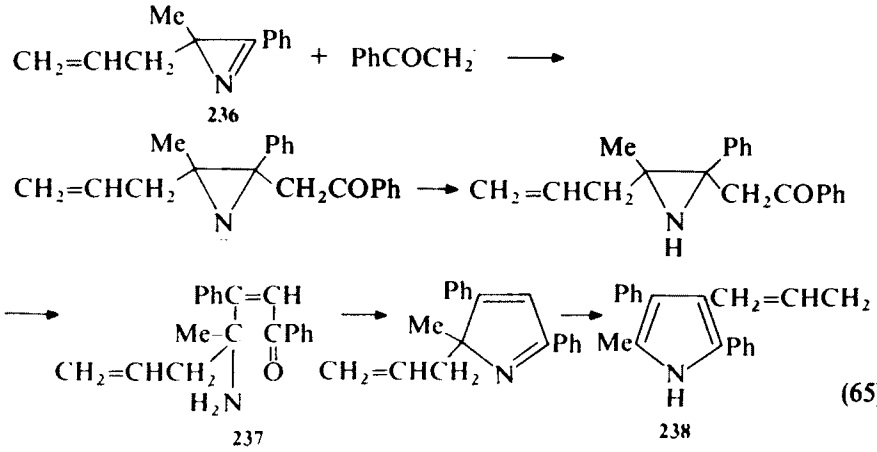




235 (64)

R^1	R^2
Ph	Ph
Ph	*p*-Tol
Ph	*p*-ClC_6H_4
p-Tol	Ph
p-Tol	*p*-Tol
p-ClC_6H_4	Ph
p-ClC_6H_4	*p*-ClC_6H_4

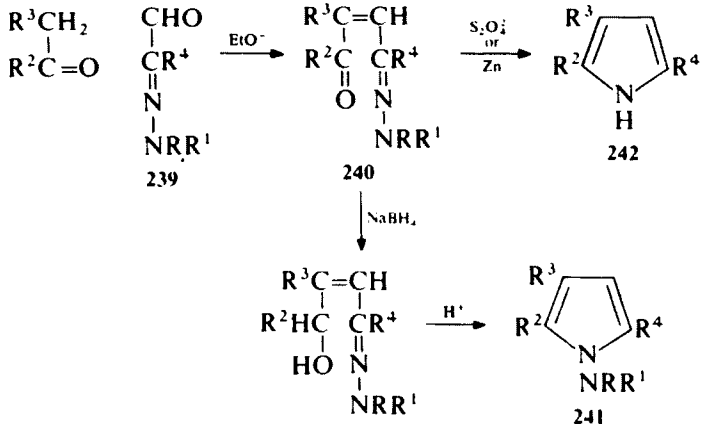
Carbanion attack on the geminally disubstituted azirine **236** involves the initial addition, followed by proton transfer and ring opening to yield **237**. Ring closure gives a 2*H*-pyrrole which readily rearranges to the 1*H*-pyrrole **238** by a [3,3]-sigmatropic shift followed by a [1,3]-hydrogen migration:[261]



236 237 238 (65)

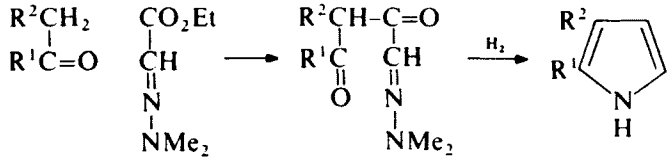
2.3.9. Miscellaneous Reactions

In a number of papers, Severin has reported the synthesis of pyrroles and 1-aminopyrroles by the condensation of glyoxalhydrazones **239** with ketones to give, initially, the hydrazone of the unsaturated 1,4-diketone **240**. Reduction with sodium borohydride and cyclization with acid produces the 1-amino-pyrroles **241** (Scheme 18; see also Table 2.19). If the reduction is conducted with zinc or sodium dithionite, the amino group is lost and the pyrrole **242** is obtained (see Table 2.20).



Scheme 18

A similar reaction occurs with the hydrazone of ethyl glyoxalate:[268]



(66)

R^1	R^2
Ph	H
p-Tol	H
p-$MeOC_6H_4$	H
2-Pyridyl	H
$-(CH_2)_4-$	
$-(CH_2)_5-$	
$-o-C_6H_4CH_2CH_2-$	

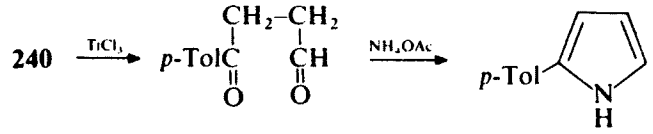
TABLE 2.19. 1-AMINOPYRROLES (241) FROM GLYOXALHYDRAZONES

R^2	R^3	R^4	R	R^1	Ref.
H	Me	Et	Ph	Me	262
H	Et	Et	Ph	Me	262
H	Ph	Et	Ph	Me	262
Ph	H	H	Ph	Me	263
p-$MeOC_6H_4$	H	Me	Me	Me	264
$-o-C_6H_4CH_2-$		Me	Me	Me	264
$-o-C_6H_4CH_2CH_2-$		Me	Me	Me	264

TABLE 2.20. PYRROLES (242) FROM GLYOXALHYDRAZONES

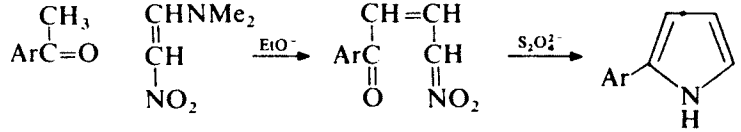
R^2	R^3	R^4	R	R^1	Ref.
H	Ph	H	Me	Me	265
Et	Me	H	Me	Me	265
$-(CH_2)_4-$		H	Me	Me	265
p-Tol	H	H	Me	Me	265
p-$MeOC_6H_4$	H	H	Me	Me	265
p-$MeSC_6H_4$	Ph	H	Me	Me	266
3-Pyridyl	H	H	Me	Me	265
Me	H	Me	Ph	H	267
Ph	H	Me	Ph	H	267
p-$MeOC_6H_4$	H	Me	Ph	H	263, 267
2-Pyridyl	H	Me	Ph	H	267
2-Furyl	H	Me	Ph	H	267

When $TiCl_3$ is used, the 1,4-diketone is formed, which undergoes the Paal–Knorr reaction:[265]



(67)

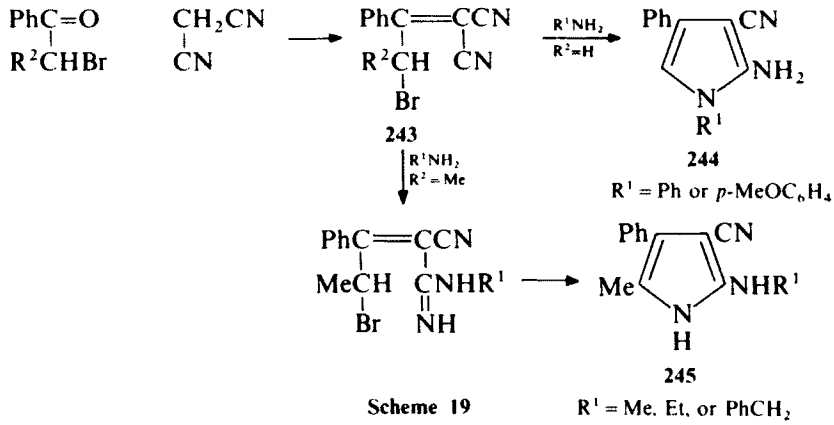
Related to these reactions is the reaction of the ketone with 1-nitro-2-dimethylaminoethene in place of the hydrazone:[269]



(68)

Ar = Ph, *p*-$MeOC_6H_4$, or *p*-BrC_6H_4

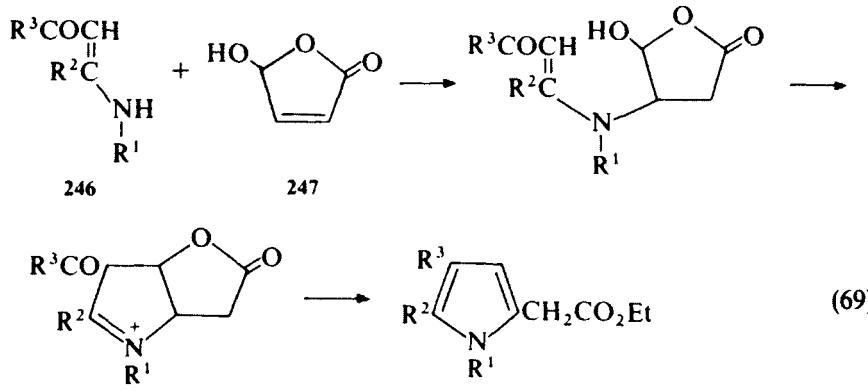
The reaction of phenacyl bromides with malononitrile gives the α-cyano-γ-bromocrotonitrile **243**, which undergoes a ring closure with arylamines to



Scheme 19

produce the 2-amino-3-cyanopyrrole **244**. With the more strongly basic alkylamines addition to the nitrile occurs leading to the substituted 2-aminopyrrole **245** (Scheme 19).[270]

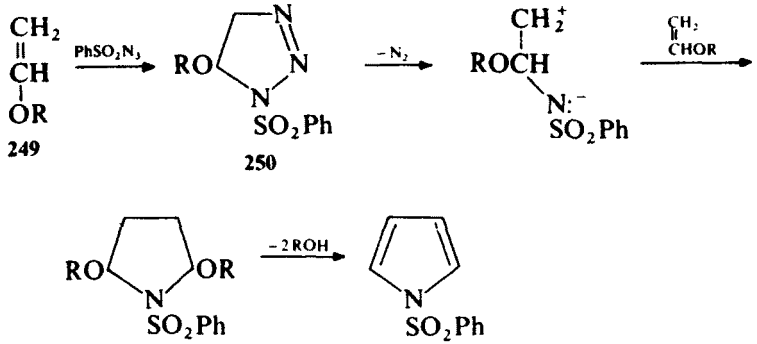
Addition of an enamine **246** to the 2-butenolide **247**, produced by the photochemical oxidation of furfural, results in the formation of (3-acylpyrrol-2-yl)acetates **248**:[271]



246 **247** **248** (69)

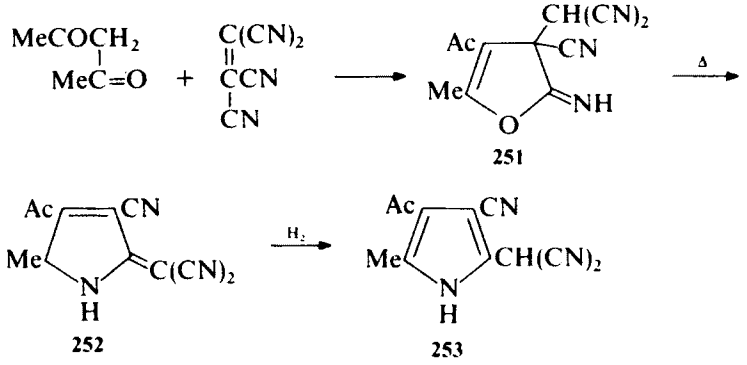
R^1	R^2	R^3
H	H	Me
H	$-(CH_2)_3-$	
$PhCH_2$	$-(CH_2)_3-$	

The triazole **250**, formed by the addition of benzenesulfonylazide to an enol ether **249**, loses nitrogen, and the resulting nitrene adds to a second molecule of **249** to give ultimately 1-benzenesulfonylpyrrole:[272]



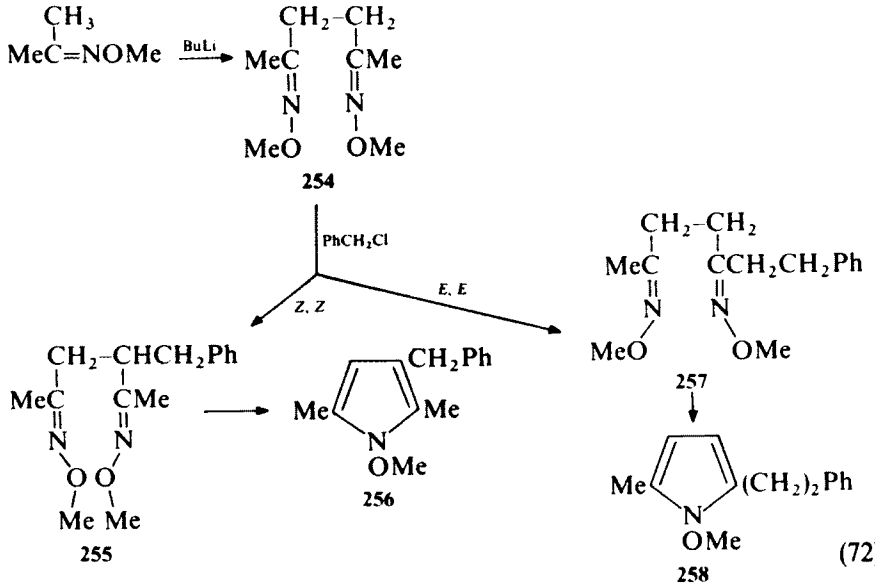
249 **250** (70)

Michael addition of pentanedione to tetracyanoethene initially forms the iminofuran **251**, which on heating rearranges to **252**. Careful hydrogenation leads to **253**:[273]



(71)

Treatment of the *O*-methyloxime of acetone with butyllithium produces two stereoisomers of the dioxime of 2,5-hexanedione (**254**). Alkylation of the *Z,Z*-isomer with benzyl chloride yields **255**, which cyclizes to give the 1-methoxy-3-benzylpyrrole **256**. Since the *E,E*-isomer is alkylated on the terminal carbon atom to give **257**, the 5-(phenylethyl)pyrrole **258** is produced instead:[274]



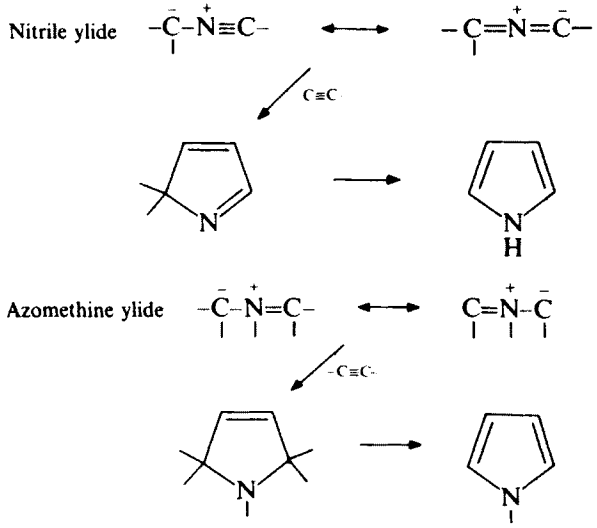
(72)

2.4. FORMATION OF PYRROLES VIA 1,3-DIPOLAR CYCLOADDITION REACTIONS

The synthesis of 5-membered heterocycles by 1,3-dipolar additions is analogous to the use of the Diels–Alder additions for 6-membered heterocycles. Both reactions are [$\pi 4s + \pi 2s$] cycloadditions. Since 1963, when Huisgen recognized

1,3-dipoles, a wide variety of 5-membered ring systems have been formed by the addition of these dipolar species to double or triple bonds.[275] The general features of 1,3-dipolar additions have been reviewed by several authors in a monograph.[276]

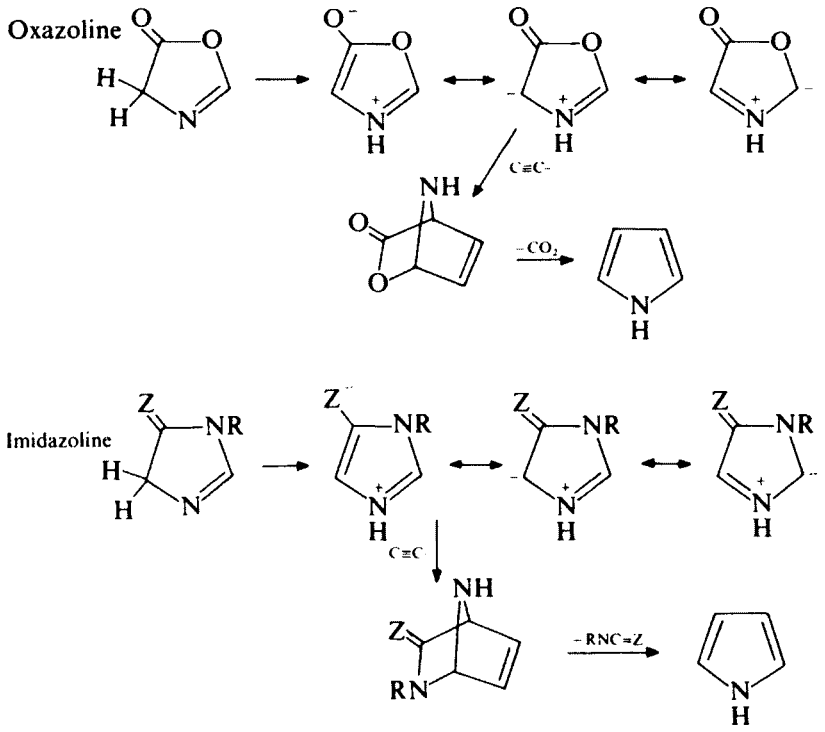
For the preparation of pyrroles, there are two possible dipolar systems: nitrile ylides and azomethine ylides. The dipolarophiles are either alkynes, particularly dimethyl acetylenedicarboxylate or methyl propiolate, or a substituted alkene that can undergo an elimination as shown in Scheme 20. Alternatively, if a pyrroline results, oxidative aromatization may be necessary.



Scheme 20

In addition to the obvious nitrile and azomethine ylides, certain cyclic systems can be "masked 1,3-dipoles." The dehydration of *N*-acylamino acids produces the "azlactone" or 5-oxazolone. The tautomeric shift of a proton produces the dipolar species, which is an azomethine ylide. Likewise, the loss of a proton from a *N*-substituted 5-oxazolonium ion gives a dipolar species. Replacement of the oxygen by sulfur yields the corresponding thiazolones and thiazolium ions; with two nitrogen atoms, one has the imidazolone and imidazolium ions (Scheme 21). Aziridines and azirines can open to form azomethine and nitrile ylides, respectively.

1,3-Dipolar additions, like other cycloadditions, have attracted a number of theoretical studies. Two particularly important factors have been clarified. The regiospecificity of the addition, that is, the orientation of the substituents when both the dipolar species and the dipolarophile are not symmetrical, and the question of synchronous bond formation. Molecular orbital calculations indicate that the orientation depends to a great extend on the coefficients of the HOMO and LUMO of the reacting species and regiospecificity is highest when



Scheme 21

there is optimal overlap of these orbitals.[277] The reactivity of the dipolar species is aided by an unsymmetrical charge distribution that raises the HOMO. Most authors now agree that there is an early transition state and that bond formation is concerted but not necessarily synchronous.[278]

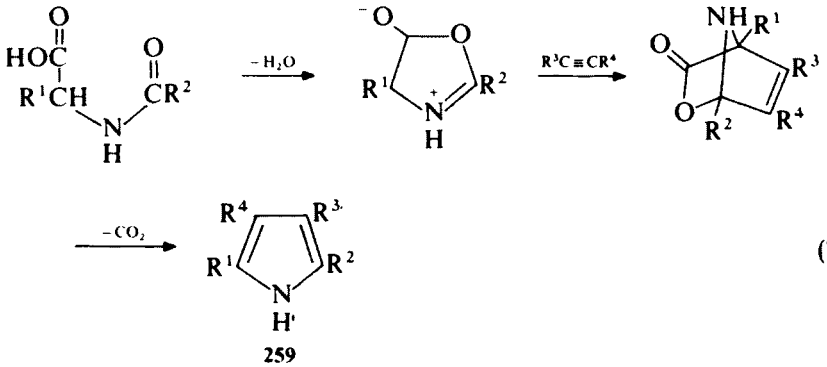
Unfortunately from the synthetic standpoint, many of the reports of the preparation of pyrroles by dipolar addition have emphasized methods for the generation of the dipole and the pyrroles were prepared only by the reaction with DMAD (the most common dipolarophile).

2.4.1. From 5-Membered Ring Heterocycles as Dipolar Species

2.4.1.1. Oxazoles

Because of the ease of preparation of azlactones by the dehydration of *N*-acylamino acids, most of the early examples of the formation of pyrroles via 1,3-dipolar additions utilize this route (Eq. 73). Although the dehydration has usually been carried out by heating the *N*-acylamino acid in acetic anhydride,

more recently the use of either dicyclohexylcarbodiimide or the water-soluble *N*-ethyl-*N'*-dimethylaminopropylcarbodiimide has given improved yields.[279,280] Silicon tetrachloride has also been used as a dehydrating agent.[280]



259 (73)

Tables 2.21 and 2.22 list the various pyrroles that have been produced from azlactones.

TABLE 2.21. PYRROLES (**259**, $R^3 = R^4 = CO_2Me$) FROM DIPOLAR ADDITION OF DMAD TO AZLACTONES

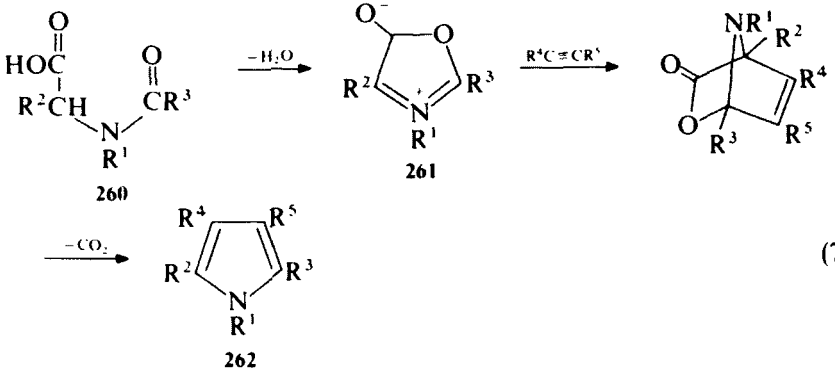
R^1	R^2	Ref.
Me	Ph	279, 281–282
Ph	Me	279, 281–282
Ph	cyclo-C_6H_{11}	282
Ph	Ph	281–282
Ph	*o*-$MeOC_6H_4$	279
Ph	*p*-$MeOC_6H_4$	281–282
Ph	*p*-ClC_6H_4	282
Ph	*p*-$NO_2C_6H_4$	282
Ph	1-Naphthyl	282
o-$NO_2C_6H_4$	Ph	281–282

TABLE 2.22. PYRROLES (**259**, R^4 = H) FROM DIPOLAR ADDITION OF OTHER ALKYNES TO AZLACTONES

R^1	R^2	R^3	Ref.
Ph	Ph	CO_2Me	281, 282
Me	Ph	CO_2Me	281–282[b]
Ph	Me	CO_2Me	282[b]
Me	Me	CN	283[a]
Ph	H	CN	283[a]
Ph	Ph	CN	283[a]
Ph	Me	CN	283[a]

[a] From 1-chloroacrylonitrile.
[b] Mixture of isomers.

The dehydration of *N*-substituted *N*-acylamino acids **260** gives mesoionic compounds **261**, whose zwitterionic structures can be considered as azomethine dipolar species (Eq. 74). These so-called Münchnones may also be referred to as *oxazolium compounds* or *anhydro-5-hydroxyoxazolium hydroxides.*

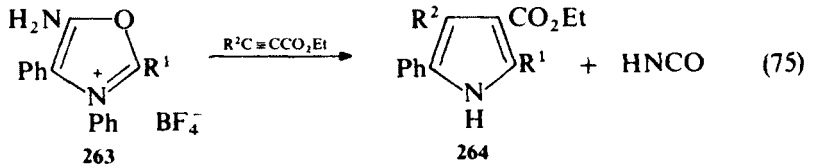


(74)

Various pyrroles prepared in this manner are listed in Tables 2.23 and 2.24.

The addition of alkenes to the Münchnones yields pyrrolines, which can be aromatized by either dehydrogenation with palladium or heating when there are groups present that can be easily eliminated. Pyrroles formed in this manner are listed in Table 2.25.

The 5-amino-oxazolonium salt **263** adds to alkynes with the loss of HNCO to give the pyrrole **264**:[294]



(75)

R^1	R^2
p-Tol	H
p-$NO_2C_6H_4$	H
p-$MeOC_6H_4$	H
p-Tol	Ph
p-$NO_2C_6H_4$	Ph
p-$MeOC_6H_4$	Ph

In an interesting competitive reaction, the Diels–Alder adduct of furan and DMAD **265a** was used as the dipolarophile with the oxazolium compound **266** to give the two quadracyclic compounds, **267a** and **268a**, which then reverted to the four possible pyrroles, **269** and **271**, and furans, **270a** and **272a**. The ratio of **269** to **271** was 3:2, indicating that, in spite of the steric factors, the DMAD

TABLE 2.23. PYRROLES (**262**, $R^4 = R^5 = CO_2Me$) FROM DIPOLAR ADDITION OF DMAD TO MÜNCHNONES

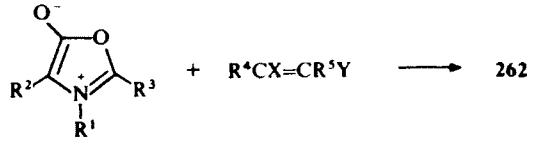
R^1	R^2	R^3	Ref.
Me	H	Ph	284
Me	Ph	Ph	285, 286
Me	Me	Ph	285
Me	Ph	Me	285, 286
Me	H	Me	285
Me	Ph	H	284
Me	Ph	2-Thienyl	286
Me	Ph	cyclo-C_6H_{11}	286
Ph	H	Ph	287
Ph	Me	Me	280, 285, 286
Ph	H	Me	286
cyclo-C_6H_{11}	Me	Me	286
$-(CH_2)_3-$		Me	285
$-(CH_2)_3-$		Ph	280

TABLE 2.24. PYRROLES (**262**) FROM DIPOLAR ADDITION OF ALKYNES TO MÜNCHNONES

R^1	R^2	R^4	R^5	R^3	Ref.
Me	Me	CO_2Me	CO_2Me	Me	286
Me	Me	Ph	H	Ph	286
Me	Ph	H	H	Ph	286
Me	Ph	H	CO_2Me	Ph	285
Me	Ph	H	Ph	Ph	285
Me	Ph	Ph	Ph	Ph	285, 286
Me	Ph	CO_2Et	Ph	Ph	285, 286
Me	Ph	CO_2Et	Ph	Me	285[a], 286
Me	Ph	CO_2Et	H	Me	288
Me	Ph	CO_2Et	H	H	284
Me	Ph	CO_2Et	Ph	H	284, 286
Me	Ph	*n*-Bu	H	Ph	285, 286
Me	Ph	C_6H_{13}	H	Ph	286
Me	Ph	Ph	H	Me	285[a]
Me	Ph	Me	CO_2Me	Ph	280, 286
Me	Ph	PhCO	Ph	Ph	286, 289
Me	Ph	H	CO_2Et	Ph	280
Me	$PhCH_2$	CO_2Et	H	Me	288
Ph	H	H	CO_2Et	Me	288
Ph	H	CO_2Et	H	CF_3	288
Ph	Me	Ph	H	Me	286
Ph	Me	CO_2Et	Ph	H	285
Ph	Me	CO_2Me	Ph	Me	286

[a] Mixture of isomers.

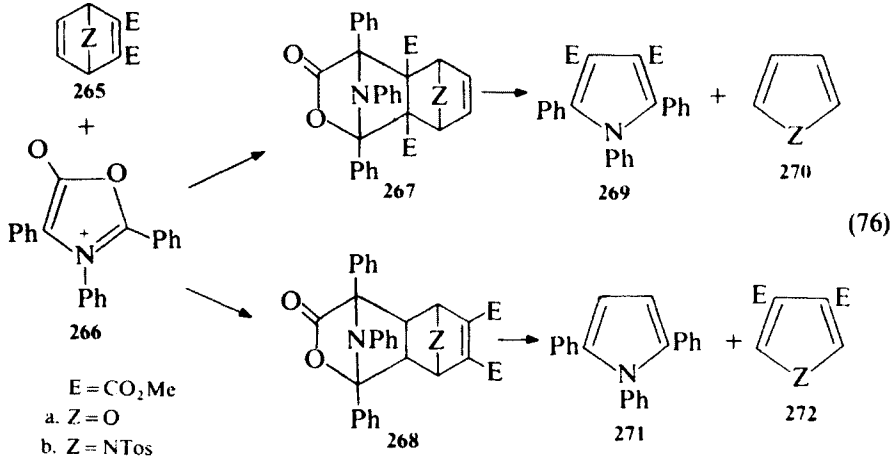
TABLE 2.25. PYRROLES (**262**) FROM DIPOLAR ADDITION OF ALKENES TO MÜNCHNONES



R^1	R^2	R^3	R^4	R^5	X	Y	Ref.
Me	Me	Me	CO_2Me	CO_2Me	H	H	290[a]
Me	Ph	Ph	*n*-Bu	H	H	H	290[a]
Me	Ph	Ph	Ph	H	H	H	290[a]
Me	Ph	Ph	Ph	Ph	H	H	290[a]
Me	Ph	Ph	H	H	H	H	290[a]
Me	Ph	Ph	Me	H	H	H	290[a]
Me	Ph	Ph	Ph	CO_2Et	H	H	290[a]
Me	Ph	Ph	CO_2Me	H	H	H	290[a]
Me	Ph	Ph	PhCO	PhCO	H	H	290[a]
Me	Ph	Ph	H	NO_2	Cl	H	291
Me	Ph	Me	Ph	CN	H	CN	292
Ac	Me	Ph	Ph	CN	H	CN	293
Ac	Ph	Me	Ph	CO_2Me	H	CN	291
Ac	Ph	Ph	Ph	CN	H	CN	293
Ac	Me	Ph	Ph	CO_2Me	H	CN	293
Ph	Me	Me	CO_2Me	CO_2Me	H	H	290[a]
Ph	H	Me	CO_2Me	CO_2Me	H	H	290[a]

[a] Palladium dehydrogenation.

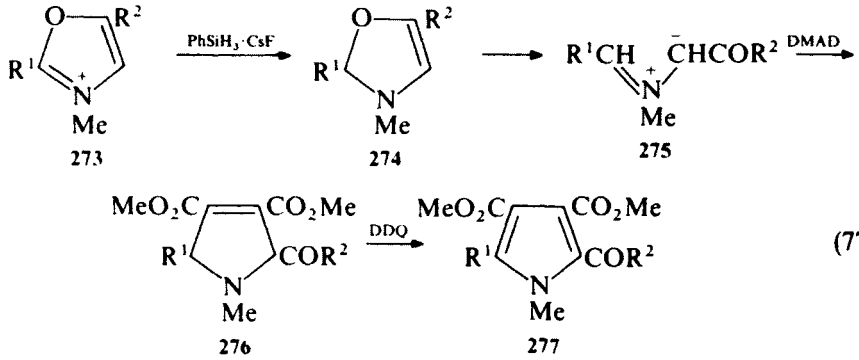
moiety was the more reactive.[295] In a similar manner, the adduct of 1-tosylpyrrole **265a** with DMAD gave about equal amounts of **269** and **271**.[296]



(76)

Reduction of the oxazolium salt **273** produces the unstable 4-oxazoline **274**, which spontaneously opens to the azomethine ylide **275**. In the presence of

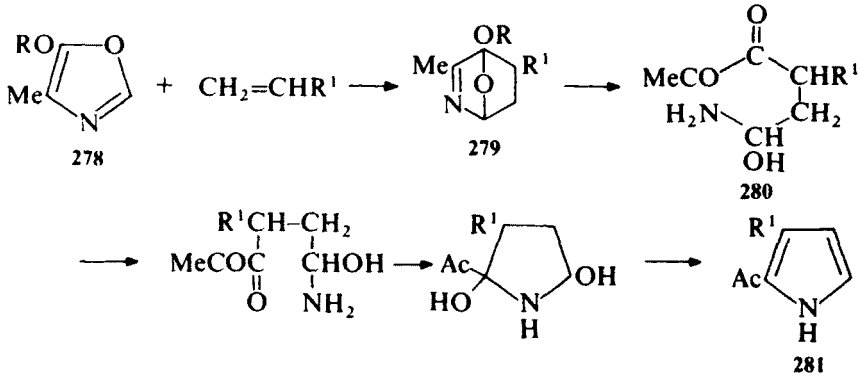
DMAD, the ylide is trapped as the pyrroline **276**, which can be converted into the pyrrole **277** by oxidative aromatization with DDQ:[297]



(77)

R^1	R^2
Ph	Ph
Ph	Me
Ph	EtO
Me	EtO
Me	Ph

The 5-alkoxyoxazole **278** can be considered as the enol ether of a 5-oxazolone but acts as a diene rather than a dipolar species. Thus, it adds to dienophiles in a Diels–Alder-type reaction to give initially the bicyclo adduct **279**. Under hydrolytic conditions, **279** opens to give **280**, which undergoes ring closure to yield the 2-acylpyrrole **281**:[298–300]

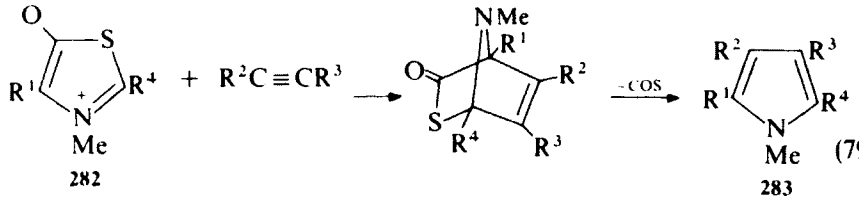


(78)

R	R^1
Pr	NO_2
Et	CO_2Et
Et	Ac
Et	PhCO

2.4.1.2. *Thiazoles*

Thiazolium, or anhydro-5-hydroxythiazolium, salts **282** behave similar to the oxazolium salts and add alkynes to give pyrroles **283** through the loss of COS:[301]

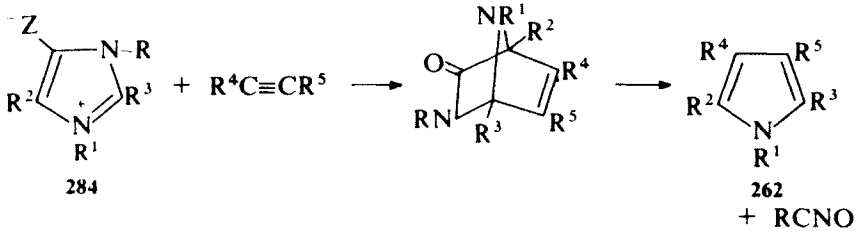


(79)

R^1	R^2	R^3	R^4
H	CO_2Me	CO_2Me	p-$MeOC_6H_4$
H	CO_2Me	CO_2Me	Ph
H	Ph	CO_2Me	Ph
Ph	Ph	CO_2Me	Ph

2.4.1.3. *Imidazoles*

Imidazolium, or anhydro-4-hydroxyimidazolium, salts **284** have been used as masked dipolar species. Reaction with dipolarophiles give the pyrroles **262** by the extrusion of an isocyanate:



(80)

The pyrroles prepared by this method are listed in Table 2.26.

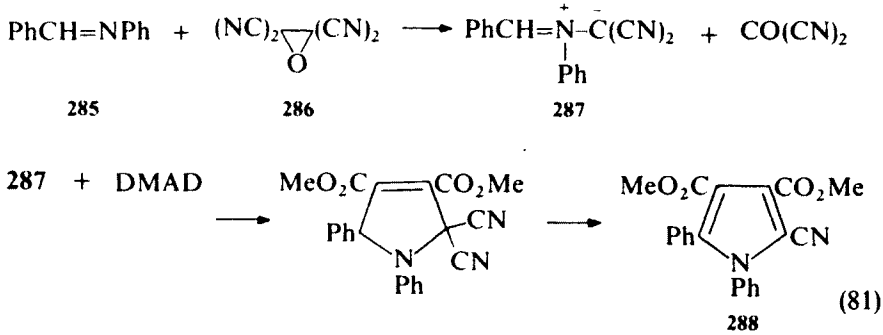
2.4.2. From Open-Chain Dipolar Species

2.4.2.1. *Azomethine Ylides*

An azomethine ylide **287** can be produced by the reaction of tetracyanoepoxide **286** to transfer a dicyanocarbene to the anil **285**; addition of the ylide to DMAD gives the expected pyrrole **288**:[306]

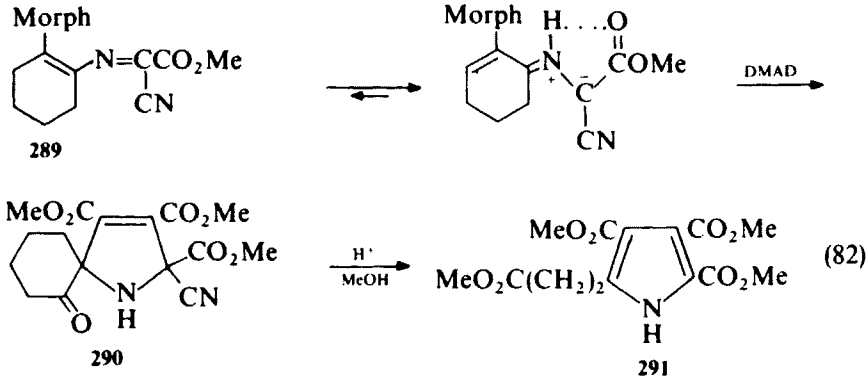
TABLE 2.26. PYRROLES (262) FROM ADDITION OF ALKYNES TO IMIDAZOLIUM SALTS (284)

R^1	R^2	R^3	R^4	R^5	Z	R	Ref.
Me	H	Ph	CO_2Me	CO_2Me	PhCON	Ph	302
Ph	Ph	Ph	CO_2Me	CO_2Me	O	Ph	303
Ph	Ph	Ph	H	CO_2Me	O	Ph	303
Ph	Ph	Ph	H	Ph	O	Ph	303
Me	Ph	Ph	CO_2Me	CO_2Me	O	Ph	304
Me	Ph	Ph	PhCO	PhCO	O	Ph	304
Me	Ph	Ph	CO_2Me	H	O	Ph	304
Me	Ph	Ph	CO_2Me	Me	O	Ph	304
Me	Ph	Ph	CO_2Me	Ph	O	Ph	304
Me	Ph	Ph	Ph	H	O	Ph	304
Ph	Ph	Me	CO_2Me	CO_2Me	O	Ph	304
Ph	Ph	MeS	CO_2Me	CO_2Me	O	Ph	305
Ph	Ph	MeS	PhCO	PhCO	O	Ph	305
Ph	CO_2Et	Ph	CO_2Me	CO_2Me	O	Ph	305



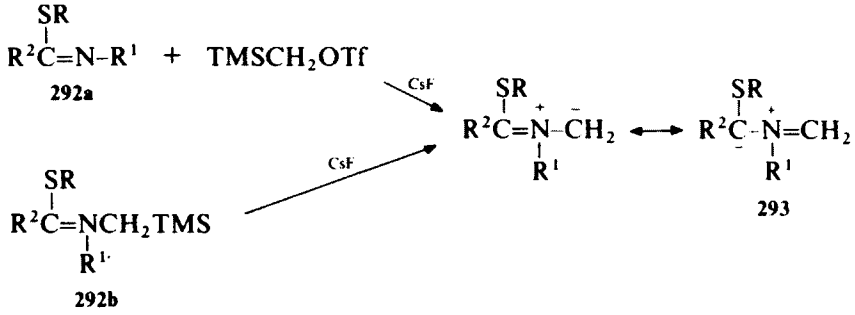
(81)

A more stable tautomeric form of **289**, where there is hydrogen bonding, is effectively an azomethine ylide and, as such, adds DMAD to form initially the spiro compound **290**. Elimination of HCN and solvolytic opening of the 6-membered ring leads to the pyrrole **291**:[307]



(82)

More recently, the formation of carbanions by treatment of trimethylsilyl compounds with fluoride ion has been utilized to generate azomethine ylides. Thus, thioimidates containing trimethylsilyl groups **292** are converted into azomethine ylides **293** (Scheme 22). Several routes to the thioimidates have been developed, and Table 2.27 lists the pyrroles that have been prepared by the addition of **293** to alkynes.



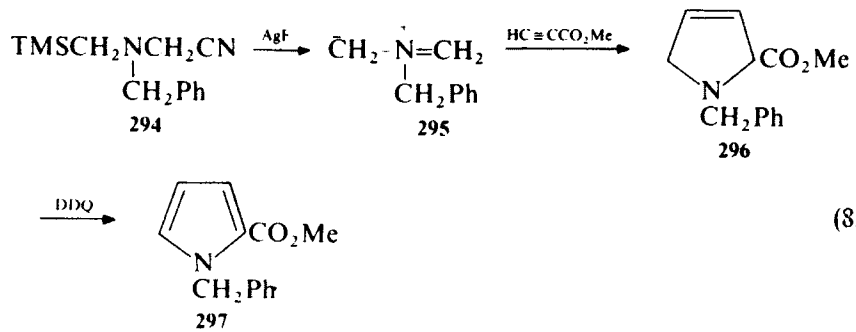
Scheme 22

TABLE 2.27. PYRROLES (**262**) FROM ADDITION OF ALKYNES ($R^4C{\equiv}CR^5$) TO AZOMETHINE YLIDES (**293**)

R^1	R^2	R^4	R^5	Ref.
Me	Ph	CO_2Me	CO_2Me	308, 309
$PhCH_2$	H	CO_2Me	CO_2Me	310
$PhCH_2$	H	CO_2Me	H	310
$PhCH_2$	Me	CO_2Me	H	311[a]
$PhCH_2$	Ph	CO_2Me	H	309[a]
$-(CH_2)_3-$		CO_2Me	CO_2Me	311
$-(CH_2)_4-$		CO_2Me	CO_2Me	311

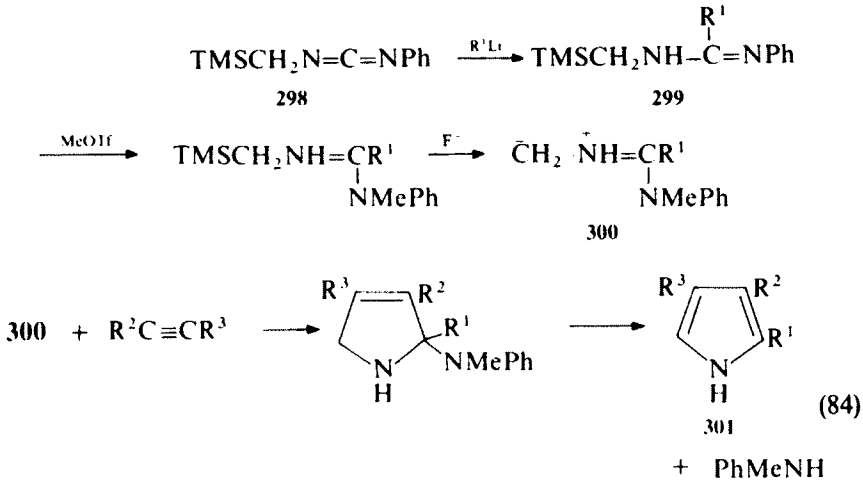
[a]Mixture of isomers.

In a similar manner, disilylation of **294** and loss of cyanide generates the azomethine ylide **295**. Addition to an alkyne gives the pyrroline **296**, which is converted by DDQ into the pyrrole **297**:[312,313]



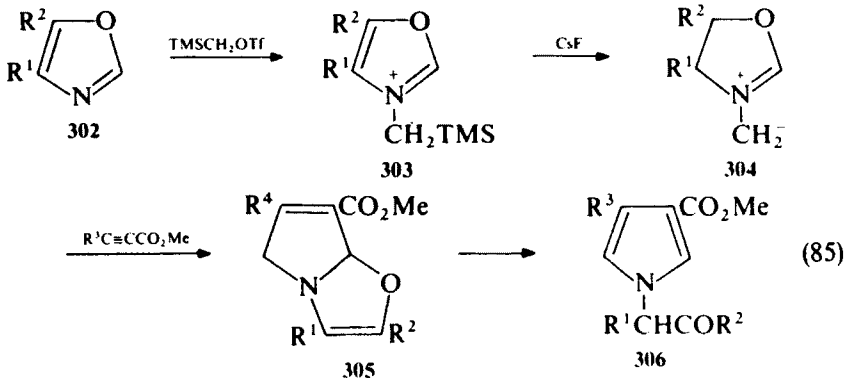
(83)

An *N*-silylmethylamide **299** results from the treatment of heterocumulene **298** with an organolithium. This is converted into the *N*-protonated azomethine ylide **300** by methylation with methyl triflate and subsequent fluoride ion disilylation. Addition to an alkyne and loss of *N*-methylaniline yields the pyrrole **301**:[314,315]



(84)

Trimethylsilylmethyl alkylation of the oxazole **302** produces an oxazolium salt **303**, which can be converted into the exocyclic azomethine ylide **304** by desilylation. The cycloadduct **305**, formed by the addition to an alkyne, undergoes a 1,4-elimination to yield the 1-substituted pyrrole **306**:[316]

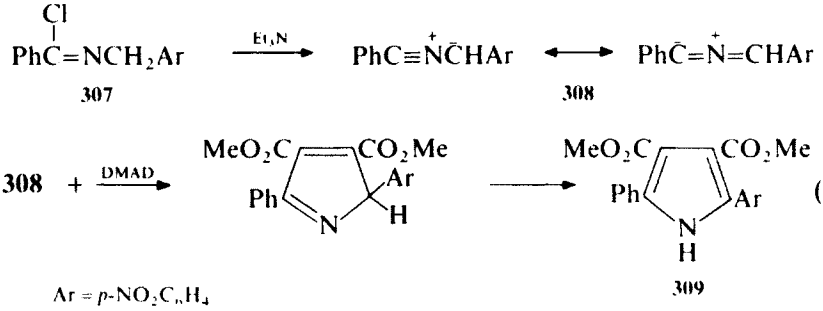


(85)

R^1	R^2	R^3
H	Ph	H
H	Ph	CO_2Me
Ph	H	H
Ph	H	CO_2Me

2.4.2.2. *Nitrile Ylides*

Nitrile ylides are generally produced by the dehydrohalogenation of an imidoyl chloride, for example, by treatment of *N*-*p*-nitrobenzylbenzimidoyl chloride (**307**) with triethylamine. The dipole **308** can be trapped with DMAD to give **309**:[317]



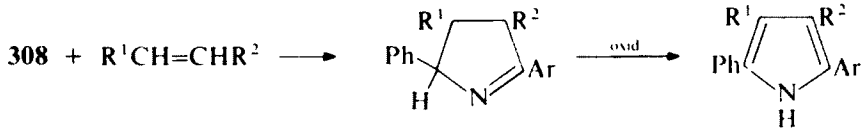
(86)

Other examples are given in Table 2.28.

TABLE 2.28. PYRROLES OBTAINED BY ADDITION OF NITRILE YLIDES ($R^1C\bar{H}-\overset{+}{N}\equiv CR^2$) TO ALKYNES ($R^3C\equiv CR^4$) (cf. Eq. 86)

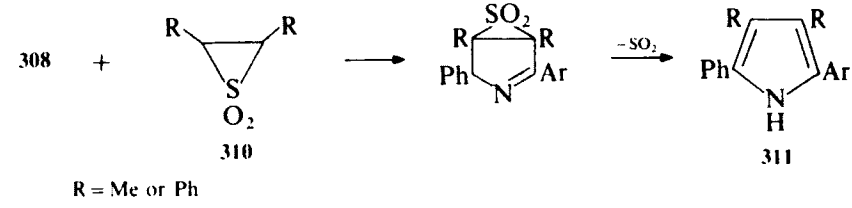
R^1	R^2	R^3	R^4	Ref.
p-$NO_2C_6H_4$	Ph	CO_2Me	H	318
p-$NO_2C_6H_4$	Ph	Ph	CO_2Et	318
Ph	CF_3	CO_2Me	CO_2Me	319

The reaction of nitrile ylides with alkenes give pyrrolines that can be aromatized to the corresponding pyrroles.[318,320]



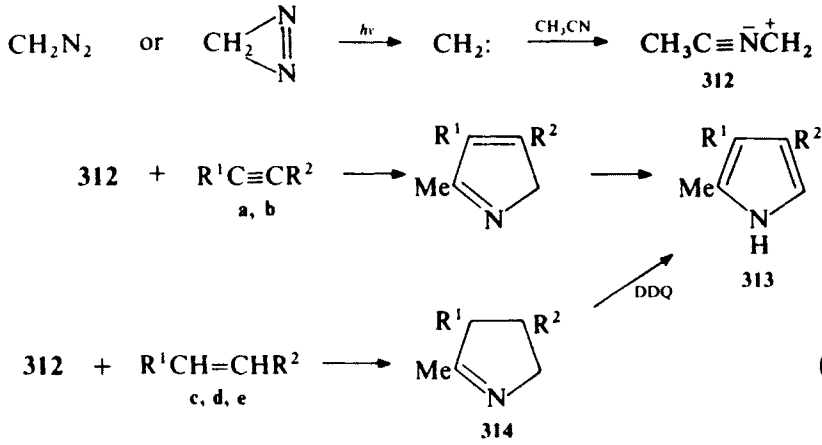
(87)

The nitrile ylide **308** adds to thiirine 1,1-dioxides **310** to yield pyrroles **311** with the extrusion of sulfur dioxide:[321,322]



(88)

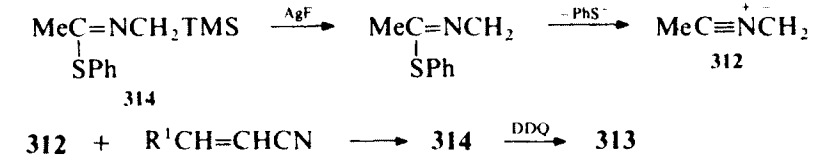
The reaction of methylene, generated by the photolysis of either diazomethane or diazirine, with acetonitrile produces the very simple nitrile ylide **312**, which has been reacted with a number of dipolarophiles to give either the pyrroles **313**, or pyrrolines **314**:[323,324]



(89)

	R^1	R^2
a.	CO_2Me	CO_2Me
b.	CO_2Me	H
c.	CN	CN
d.	CN	H
e.	CO_2Me	H

The ylide **312** has been prepared by disilylation of the silylthioimidate **315** with silver fluoride. When trapped by either acrylonitrile or maleonitrile, the ylide gave the pyrrolines **314c** and **314d**, which were converted into the corresponding pyrroles **313**:[323,324]



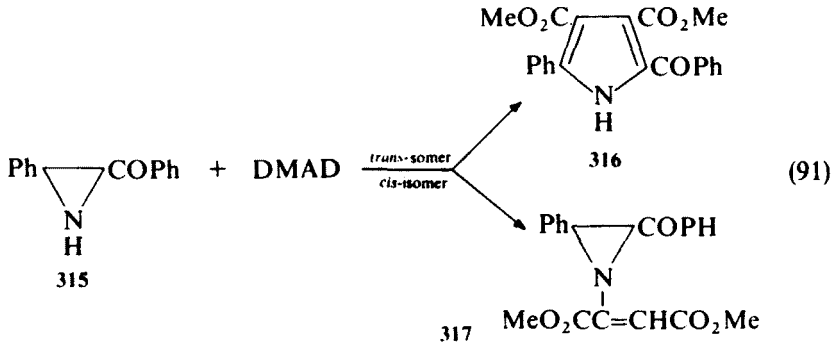
(90)

2.4.3. Formation of Dipolar Species via Ring Opening of 3-Membered Ring Compounds

2.4.3.1. From Aziridines

Theromolytic ring opening of aziridines generates an azomethine ylide, which can then undergo a 1,3-dipolar addition. The *trans*-isomer of the unsubstituted

aziridine **315** adds DMAD to give the pyrrole **316**, but the *cis*-isomer is less susceptible to ring cleavage and the adduct **317** is formed instead. When there is a substituent on the nitrogen atom, however, the ring of both the *cis*- and *trans*-isomers will open, although the ring cleavage of the former is probably slower:[325]

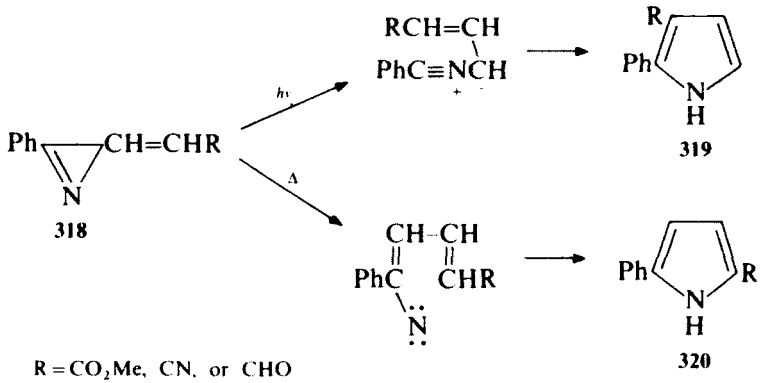


(91)

Other examples of the addition of alkynes to aziridines are given in Table 2.29. Generally the yields are quite good, and some are quantitative, although with some dipolarophiles there is a lack of regiospecificity.

2.4.3.2. From Azirines

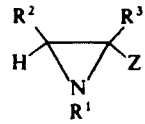
Although thermolysis of aziridines leads to ring opening to produce the azomethine ylide, azirines open to give vinyl nitrenes. However, the photolytic ring-opening reaction yields the nitrile ylide. Therefore, the vinylazirine **318** can give two different products **319** and **320** depending on the conditions use, as shown in Scheme 23.[126,336,337]



Scheme 23

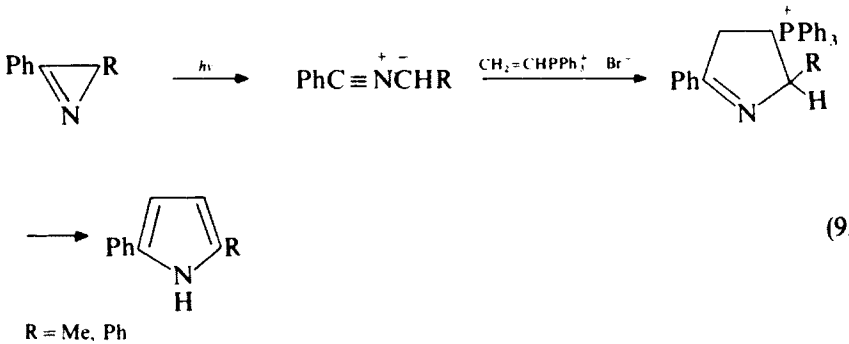
Azirines add to vinyl Wittig reagents, as shown in Eq. 92 when photolyzed.[338,339]

TABLE 2.29. PYRROLES (**262**) FROM ADDITION OF ALKYNES ($R^4C{\equiv}CR^5$) TO



R^1	R^2	R^3	R^4	R^5	Z	Ref.
cyclo-C_6H_{11}	Ph	H	H	Ph	CN	326
cyclo-C_6H_{11}	Ph	H	CO_2Me	CO_2Me	CN	326
$PhCH_2$	Ph	H	CO_2Me	CO_2Me	CN	326
t-Bu	Me	COPh	CO_2Me	CO_2Me	H	255
Ph	Pyrrolidinyl	Me	CO_2Me	CO_2Me	CN	327
Ph	Ph	H	H	CO_2Me	CN	328
Ph	Ph	H	Ph	CO_2Me	CN	328
Ph	Ph	H	H	Ph	CN	328
$PhCH_2$	Ph	H	H	CO_2Me	CN	328
$PhCH_2$	Ph	H	Ph	CN	CN	328
TMS	H	CO_2t-Bu	CF_3	CF_3	F	329
H	Ph	H	CO_2Et	H	CN	330
H	Ph	COPh	CO_2Et	H	H	330
Ph	Ph	Cl	CO_2Me	CO_2Me	Cl	320
Ph	Ph	H	CO_2Me	CO_2Me	PhSO	331
Ph	*p*-ClC_6H_4	H	CO_2Me	CO_2Me	PhSO	331
Ph	*p*-$NO_2C_6H_4$	H	CO_2Me	CO_2Me	PhSO	331
Ph	*m*-ClC_6H_4	H	CO_2Me	CO_2Me	PhSO	331
p-BrC_6H_4	Ph	H	CO_2Me	CO_2Me	PhSO	311
p-Tol	Ph	H	CO_2Me	CO_2Me	PhSO	331
$PhCH_2$	CO_2Me	H	$(CH_2)_2OH$	Ac	H	332
cyclo-C_6H_{11}	Ph	CN	CO_2Me	CO_2Me	CN	333
cyclo-C_6H_{11}	Ph	CO_2Et	CO_2Me	CO_2Me	CN	333
cyclo-C_6H_{11}	Ph	COPh	CO_2Me	CO_2Me	CN	333
cyclo-C_6H_{11}	*i*-Pr	COPh	CO_2Me	CO_2Me	CN	333
cyclo-C_6H_{11}	*i*-Pr	CN	CO_2Me	CO_2Me	CN	333
cyclo-C_6H_{11}	*i*-Pr	COPh	CO_2Me	CO_2Me	CN	333
t-Bu	CO_2Me	H	F	F	Cl	334
cyclo-C_6H_{11}	Ph	CO_2Et	Ph	Ph	H	335
cyclo-C_6H_{11}	Ph	CO_2Et	Ph	Ph	CO	335[a]

[a] From diphenylcyclopropenone.



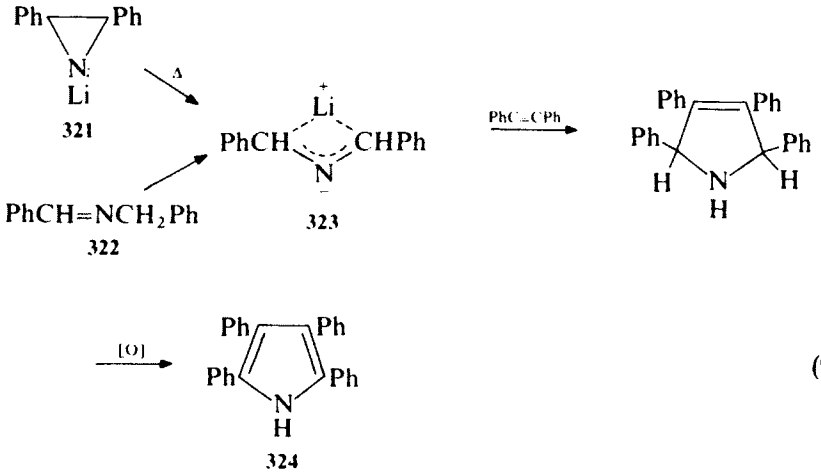
(92)

R = Me, Ph

2.5. FORMATION OF PYRROLES VIA NONSIMULTANEOUS FORMATION OF C_2–C_3 AND C_4–C_5 BONDS

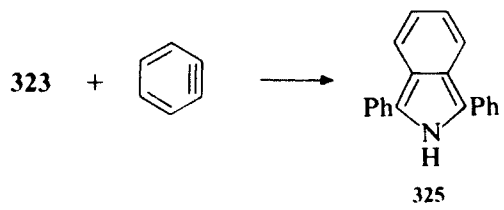
2.5.1. From Aza-allyl Anion

1,3-Diphenyl-2-aza-allyllithium (**323**) can be prepared from either the ring opening of the lithium salt of the aziridine **321** or from the Schiff base of benzaldehyde and benzylamine **322**.[340] In either case, it adds to diphenylethyne to give 2,3,4,5-tetraphenylpyrrole (**324**) (83%) (Eq. 93)[341] via the Δ^3-pyrroline, which spontaneously aromatizes in air. It is conceivable that the reaction involves a 1,3-dipolar cycloaddition, since the aza-allyl anion is the conjugate base of the azomethine species.[340]



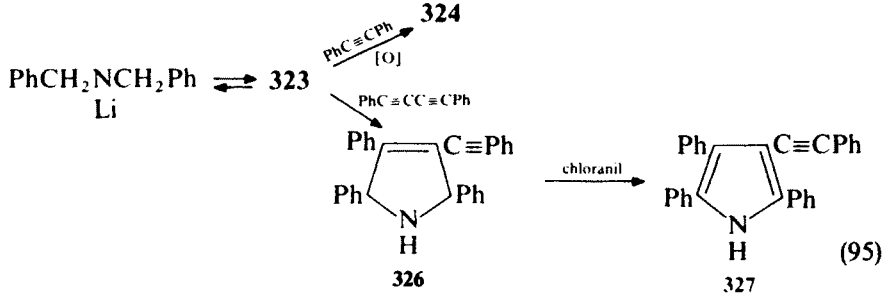
(93)

Addition of **323** to benzyne yields the isoindole **325**:[340]



(94)

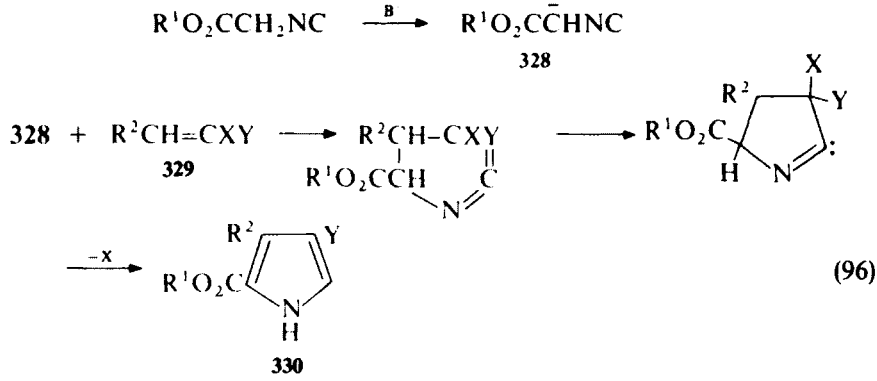
In a similar manner, the lithium salt of dibenzylamine reacts with diphenylethyne to give **324**, possibly through the formation of a small amount of **323**. With 1,4-diphenyl-1,3-butadiyne, the Δ^3-pyrroline **326** is isolated and can be aromatized by oxidation with chloranil to yield **327**:[341]



(95)

2.5.2. From Isocyanoacetate Anions

The addition of the anion of isocyanoacetate esters **328** to alkenes **329** having a potential leaving group has been exploited for the synthesis of 2-pyrrolecarboxylates unsubstituted at the 5 position **330**:



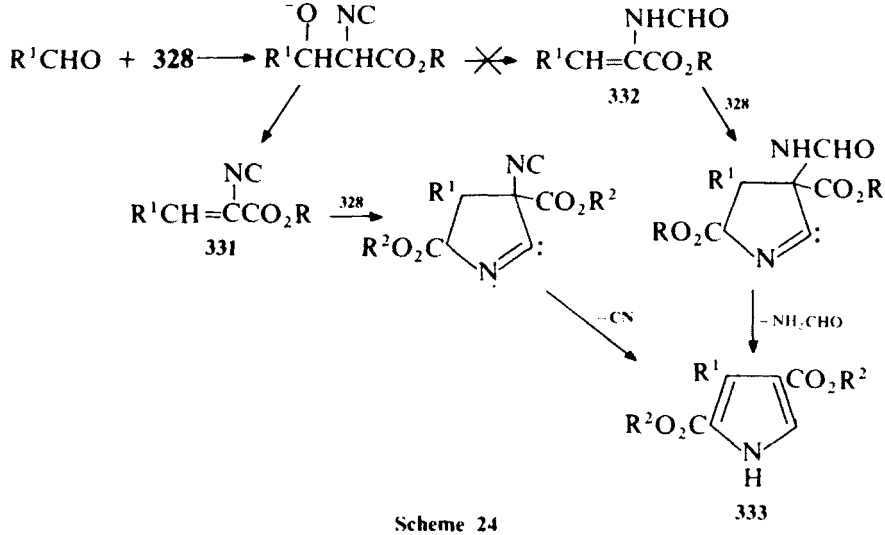
(96)

TABLE 2.30. PYRROLES (**330**) BY ADDITION OF ISOCYANOACETATES TO ALKENES

R^1	R^2	X	Y	Ref.
Me	Me	NO_2	H	342
Et	*p*-ClC_6H_4	NO_2	Me	342
t-Bu	Et	NO_2	Et	342
t-Bu	Me	NO_2	Et	342
t-Bu	Et	NO_2	Me	342
t-Bu	Me	NO_2	CH_2CO_2H	342
t-Bu	*p*-$MeOC_6H_4$	NO_2	Me	342
Et	*o*-ClC_6H_4	*p*-Tos	H	342
Ett	*o*-ClC_6H_4	CN	CN	343

An interesting variation on this route has been the formation of the substituted alkene **331** by condensation of an aldehyde with the isocyanoacetate. Subsequent addition of a second molecule of the ester gives the 3-substituted

pyrrole-2,4-dicarboxylate **333**. Originally, it was believed that the product of the initial condensation was a formamidoacrylate **332**, formed from a transfer of oxygen to the isocyano group, but it is more likely that it is the isocyanoacrylate **331**, which then eliminates the cyanide ion (Scheme 24).[344,345]



Scheme 24

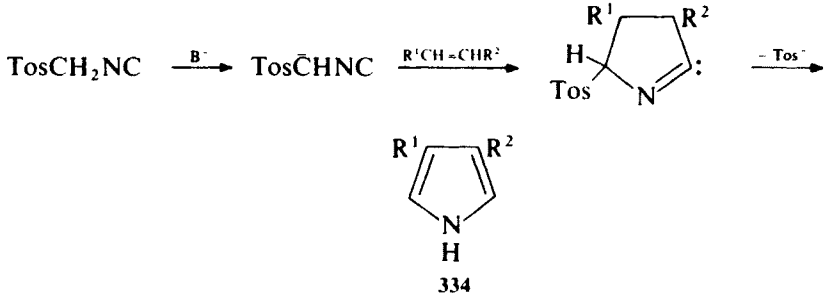
TABLE 2.31. PYRROLES (333) OBTAINED FROM ALDEHYDES AND ISOCYANOACETATES

R^2	R^1	Ref.
Me	H	344, 346[a]
i-Pr	Me	346[a]
Et	Et	346[a]
Me	Ph	346[a]
Me	*p*-$MeOC_6H_4$	346[a]
Me	3,4,5-$(MeO)_3C_6H_2$	346[a]
Me	3-Pyridyl	346[a]–347
Me	3-Indolyl	346[a]
Et	Ph	345
Et	Me	345
Me	*p*-ClC_6H_4	348[b]
Me	Ph	347[a], 348[b]
Me	*p*-Tol	347[b]
Me	*p*-$Me_2NC_6H_4$	347[b]
Me	*p*-ClC_6H_4	347[b]
Me	Et	349[b]
Me	H	347[a]
Me	Me	347[a]

[a] DBU used as base.
[b] NaH used as base.

2.5.3. From Tosylmethylisocyanides

Van Leusen has developed a method that has found wide application for the synthesis of pyrroles, particularly those substituted only at positions 3 and 4.[350] *p*-Toluenesulfonylmethylisocyanide (TOSMIC) adds to alkenes in the presence of a very strong base, such as sodium hydride. The deprotonated TOSMIC undergoes a Michael-type addition, followed by displacement of the sulfinate anion and hydrogen migration to give the pyrrole, as shown in Scheme 25.



334

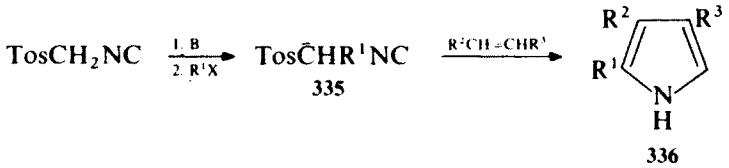
Scheme 25

TABLE 2.32. PYRROLES (334) BY ADDITION OF TOSMIC TO ALKENES

R^1	R^2	Ref.
H	CO_2Me	351–353
H	Ac	352
Me	CO_2Me	352
Me	CO_2Et	354, 355
Me	Ac	352
Me	$CH{=}CHCO_2Et$	355
n-Pr	$COCH_2Ph$	356
n-Bu	COC_3H_7	356
C_5H_{11}	COC_4H_9	356
C_6H_{13}	COC_5H_{11}	356
C_8H_{17}	COC_6H_{13}	356
C_8H_{17}	COC_7H_{15}	356
Ph	CO_2Me	352
Ph	CN	357[a], 358
Ph	COPh	352
2-Furyl	CN	351, 359[a]
2-Furyl	Ac	352
2-Thienyl	CN	359[a]
3-Pyridyl	CN	359[a]
4-Cl-2-$PhCOC_6H_3$	CN	360
Ac	CO_2Me	352
PhCO	CO_2Me	351, 352
PhCO	COPh	352
CO_2Me	CO_2Me	351, 352

[a] From $R^1CH{=}CCNCO_2Et$.

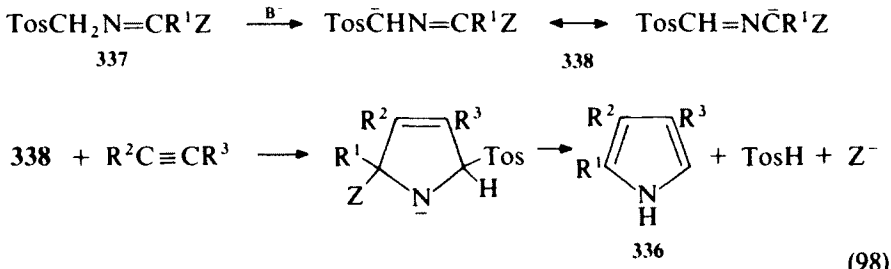
Since the anion of *p*-toluenesulfonylmethylisocyanide can be alkylated **335** the procedure can be utilized to prepare 2,3,4-trisubstituted pyrroles **336**:[361]



(97)

R^1	R^2	R^3	Ref.
Me	Me	CO_2Me	361
Me	Ph	COPh	361
Me	H	$CH{=}CHSO_2Ph$	362
allyl	Ph	COPh	361
$PhCH_2$	Me	CO_2Me	361
$PhCH_2$	Ph	CN	361
$PhCH_2$	Ph	COPh	361

Treatment of tosylimidates and thioimidates (**337**) with a strong base generates an aza-allyl anion **338** whose behavior is similar to that from TOSMIC. Loss of the sulfinate anion and the alkoxide or the thioalkoxide anion gives the pyrrole **336**:[350,363]



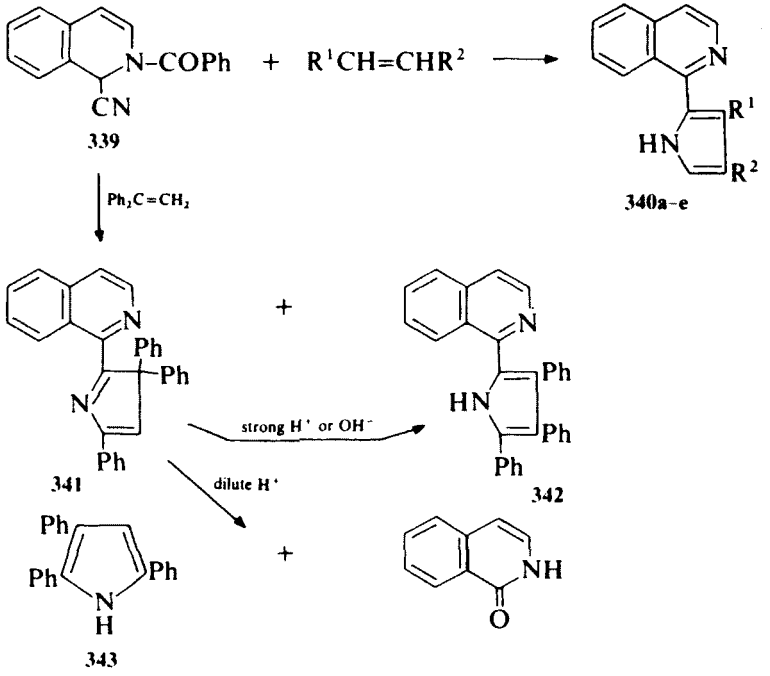
(98)

TABLE 2.33. PYRROLES (**336**) FROM TOSYLIMIDATES OR THIOIMIDATES WITH ALKENES

R^1	R^2	R^3	Z	Ref.
Me	COPh	Ph	MeO	363
Me	COPh	Ph	MeS	350
MeO	COPh	Ph	MeO	350
MeS	COPh	Ph	MeS	350
Ph	CO_2Me	Ph	MeS	350, 363
Ph	CO_2Et	CH_2CO_2Et	MeS	363
Ph	CN	Me	MeS	363
Ph	Ac	Me	MeS	363
Ph	CN	Ph	MeS	363
Ph	COPh	Ph	MeS	350, 363

2.5.4. From Reissert Compounds

In a series of papers, McEwen has reported that, under acidic conditions, the Reissert compound **339** will add an alkene to produce the 2-(1-isoquinolyl)-5-phenylpyrrole **340**:[364-366]

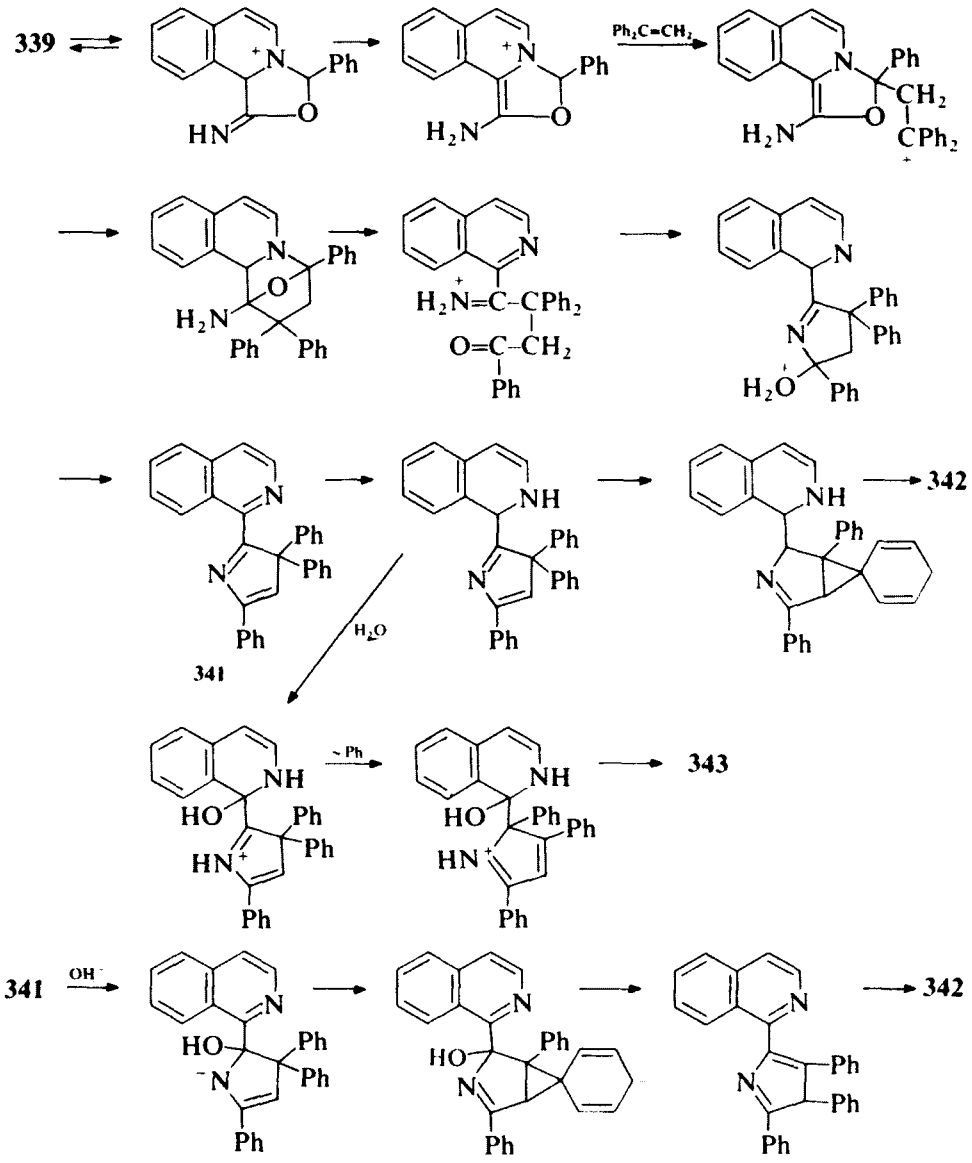


(99)

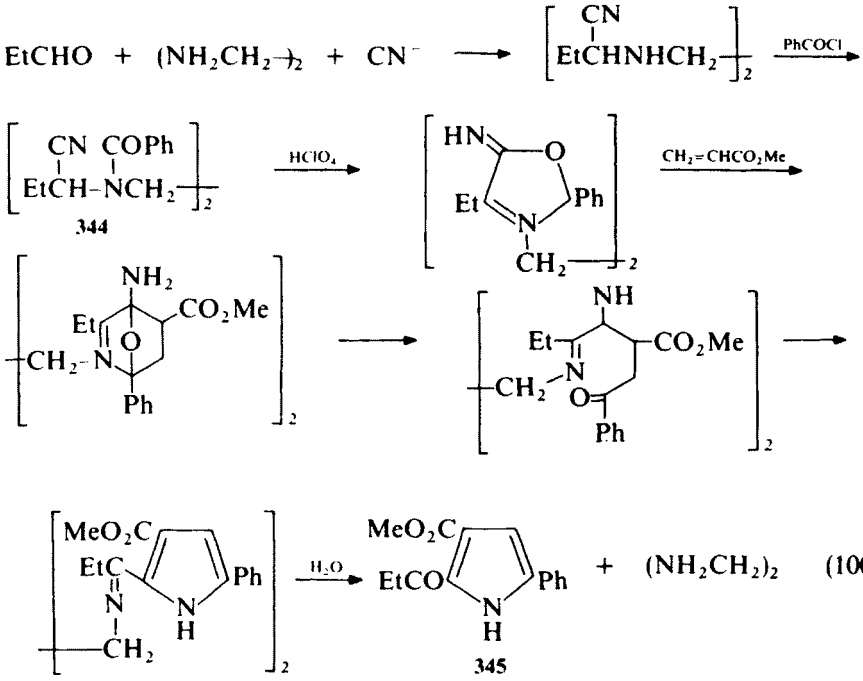
	R^1	R^2
a.	H	CO_2Et
b.	H	CN
c.	Ph	Ph
d.	Ph	CO_2Et
e.	*p*-$NO_2C_6H_4$	CO_2Et

With 1,1-diphenylethene, an equal amount of the intermediate pyrroline **341** and the pyrrole **342** are isolated. Treatment of **341** with either strong acid or strong base converts it into **342**. In weakly acidic media, triphenylpyrrole (**343**) is formed instead. Using labeled compounds, McEwen was able to show that the reaction proceeded through the series of steps, outlined in Scheme 26.[367-369]

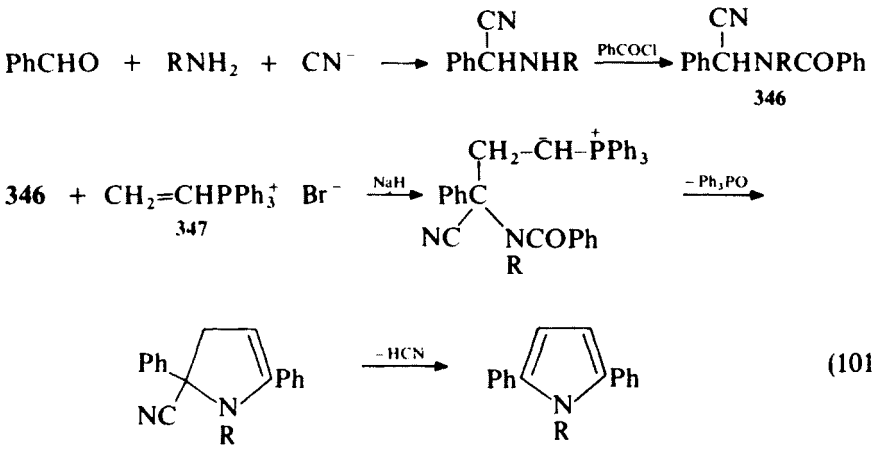
A similar reaction occurs with the open-chain Reissert compound **344** and methyl acrylate to yield the 2-acyl-5-phenylpyrrole **345** (60%):[370]


339
Ph
HN
O
H2N
Ph2C=CH2
CH2
CPh2
H2O
H2N=C–CPh2
O=C–CH2
341
342
343
H2O
OH
HO
HN

Scheme 26



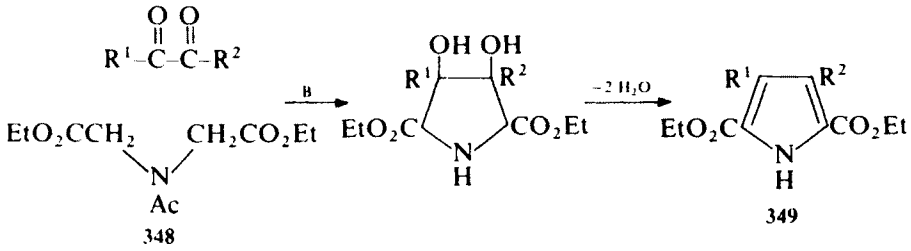
A more straightforward addition reaction occurs with the open-chain Reissert compound **346** and the vinylphosphonium salt **347**:[371,372]



R = Ph, *o*-$MeOC_6H_4$, *p*-ClC_6H_4, cyclo-C_6H_{11}

2.5.5. Miscellaneous Reactions

A number of papers and patents have described the use of **348** in a double Dieckmann condensation to prepare the pyrrole-2,5-dicarboxylates **349**:



R^1	R^2	Ref.
Ph	Ph	373, 374
4-Cl-3-$NO_2C_6H_4$	H	375–377

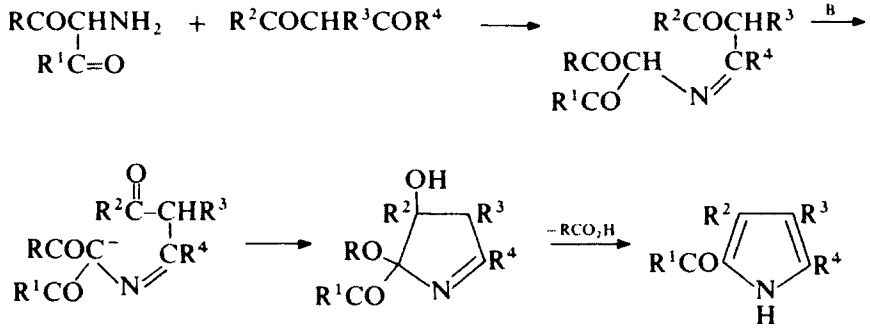
(102)

With diethyl oxalate, the 3,4-dihydroxypyrrole is formed.[378]

2.6. FORMATION OF PYRROLES FROM A 3-CARBON UNIT AND A 1-CARBON UNIT

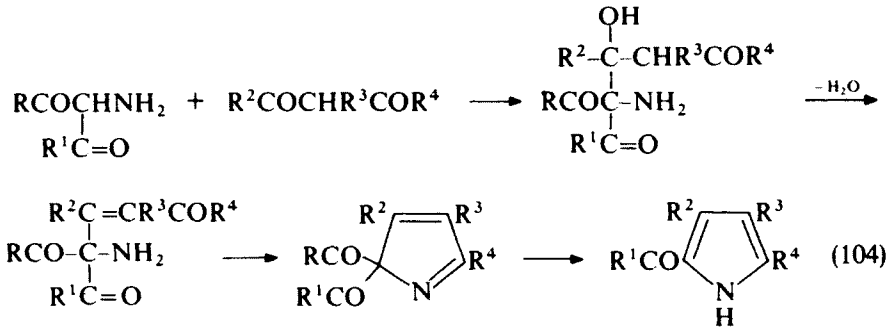
2.6.1. Condensation of α-Aminoketones with β-Dicarbonyl Compounds: The Fischer–Fink Synthesis

As discussed in Section 2.2.1.1, the use of a β-diketone in the condensation with an α-aminoketone (the Knorr synthesis) may lead to an alternate ring closure through the carbonyl group of the diketone and the α-carbon atom of the aminoketone (Eq. 103). Aromatization occurs by loss of an acyl or carboxy group. This alternative is often referred to as the *Fischer–Fink synthesis.*[379–380]

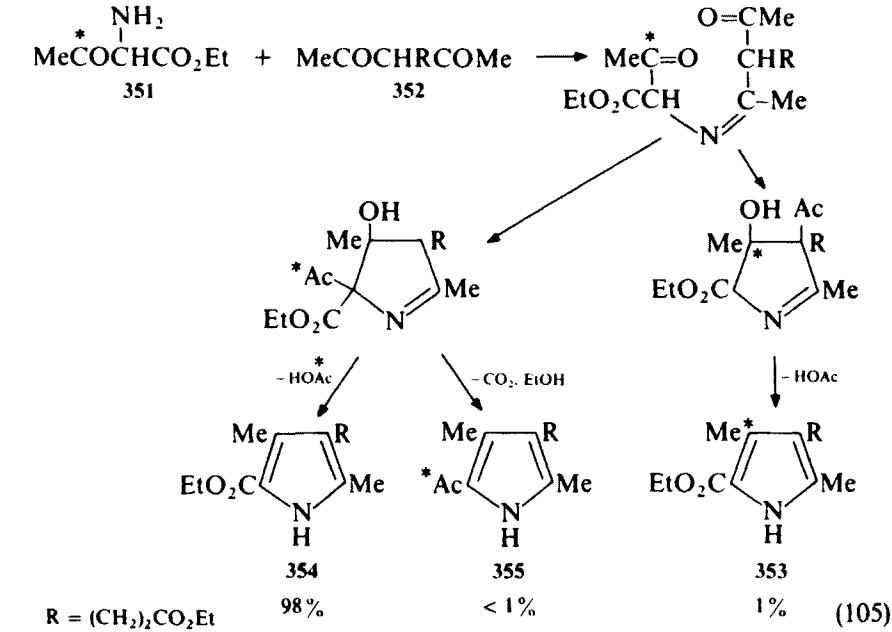


(103)

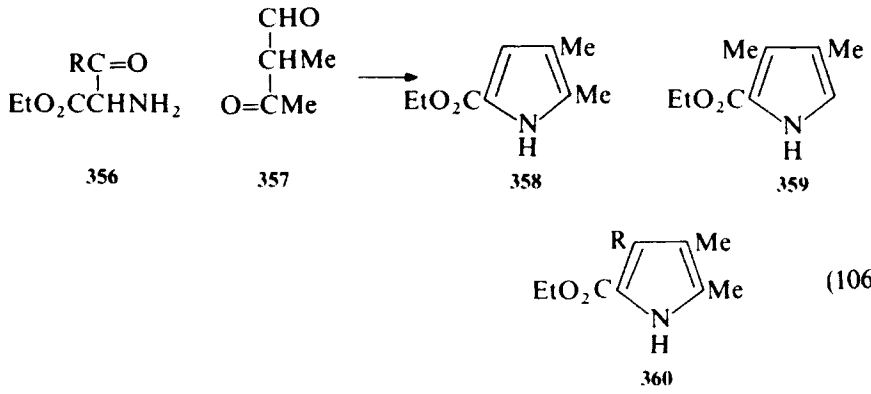
An alternative mechanism (Eq. 104) has been suggested, which involves the initial formation of a carbon–carbon bond by the aldol-like condensation of the α-carbon atom of the aminoketone with the dicarbonyl compound.[381]



Originally the typical Fischer–Fink synthesis was, carried out under the conditions used for the Knorr synthesis: nitrosation of a ketoester, such as ethyl acetoacetate, followed by reduction of the nitroso compound in the presence of the diketone. Under these conditions, pentane-2,4-dione gives almost entirely the Knorr product, whereas use of the 3-methylpentane-2,4-dione leads to the Fischer–Fink product.[382] An unsymmetrical diketone can give two different products, depending on which carbonyl group forms the imine. When the amino compound is derived from a ketoester, there is also the possibility that either an acyl or alkoxycarbonyl group may be lost. Generally an acyl group is a much better leaving group. Using the ^{14}C-labeled acetoacetic ester (**351**) in the reaction with ethyl 4-acetyl-5-oxohexanoate (**352**), Rapoport showed that less than 1% of the pyrroles **354** and **355**, resulting from the Fischer–Fink reaction, involved loss of the alkoxycarbonyl group.[383] Also, in this case, only about 1% of the Knorr product **353** was formed.



An interesting study by Falk et al.[384] gives some insight into the factors controlling the divergence between the Knorr and the Fischer–Fink reactions. The results of the reaction of 3-oxo-2-methylbutanal **357** with several aminoketones **356** are illustrated in Eq. 106. The unsymmetrical dicarbonyl compound can lead to two possible Fischer–Fink products **358** and **359**, in addition to the Knorr product **360** in which the formyl group has been lost.

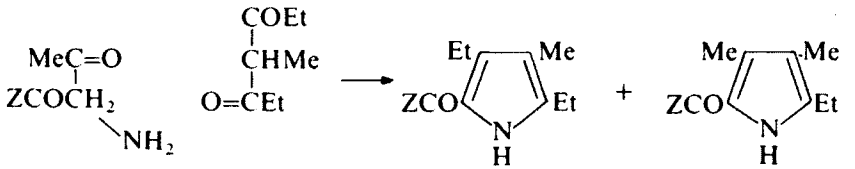


356 **357** **358** **359** **360** (106)

R	358 (%)	359 (%)	360 (%)
Me	76	7.5	16.5
Et	85.5	13.5	< 1
i-Pr	88.5	10.5	< 1
EtO	20.5	79.5	0

As the size of R is increased, the amount of the Knorr product decreases while the proportion of the two Fischer–Fink products is relatively unchanged. However, when R is an alkoxy group, that is, the leaving group is alkoxycarbonyl instead of an acyl group, the order of the Fischer–Fink products is reversed and the formation of the Knorr product is completely suppressed.

Paine has observed that, whereas the reaction of ethyl aminoacetoacetate (**361a**) with a meso-substituted diketone **362** gives the expected Fischer–Fink product **363**, it is the Knorr product **364** that results when the amide **361b** is used.[385] It has been suggested that the amide function is less able to stabilize the adjacent methine anion that is necessary for condensation with the carbonyl

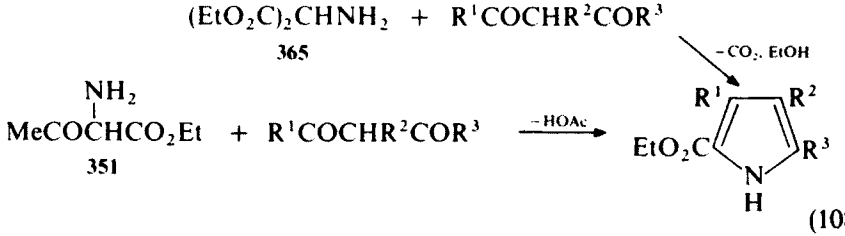


361 **362** **363** **364**

a. Z = OEt
b. Z = NEt_2 (107)

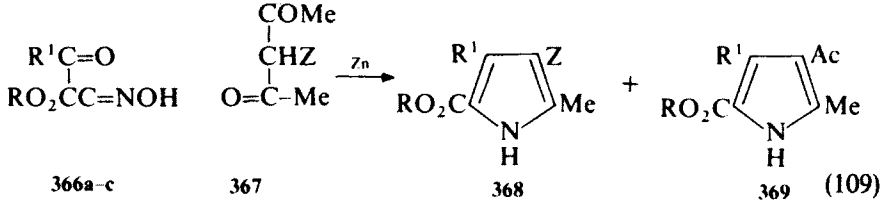
group of the diketone. Instead, the Knorr-type condensation occurs on the carbonyl group from the aminoketone. In this case there must be a loss of the propionyl group in order to give the pyrrole.

Kleinspehn developed the use of the diethyl aminomalonate (**365**), obtained from the reduction of diethyl oximinomalonate, to force the (1 + 3) mode of condensation, and this reaction is often referred to as the *Kleinspehn procedure*[386] while the use of ethyl aminoacetoacetate (**351**), from ethyl oximinoacetoacetate, is referred to as the *Johnson procedure.*[382,387]



(108)

The Kleinspehn procedure has the advantage of precluding the Knorr product, but the loss of the ethoxycarbonyl group is slower than the loss of acetyl group that occurs in the Johnson procedure. Also, since various esters and amides of acetoacetic acid are available, the Johnson procedure provides a greater variety of substituents at position 2. For example (Eq. 109), the reaction of the oximinoacetoacetate **366a,b** with the substituted diketone **367** gives both the Fischer–Fink **368** and Knorr product **369**, but the oximinomalonate **366c** yields only **368**.[388] Interestingly, in this case it is the 2-aminoethyl group, rather than the acetyl group that is lost from the Knorr product.



(109)

Z = $CH_2CH_2NEt_2$

	R^1	R	**368** (%)	**369** (%)
a.	Me	Et	29	9
b.	Me	$PhCH_2$	19	17
c.	EtO	Et	32	0

In an investigation of the Kleinspehn procedure, Paine and Dolphin have found that, with an unsymmetrical meso-substituted diketone, the amino group condenses with the *least* hindered carbonyl group, which is kinetically favored but is less stable thermodynamically.[389] Thus, the resulting pyrrole has the smaller group at the 5 position in preference to the 3 position. When there is no meso-substituent, however, the larger group is located at the 5 position, via the

thermodynamically more stable condensation product. Although with the Kleinspehn procedure the 2-acylcyclohexanones yield the expected tetrahydroindoles, 2-acylcyclopentanones cyclize with the opposite orientation. Paine has suggested that this is the result of the cyclohexanone being primarily in the endocyclic enolic form whereas the more strained cyclopentanone prefers to exist with the exocyclic enol structure. Thus, he has expressed the rule that "the dominant pyrrolic products are those whose enaminone precursors were the aza analogues of the preferred enols."[390]

Lists of pyrroles prepared by the Johnson and by the Kleinspehn procedures are given in Tables 2.34 and 2.35, respectively.

TABLE 2.34. PYRROLES FORMED FROM β-KETOESTERS BY THE JOHNSON PROCEDURE (Eq. 108)

R	R^1	R^2	R^3	Ref.
OCH_2Ph	Me	Et	Me	391
OEt	H	Me	Me	392
OEt	H[a]	H	Me	379, 380
NMe_2	Me	Me	Me	46
Me	Me	Me	Me	393[b]
Me	Me	Et	Me	393, 387[b]
Ph	Me	Et	Me	387[b]

[a] Acetal used.
[b] From $(R^1CO)_2C{=}NOH$.

TABLE 2.35. PYRROLES FORMED FROM DIETHYL AMINOMALONATE BY THE KLEINSPEHN PROCEDURE (Eq. 108)

R^1	R^2	R^3	Ref.
Me	Me	H	387, 394
Me	H	Me	386
Me	$(CH_2)_2CO_2H$	Me	395
Me	$(CH_2)_2NEt_2$	Me	396
$(CH_2)_2CO_2Et$	H	Me	397
$(CH_2)_2CO_2Et$	CH_2CO_2Et	Me	397
H	H	*m*-ClC_6H_4	398

Paine and Dolphin have obtained excellent yields of pyrroles by adding the preformed aminomalonate, obtained by catalytic reduction of the oximino compound, and diketone to boiling acetic acid (Table 2.36).[389] Under these conditions, the kinetically favored enamine is formed by attack at the least hindered carbonyl group and cyclization occurs before equilibration can occur.

Although the Fischer–Fink reaction was developed from the Knorr reaction, and reduction of the nitroso compound is generally carried out in acetic acid, the

TABLE 2.36. PYRROLES PRODUCED FROM DIKETONES ($R^1CO{\cdot}CHR^2{\cdot}COR^3$) AND PREFORMED DIETHYL AMINOMALONATE (Eq. 108)

R^1	R^2	R^3
Me	H	Me
Me	Me	Me
Me	Et	Me
Me	Pr	Me
Me	CH_2CO_2Me	Me
Me	$(CH_2)_2CO_2Me$	Me
Et	Me	Me
Et	Et	Me
Et	H	Et
Et	Me	Et
Et	Et	Et
Pr	Me	Me
Pr	Et	Me
Pr	Pr	Me
$(CH_2)_2CO_2Me$	Me	Me

most accepted mechanism for the Fischer–Fink reaction involves the formation of a carbanion at the α-carbon of the aminoketone. This site is, of course, more acidic since a ketoester or malonate is used. In a series of papers and patents from Umio and his co-workers at Fujisawa Pharmaceutical concerning the preparation of pyrrolnitrin and its analogs, the base-catalyzed reaction of the preformed diethyl aminomalonate with diketones gives the isolatable enamine **369**, which cyclizes to produce the pyrrole **370**, either under acidic (e.g., ethyl polyphosphate) or basic (e.g., alkoxide ion) conditions:

$$(EtO_2C)_2CHNH_2 + R^1COCHR^2COR^3 \longrightarrow \underset{\textbf{370}}{(EtO_2C)_2CHN{=}\overset{\displaystyle R^1}{\overset{|}{C}}CHR^2COR^3}$$

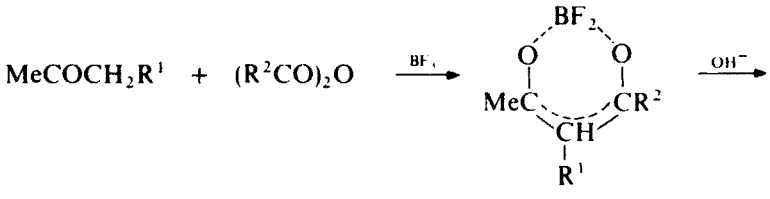
$$\longrightarrow \underset{\textbf{371}}{\text{ethyl 2-}R^1\text{-3-}R^2\text{-4-}R^3\text{-pyrrole-5-carboxylate}} + EtOH \qquad (110)$$

The use of the BF_2 complex **372** in the method developed by Wang and Chang for the preparation of unsymmetrical diketones **373** has made available the pure diketones, which have been utilized in the Fischer–Fink reaction:[408]

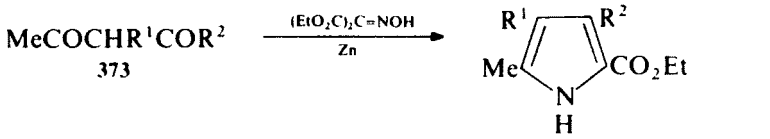
TABLE 2.37. PYRROLES (371) FORMED via ISOLATED IMINES (370)

R^1	R^2	R^3	Conditions	Ref.
Et	H	3-Cl-2-$NO_2C_6H_3$	*a*	399
Me	H	*o*-$NO_2C_6H_4$	*b*	60
Me	H	Ar	*a*, *b*	400–402
o-$NO_2C_6H_4$	H	CO_2Et	*b*	403
p-$MeOC_6H_4$	H	CO_2Et	*b*	404
Me	H	4-Pyridyl	*a*	405
Me	H	2-Furyl	*b*	406
CO_2Et	Ph	HO[c]	*a*	407

[a] Ring closure in acid.
[b] Ring closure in base.
[c] Closure on ester function.



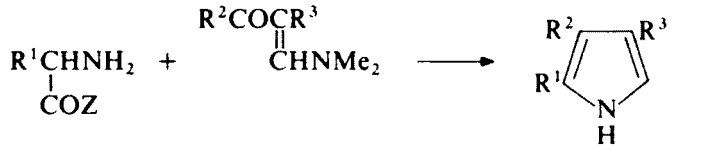
372



(111)

R^1	R^2
Me	Me
Me	Et
Et	Me
Et	Et
n-C_5H_{11}	Me

An interesting variation on the Fischer–Fink reaction makes use of the aminoalkenylketones **374**, obtained by the condensation of the acetal of DMF and a ketone.[409] The best yields of the pyrrole **375** (up to 97%) are obtained when the leaving group (COZ) is either acyl or aminocarbonyl:



(112)

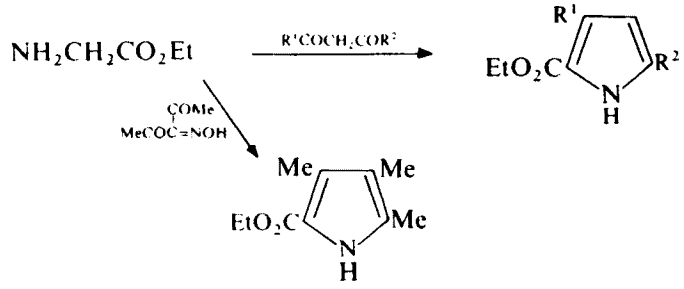
374 375

R^1	R^2	R^3	Z
$CONH_2$	Me	CO_2Et	NH_2
CN	Me	CO_2Et	NH_2
Ac	Me	CO_2Et	Me
CO_2Et	Me	Ac	Me
$CONH_2$	Me	Ac	NH_2
CN	Me	Ac	NH_2
CO_2Et	Me	PhCO	Me
$CONH_2$	Me	PhCO	NH_2
CN	Me	PhCO	NH_2
$CONH_2$	Me	Ph	NH_2
CN	Me	Ph	NH_2
CN	Et	Ph	NH_2
$CONH_2$	*n*-Pr	CO_2Et	NH_2
$CONH_2$	Me	$COCO_2Et$	NH_2
$CONH_2$	Ph	CO_2Et	NH_2

2.6.2. Condensation of α-Amino Acids

2.6.2.1. With β-Dicarbonyl Compounds

A Fischer–Fink-type reaction also occurs when a β-diketone is condensed with ethyl glycinate (Eq. 113).[410] The yields are generally good (74%) when both R^1 and R^2 are aromatic. When the oxime is used, the product is the 3-nitrosopyrrole.[411]

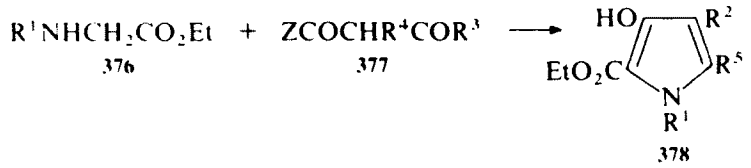


(113)

R^1	R^2
Ph	Ph
Ph	Me[a]
Me	Me

[a] Only a trace of the reverse orientation.

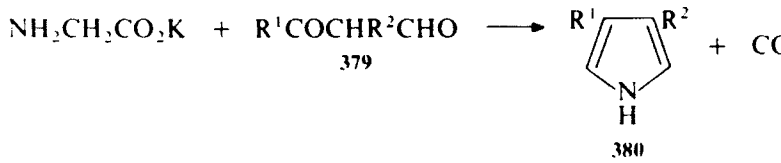
3-Hydroxypyrroles **378** result from the condensation of the amino acid **376** with either a ketoester **377** (Z = OEt) or ketoamide 2 (Z = NH_2 or NHMe):



(114)

R^1	R^2	R^3	Z	Ref.
H	Me	Me	EtO	412
H	*n*-Bu	Me	EtO	413
H	$-(CH_2)_4-$		EtO	413
H	H	Ph	EtO	414
H	H	Ph	NH_2	415
H	H	Ph	NHMe	415
Me	H	Ph	NH_2	415

The reaction of the potassium salt of glycine with the β-ketoaldehyde **379** produces the 3,4-disubstituted pyrrole **380** by ring closure and subsequent decarboxylation:[416,417]

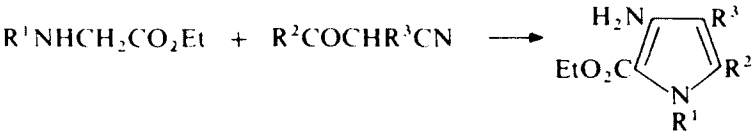


(115)

R^1	R^2
$-(CH_2)_4-$	
$CH_2CH_2CO_2Et$	CH_2CO_2Et

2.6.2.2. *With α-Cyanoketones to Give 3-Aminopyrroles*

The reaction of the ester of an α-amino acid with an α-cyanoaldehyde or ketone yields the 3-aminopyrrole-2-carboxylates:



(116)

R^1	R^2	R^3	Ref.
H	H	Me	418
$PhCH_2$	H	Me	418
$PhCH_2$	H	Ph	418
Me	Me	Me	419

2.6.2.3. *With Di-imines*

The di-imine **383**, produced by the Michael addition of a nitrile **382** to an imine **381**, is equivalent to a β-diketone and will undergo a Fischer–Fink-like

reaction with ethyl glycinate to yield **384**.[420] Although the imine can exist in a tautomeric equilibrium, the reaction is regiospecific, giving only the one product in yields of up to 80%.

$$\underset{\mathbf{381}}{PhN{=}CR^1CH_2R^2} + \underset{\mathbf{382}}{R^3C{\equiv}N} \xrightarrow{AlCl_3} \underset{\mathbf{383}}{PhN{=}CR^1CR^2{=}CR^3NH_2}$$

$$NH_2CH_2CO_2Et + \mathbf{383} \longrightarrow \underset{\mathbf{384}}{\text{ethyl 2,4,5-triarylpyrrole-3-carboxylate}} \qquad (117)$$

R^1	R^2	R^3
Ph	H	Ph
Ph	Me	Ph
Ph	Me	*p*-Tol
Ph	Me	cyclo-C_6H_{11}

2.6.3. Condensation of Aminonitriles with Unsaturated Carbonyl Compounds: The Miller–Ploechl Reaction

In a reaction to which their names have been given, Miller and Ploechl reported that the addition of the anilinophenylacetonitrile **385** ($R^1 = p$-Tol) to cinnamaldehyde yields the triarylpyrroles **386** ($R^1 = p$-Tol; $R^2 = H$).[421] Clark and Lapworth carried out a similar reaction with benzalacetophenone and **385** ($R^1 = Ph$) and obtained **386** ($R^1 = R^2 = Ph$).[422] Treibs and Derra later identified the initial step of the reaction to be the 1,2-addition of the amino group to the carbonyl group, rather than a Michael-type 1,4-addition to the unsaturated system.[423]

$$\underset{\mathbf{385}}{R^1NHCH(Ph)CN} + PhCH{=}CHCOR^2 \xrightarrow{B^-} \underset{\mathbf{386}}{\text{1,2,5-triarylpyrrole}} \qquad (118)$$

Since the initial reports, the reaction has received little attention, although Treibs and Derra[423] demonstrated its wide applicability, as illustrated in Table 2.38. One patent[424] has utilized a reaction to prepare the diarylpyrrole **387**.

$$ArCH{=}CHCOMe + ArCHC{=}NNH_2 \longrightarrow \underset{\mathbf{387}}{\text{2,4-diaryl-5-methylpyrrole}} \qquad (119)$$

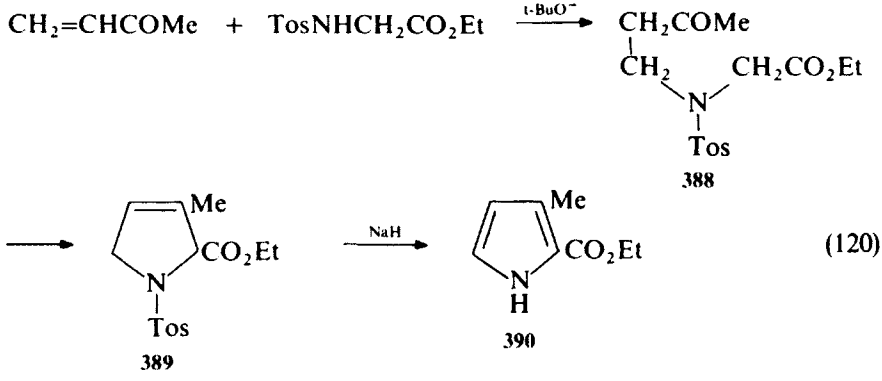
Ar = *p*-$MeOC_6H_4$

TABLE 2.38. PYRROLES FORMED BY THE MILLER–PLOECHL SYNTHESIS

R^1	R^2	R^3	R^4	R^5
H	H	H	H	H
H	H	Me	H	H
H	H	Ph	H	H
H	H	H	H	Me
H	Me	H	H	H
H	Me	Me	H	H
H	Me	Ph	H	H
H	Me	H	H	Me
H	Pr	H	H	H
H	Pr	Me	H	H
H	Pr	Ph	H	H
H	Ph	H	H	H
H	Ph	Me	H	H
H	Ph	Ph	H	H
CO_2Et	Ph	H	H	H
Ph	Me	H	H	Ph
Ph	Ph	H	H	H
Ph	Ph	Me	H	H
Ph	Ph	o-$NO_2C_6H_4$	H	H
Ph	Ph	p-$NO_2C_6H_4$	H	H
Ph	Ph	Ph	Ph	H
Ph	Ph	Ph	$PhCH{=}CH_2$	H
p-Tol	Ph	Me	H	H
1-Naphthyl	Ph	Me	H	H

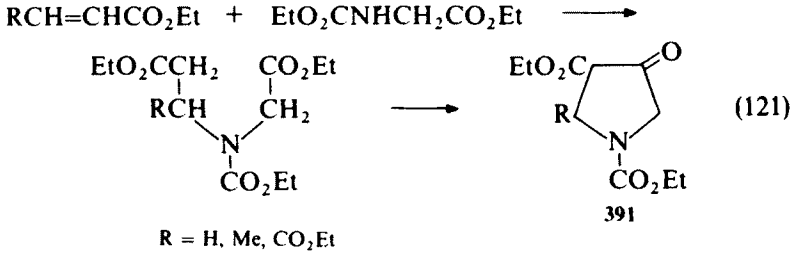
2.6.4. Michael Addition Reactions of α-Amino Acids to Unsaturated Esters or Lactones

The Michael addition of ethyl *N*-tosylglycinate to methyl vinyl ketone gives a product (**388**), which undergoes condensation through the carbanion formed from the glycinate moiety. Subsequent elimination of the tosyl group from **389** yields ethyl 3-methylpyrrole-2-carboxylate **390**:[425,426]



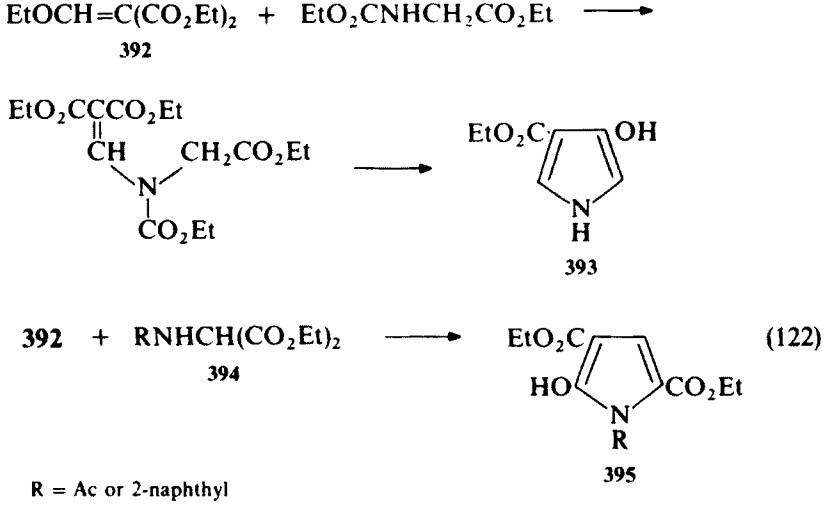
(120)

In the analogous reaction of *N*-carbethoxyglycinate ester with an acrylate ester, the product **391** results from ring closure reaction in which the carbanion is not derived from the glycinate moiety:[427]



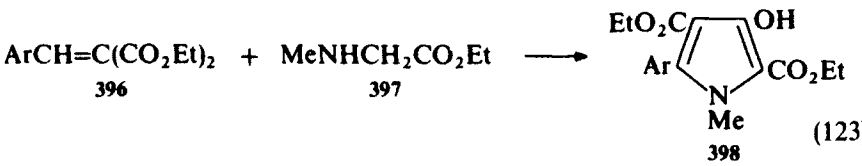
R = H, Me, CO_2Et (121)

The addition of the *N*-carbethoxyglycinate ester to the enol ether **392** leads to **393**, but in the aminomalonate **394** the cyclization appears to take place in the reverse direction (Eq. 122),[428] and it has been suggested that the reaction takes entirely different course.[429]



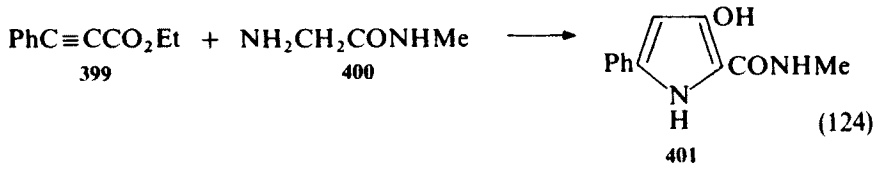
R = Ac or 2-naphthyl (122)

As in an earlier case, the pyrrole **398** is formed from the *N*-methyl glycinate (**397**) and **396** (Eq. 123). However, ethyl glycinate fails to react under these conditions.[429]



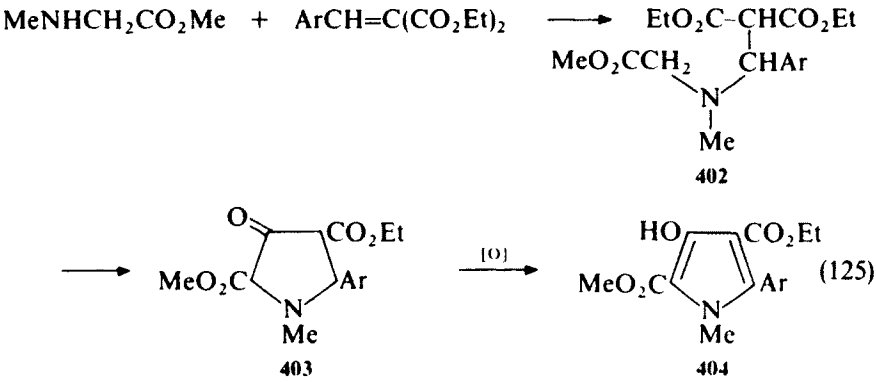
Ar = 2-pyridyl (123)

The addition of the glycylamide **400** to phenyl propiolate **399** gives the expected 3-hydroxypyrrole-2-carboxamide **401**:[415]



(124)

In a similar manner, the condensation product (**402**) of 2-formylpyridine with diethyl malonate reacts with methyl *N*-methylglycinate to produce the 3-pyrrolidone **403**, which under air oxidation is converted into the 3-hydroxypyrrole **404**:[430]



(125)

Ar = 2-pyridyl

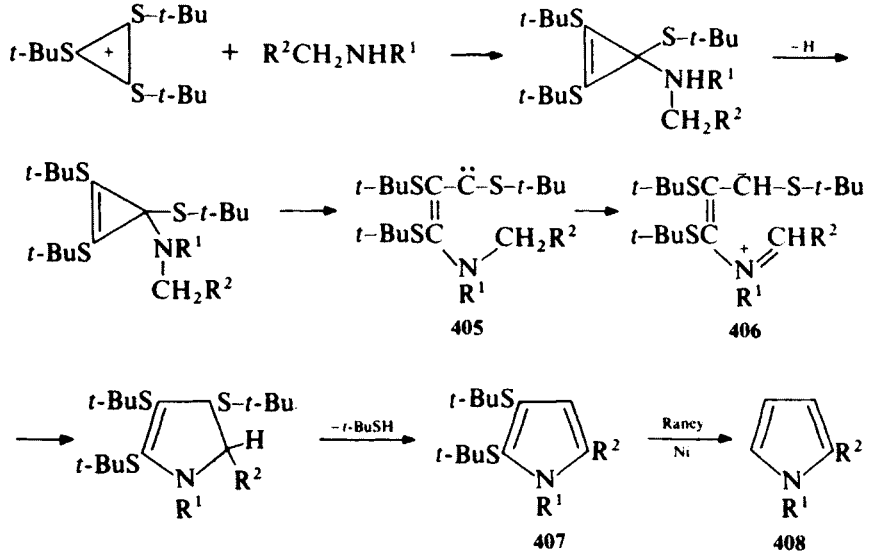
2.6.5. From Cyclopropane Derivatives

2.6.5.1. Cyclopropenium Salts with Amines

Tris(*t*-butylthio)cyclopropenium salts react with secondary amines to give the 2,3-di(*t*-butylthio)-1,5-disubstituted pyrroles **407**. Subsequent treatment with Raney nickel can be used to remove the thio groups to give 1,2-disubstituted pyrroles **408**. The mechanism is believed to involve nucleophilic attack on the cyclopropenium ion by the amine with opening of the ring to give the carbene **405**, which abstracts a hydride ion (or hydrogen atom) from an alkyl group attached to the nitrogen atom. Ring closure of **406** and loss of *t*-butanethiol gives the pyrrole **407** (Scheme 27).[431,432]

2.6.5.2. Schiff's Bases Derived from Cyclopropylamine

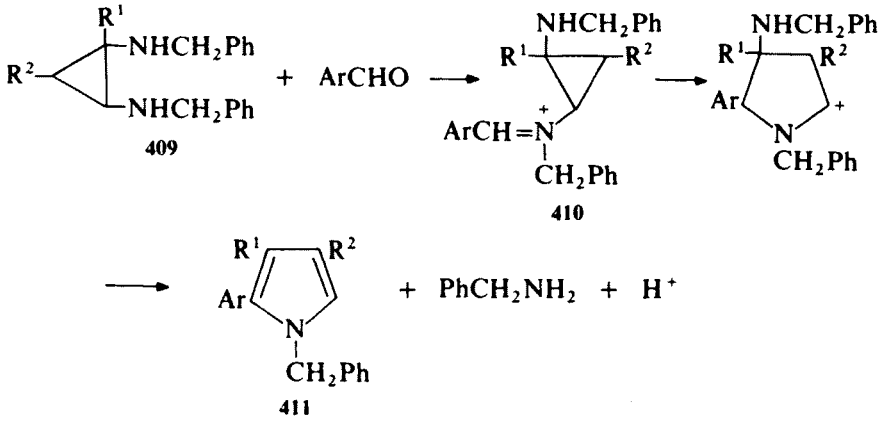
1-Benzyl-2-arylpyrroles **411** are produced from the reaction of 1,2-di(*N*-benzylamino)cyclopropane (**409**) with aromatic aldehydes.[438] The proposed



R^1	R^2	Ref.
H	Ph	432, 433
H	CN	432, 433
H	CO_2Me	432, 433
Me	H	432, 434
Me	H[a]	431, 435
Et	Me	432, 435
n-Bu	H	434
$PhCH_2$	H	434
$-(CH_2)_3-$		432, 436, 437
$-(CH_2)_4-$		432, 436, 437

[a] Hexamethylphosphoramide used as amine.

Scheme 27



Scheme 28

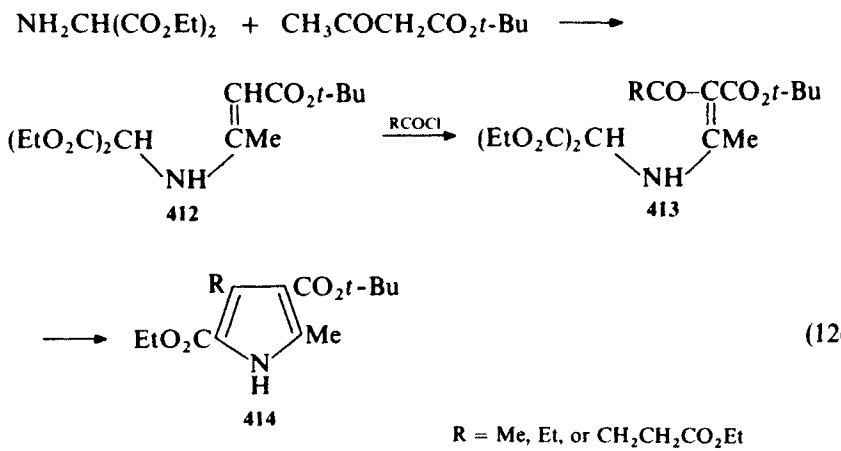
Ar	R^1	R^2
Ph	H	H
p-$NO_2C_6H_4$	H	H
p-MeC_6H_4	H	H
p-$NO_2C_6H_4$	H	Me
p-$NO_2C_6H_4$	Me	H

Scheme 28 (*Contd.*)

mechanism involves the initial formation of the iminium salt **410**, which then undergoes a ring expansion.

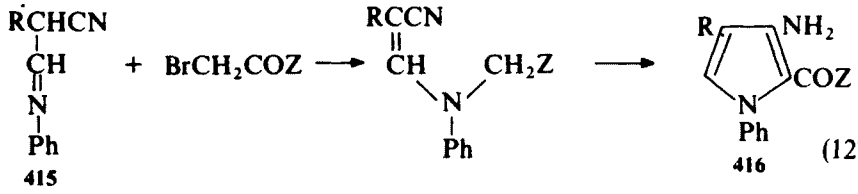
2.6.6. Miscellaneous Reactions

Acylation of the enamine **412**, formed by the reaction of diethyl aminomalonate with a ketoester gives **413**, which is equivalent to the intermediate in the Fischer–Fink synthesis and, consequently yields the pyrrole **414**:[439]



(126)

Alkylation of the imine **415** with ethyl bromoacetate or phenacyl bromide produces the 3-aminopyrrole **416** by the following sequence:[440]

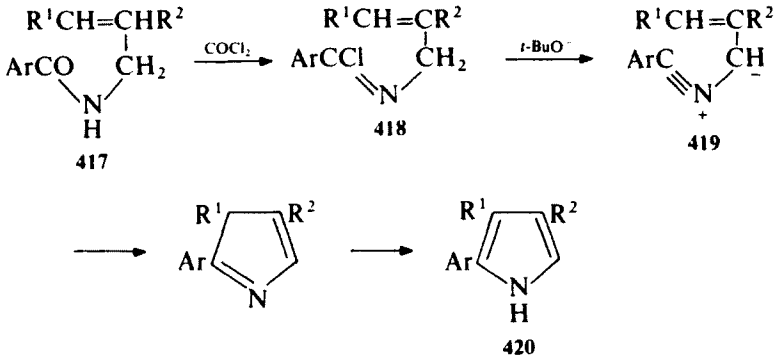


(127)

R = CO_2Et or COPh Z = OEt or Ph

A number of pyrroles **420** have been prepared in excellent yield by the cyclization of the *N*-allylcarboxamide **417**. Treatment of **417** with phosgene

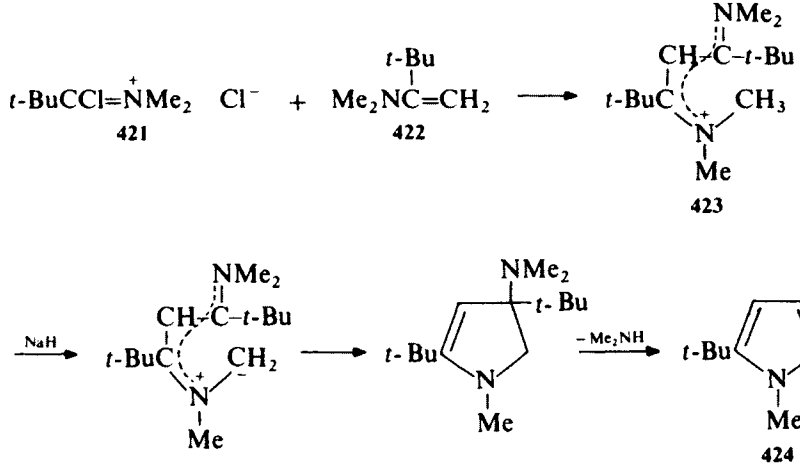
produces the nitrile ylide **419** via the imidoyl chloride **418**. An intramolecular 1,3-dipolar cycloaddition leads to **420**:[441]



(128)

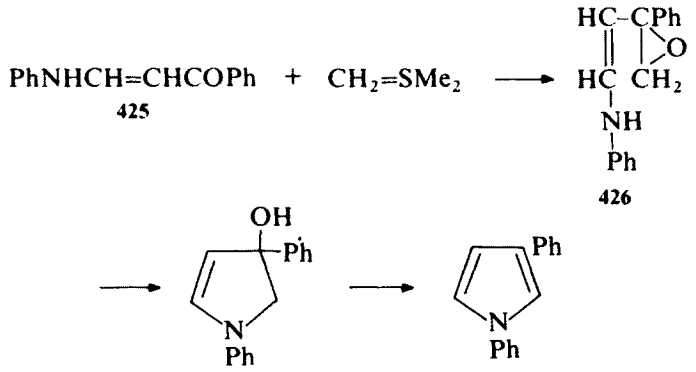
Ar	R^1	R^2
Ph	H	H
2-Furyl	H	H
2-Thienyl	H	H
t-Bu	H	H
Ph	Me	H
Ph	H	Me

The addition of the chloroiminium salt **421** to the enamine **422** gives the delocalized allylammonium ion **423**, which yields **424** (40%) when treated with a strong base:[442]



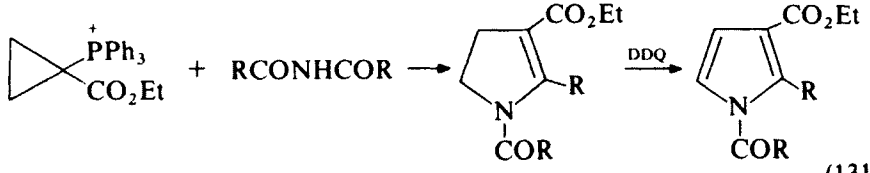
(129)

Insertion of a methylene group into the carbonyl group of the keto enamine **425** produces an epoxide **426**, which undergoes ring closure to 1,3-diphenylpyrrole:[443]



(130)

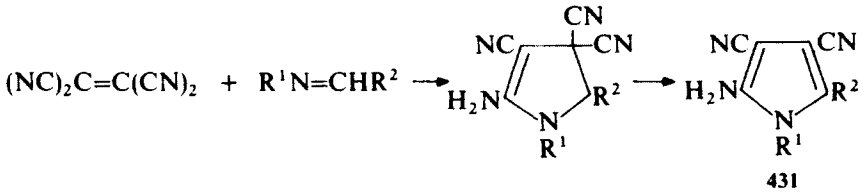
Addition of the cyclopropyl phosphonium salt **427** to the imide **428** yields the pyrroline **429**, which can be aromatized by DDQ to give the 2-substituted pyrrole-3-carboxylate **430**:[444]



427 428 429 430 (131)

R = H, Me, Ph

Several papers and a patent describe the reaction of tetracyanoethene with imines to give the 2-amino-3,4-dicyanopyrroles **431**:[445–447]

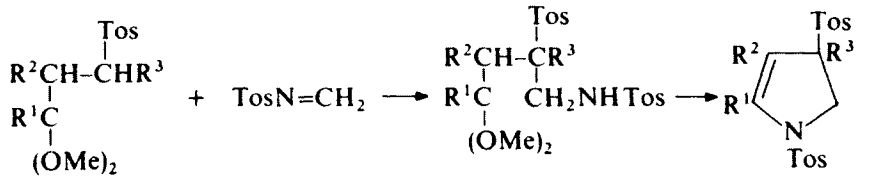


431

(132)

R^1	R^2
$PhCH_2$	*i*-Bu
Ph	Ph
Ph	2-Furyl
t-Bu	*i*-Pr
C_5H_{11}	Et
C_5H_{11}	*i*-Pr
C_5H_{11}	*i*-Bu

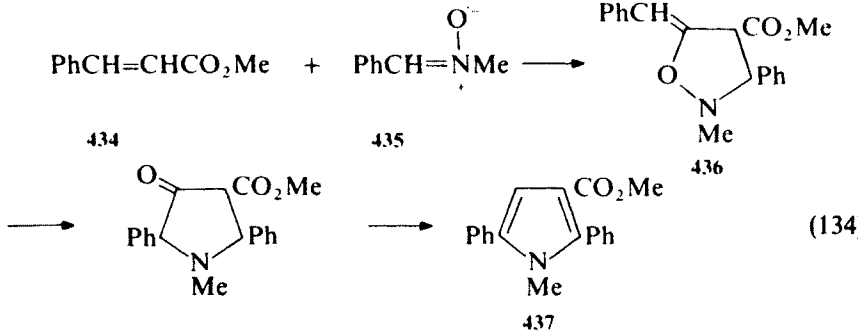
Excellent yields of the 2,4- and 2,3,4-substituted pyrroles **433** result from the addition of the acetal **433** to *N*-tosyl methyleneimine:[448]



R^1	R^2	R^3
H	H	$PhCH_2$
H	H	$PhCH_2CH_2$
Me	H	Et
Me	H	$PhCH_2$
Me	Me	Et

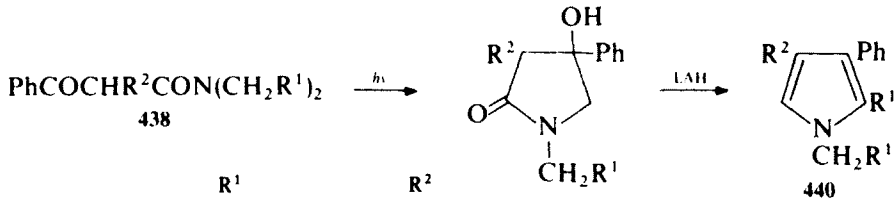
(133)

The allene **434** and imine *N*-oxide **435** react together to give the isoxazoline **436**, which is transformed into ethyl 2,5-diphenylpyrrole-3-carboxylate **437** (67%).[449]



(134)

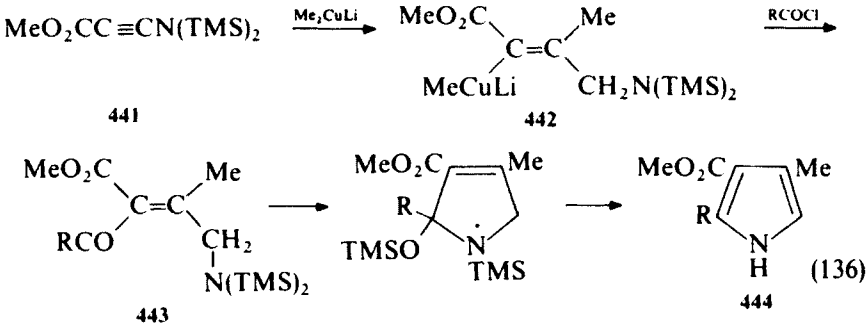
Photolysis of the β-ketoamide **438** leads to ring closure to yield the pyrrolidone **439**, which can be reduced to the pyrrole **440** (Eq. 135) in overall yields of 37–55%.[450]



R^1	R^2
H	H
Ph	H
Ph	Me
Me	H

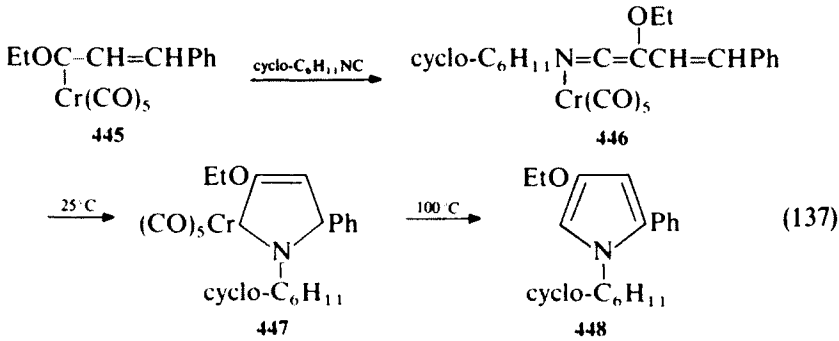
(135)

Dimethylcopper lithium adds stereospecifically to the bis(trimethylsilyl)aminoethyne **441** to give the *Z*-alkene **442**, acylation of which gives the intermediate **443**. Ring closure leads to the pyrrole **444** in yields of 44–66%:[451]



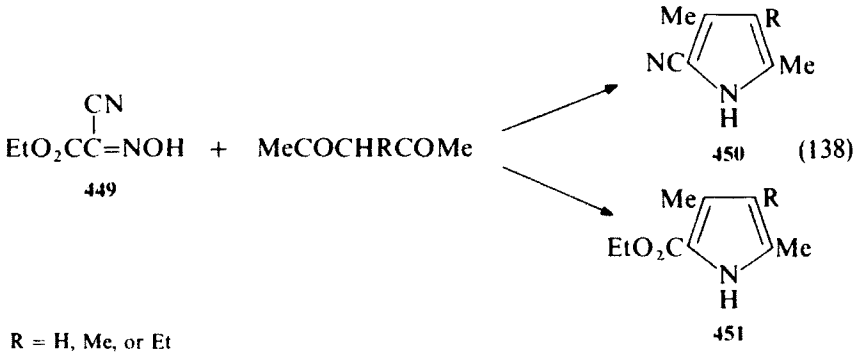
(136)

In a very different use of organometallic chemistry, the alkenylcarbene complex with chromium carbonyl **445** is allowed to react at 0°C, with cyclohexylisonitrile to form the ketenimine complex **446**. As the temperature is increased, **446** rearranges initially to the pyrroline **447** and then ultimately to give the pyrrole **448** in 56% yield:[452]



(137)

The Fischer–Fink-type reaction of the nitroso derivative of ethyl cyanoacetate (**449**) with a meso-substituted pentanedione produces an 8 : 1 mixture of the two possible products **450** and **451** irrespective of the nature of R.[453]



(138)

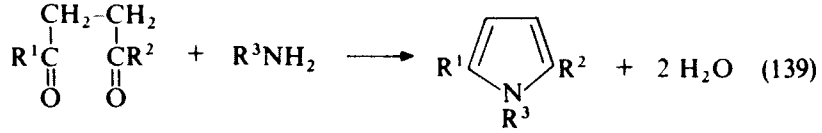
R = H, Me, or Et

2.7. FORMATION OF PYRROLES FROM 4-CARBON UNITS

2.7.1. From 4-Carbon Units and Amino Compounds

2.7.1.1. From γ-Dicarbonyl Compounds: The Paal–Knorr Synthesis

Because of its simplicity and the ready availability of γ-diketones, the use of the Paal–Knorr synthesis for the preparation of pyrroles has been reported in the greatest number of papers. Generally carried out under acid-catalyzed conditions, the condensation of the diketone with a primary amine eliminates two molecules of water to form the 1,2,5-trisubstituted pyrrole:



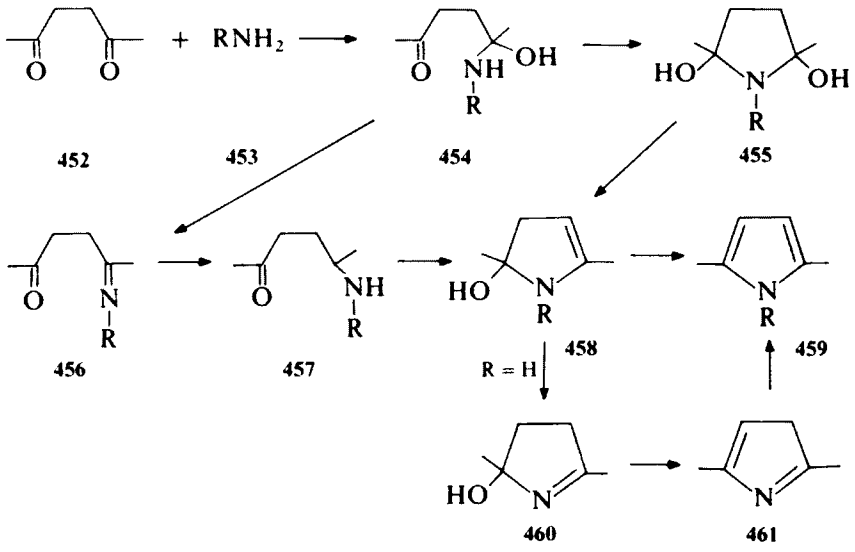
(139)

Acetic acid has been used as the catalyst for most of the reactions, but titanium(IV) chloride[454] has been found to be efficacious for sterically crowded amines, although 5 mol of the amine are then required. In some cases, no acid catalyst has been used; simply mixing the diketone with liquid ammonia has been sufficient.

The mechanism of the reaction has been studied more than any other pyrrole synthesis. Zeng has reported that, under acidic conditions, the variation in the rate of pyrrole formation versus pH takes the form of a bell shaped curve, which is typical for the formation of a carbinolamine.[455] Likewise, the reaction involves general acid catalysis with a Brønsted α of 0.25 and, as expected for the closure of a 5-membered ring, there is a large negative entropy of activation. From the reaction with a variety of substituted anilines, the reaction rate correlated well with σ^+ substituent constants, and the Hammett ρ value was found to be -0.88.[455,456] This again suggests carbinolamine formation.

As outlined in Scheme 29, there are three possible mechanisms for the Paal–Knorr synthesis. In the main, they differ in the intermediate formation of either the diol **455**, enamine **456**, or imine **460**.

Observations favoring the intermediate existence of **455** have been reported by workers in China, but the experimental details are lacking in the available literature.[457] Using ^{13}C NMR spectrometry, Katritzky and co-workers have obtained evidence for the formation and decay of **456** from the reaction of 2,5-hexanedione and a variety of primary amines in the absence of catalyst.[458] With the more sterically hindered amines, the rate of formation of **456** and its disappearance was slowed. Thus, they concluded that the pathway **454**→**456**→**457**→**458**→**459** was most reasonable, with step **452**+**453**→**454** and **457**→**458** as being rate-determining. Under acidic conditions, the formation of **454** is believed to be rate-determining. Typically, the formation of a car-

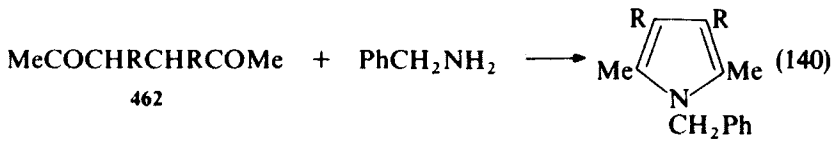


Scheme 29

binolamine such as **454** should be slow, since the dehydration to an imine **456** is generally quite rapid. The enamine **457** was not detected, since the equilibrium should favor the imine form **456**. The formation of the aromatic ring system of **459** significantly accelerates the conversion of **458** into **459**.

More recently, Sammes has reported the isolation of the hydroxypyroline **460** from the reaction of the diketones with liquid ammonia, and this observation, at least in this case, infers the alternate pathway **458**→**460**→**461**→**459**, since there is no 1-substituent.[459,460]

When there are substituents at the 3 and 4 positions, **454**, **456**, and **460** may be diastereomeric. In the reaction of benzylamine with the *dl* and meso forms of the diketones **462**, the *dl* pair was found to react more rapidly.[461] In approaching the ring-closure step there would be less eclipsing of the bulky groups in the *dl* isomers. Since this factor does influence the rate, there is still some question as to which step is rate-determining.

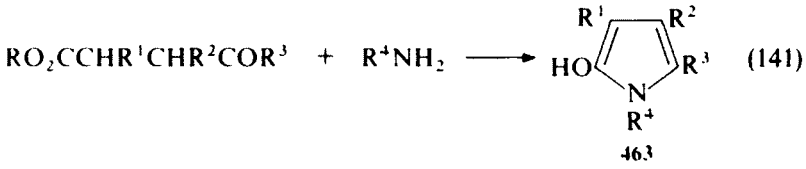


(140)

2,5-Hexanedione has been used most frequently in the Paal–Knorr synthesis, and its reaction with amines has led to the preparation of a large number of 1-alkyl or 1-aryl-2,5-dimethylpyrroles (Tables 2.39–2.41). Other 2,5-disubstituted pyrroles prepared by this method are given in Tables 2.42–2.47.

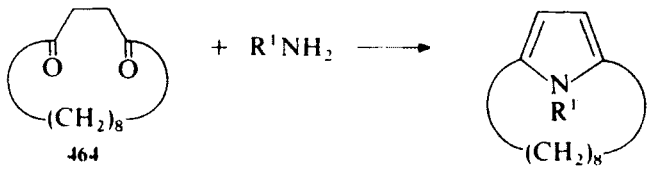
The Paal Knorr synthesis has been extended to the use of hydrazines, hydroxylamines, amides, and sulfonamides to give 1-amino, 1-hydroxyl, and 1-sulfonylpyrroles, as shown in Tables 2.48–2.50. In some cases, the 6-membered system, such as pyridazines or dihydrazones, may also be formed.

γ-Ketoesters undergo the Paal–Knorr synthesis to yield 2-hydroxypyrroles **463**.

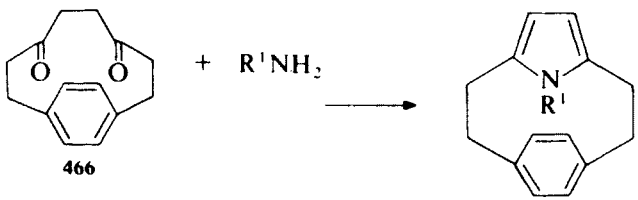


463 (141)

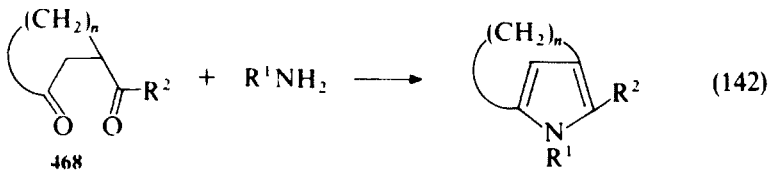
Pyrrolophanes **465** and **469** can be prepared with appropriate cyclic diketones **464** or cyclic acylketones **468**. The benzopyrrolophanes, for example, **467** can be prepared in the same manner from **466**:[464]



464 **465**

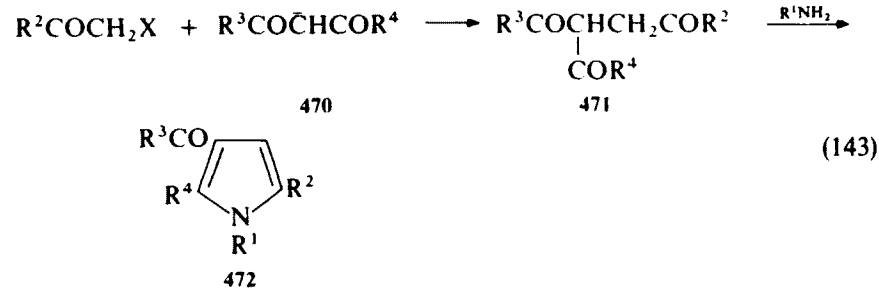


466 **467**



468 **469** (142)

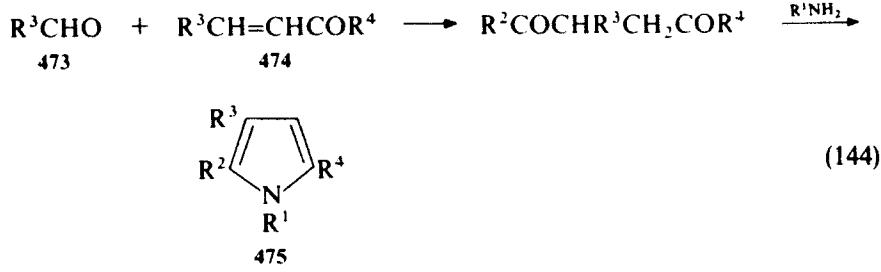
The utility of the Paal–Knorr synthesis has been greatly expanded by the development of methods to prepare 1,4-dicarbonyl compounds. For example, the reaction of α-haloketones with the anion of a β-dicarbonyl compound **470** furnishes the triketo compound **471**, which can be converted into the pyrrole **472**:[470–473]



(143)

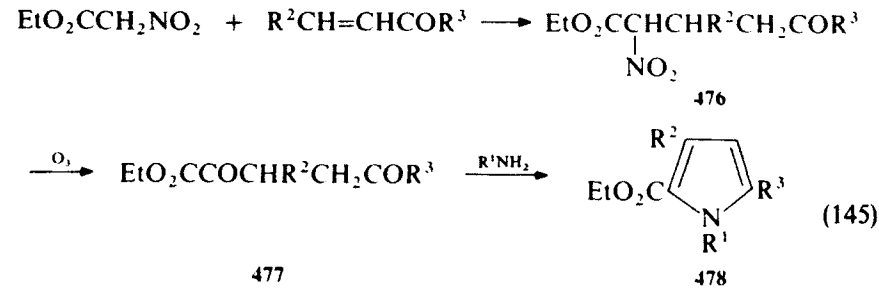
When **470** is derived from a ketoester, a pyrrole-3-carboxylate is formed from **471**.[473,474] If R^2 and R^3 are alkyl or aryl groups, however, it is important that they should be identical in order to prevent a possible mixture of pyrroles.[471]

The cyanide- or thiazolium-ion-catalyzed Michael addition of an alkyl-, aryl-, or heteroarylaldehyde **473** to a vinyl ketone **474** has been exploited for preparation of a wide variety of pyrroles **475** in excellent yields: [475-477]

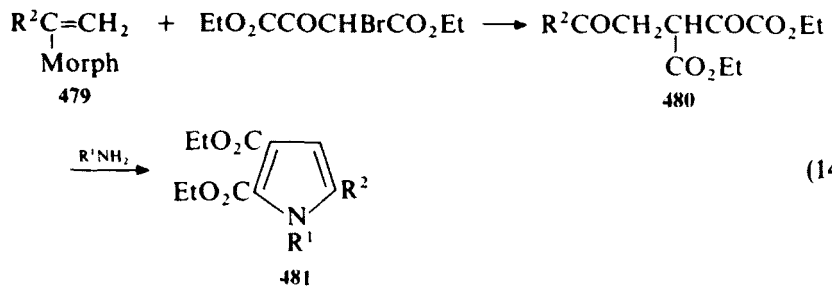


(144)

Likewise, the Michael addition of ethyl nitroacetate gives a 2-nitro-5-oxoester **476**, which on ozonolysis is converted into the 2,5-dioxoester **477**; a useful intermediate for the preparation of pyrrole-2-carboxylates **478**:[478]

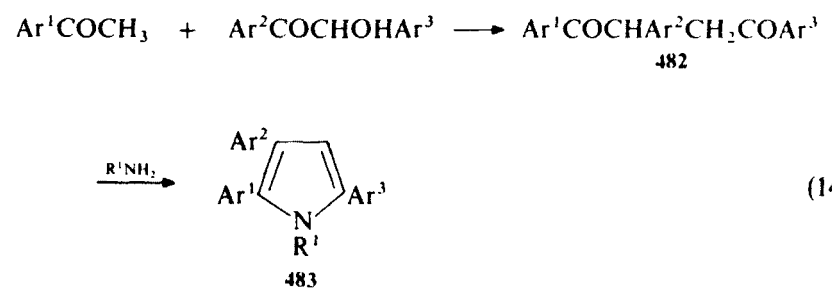


(145)



(146)

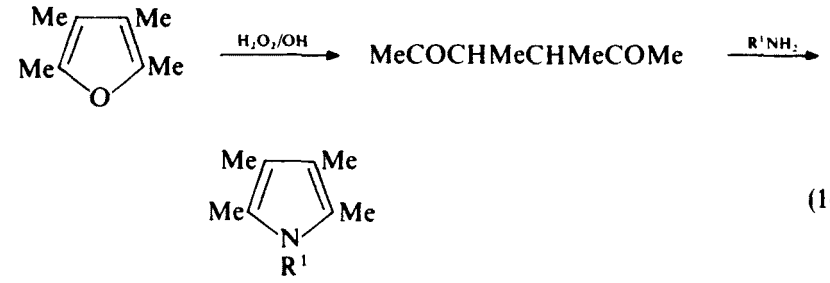
The cyanide-catalyzed condensation of methyl arylketones with benzoins gives the 1,4-dicarbonyl compound **482**, which can be converted into the triarylpyrrole **483**. It is not known whether aliphatic acyloins could be used[480,481]



(147)

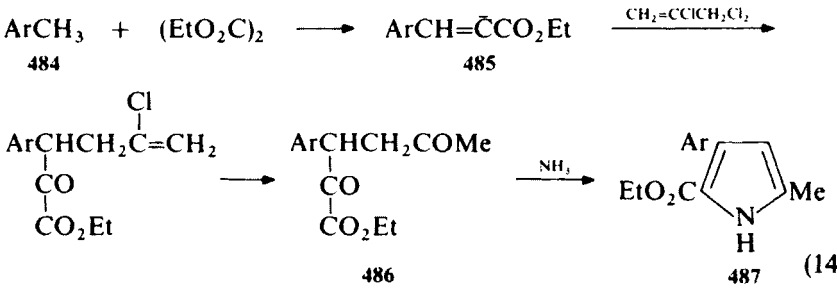
Symmetrical 1,4-dicarbonyl compounds, which can be used in the Paal–Knorr reaction, can be prepared by the oxidative dimerization of ketones by lead(IV) oxide.[461]

The oxidation of tetramethylfuran leads to the diketone **484** and thence through reaction with primary amines to 1-substituted tetramethylpyrrole,[482] but, as discussed in Section 2.7.1.2, the conversion of furans into the dialkoxytetrahydrofurans is a more useful and general route to pyrroles.



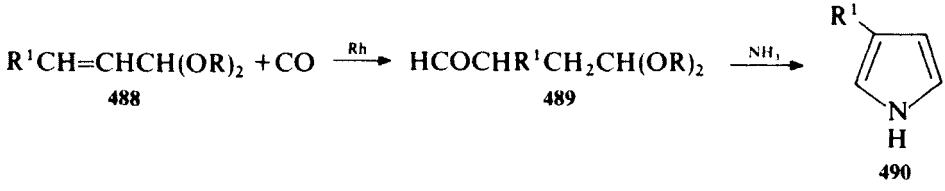
(148)

Alkylation by 2,3-dichloropropene of the anion **485**, produced by the condensation of an activated toluene **484** with diethyl oxalate, leads to the diketone **486**, which can be used in the preparation of the pyrrolonitrin analog **487**:[483]



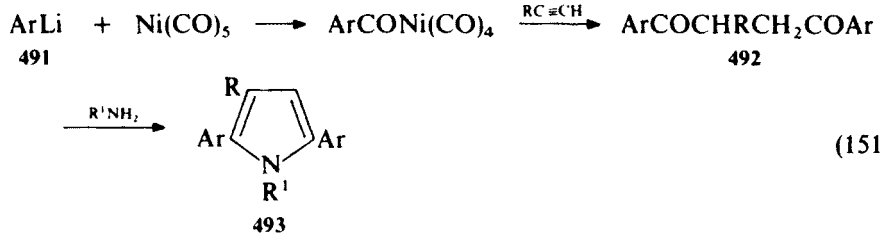
(149)

The rhodium-catalyzed carbonylation of the unsaturated acetal **488** yields a substituted succinaldehyde derivative **489**, which can be converted into pyrroles **490** having no substituents at the α positions:[484]



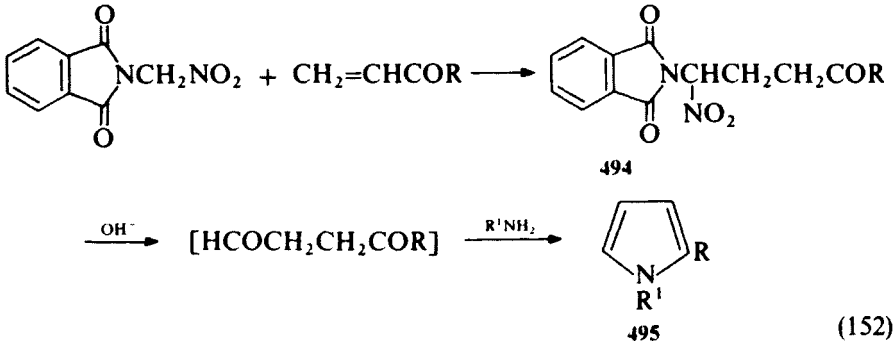
(150)

Carbonylation of an aryllithium **491**, followed by reaction with a terminal alkyne, yields a diketone **492**, which is suitable for the preparation of the 3-substituted 2,5-diarylpyrroles **493**:[485]



(151)

The Michael adduct **494** derived from the addition of *N*-nitromethylphthalimide to a vinyl ketone is effectively a formyl anion equivalent and, as such, can



(152)

TABLE 2.39. 2,5-DIMETHYLPYRROLE AND 1-ALKYL-2,5-DIMETHYLPYRROLES

1-Alkyl Group	Ref.
H	487
Me	488
Et	488
n-Pr	454, 489[a]
n-Bu	490
s-Bu	454
i-Bu	454
t-Bu	454
n-C_5H_{11}	489[a], 490
neo-C_5H_{11}	454
n-C_6H_{13}	491
n-C_8H_{17}	491
n-$C_{12}H_{25}$	491
cyclo-C_5H_9	492
cyclo-C_6H_{11}	490, 487
Allyl	490, 491
$PhCH_2$	489[a], 493, 494
$PhCH_2CH_2$	490
$Ph(CH_2)_3$	490
$-(CH_2)_2-$	490
$-(CH_2)_3-$	492
$-(CH_2)_4-$	454
$-(CH_2)_5-$	454
$-(CH_2)_6-$	490, 491
$-(CH_2)_7-$	454
$-(CH_2)_8-$	454
$-CH_2CMe_2CH_2-$	454
$-CH_2CH{=}CHCH_2-$	490
$HO-(CH_2)_2-$	487, 490, 495
$HO-(CH_2)_3-$	495
$HO-(CH_2)_4-$	495
$HO-CH_2CMe_2-$	495
$HO_2C-(CH_2)_5-$	494
$H_2N-(CH_2)_2-$	487
$H_2N-(CH_2)_4-$	495
$Et_2N-(CH_2)_3-$	490, 492, 498
$Et_2N-(CH_2)_4-$	492
$(i\text{-Pr})_2NCH_2CH_2CH(CONH_2)$	497
H_2NCOCH_2	498
$H_2NCO(CH_2)_2$	498
$NC(CH_2)_2$	498
$NCCMe_2$	487
$PhCOCH_2$	499
p-$TolCOCH_2$	499
p-$AcC_6H_4COCH_2$	499
p-$NO_2C_6H_4COCH_2$	499
o-$NO_2C_6H_4COCH_2$	499
MeCO	500
PhCO	500
$PhCH_2OCO$	501

[a] Via reductive hydrogenation of nitrile.

TABLE 2.40. 1-PHENYL- AND SUBSTITUTED 1-PHENYL-2,5-DIMETHYLPYRROLES

Substituent on a 1-Phenyl Group	Ref.
H	487, 488, 493
o-Me	488, 490, 493
m-Me	488, 493
p-Me	488, 493, 502
2,4-diMe	488
2,6-diMe	488, 493
m-Et	503
p-Et	490
p-*i*-Pr	490
o-*t*-Bu	504
p-*t*-Bu	505
o-CF_3	504
m-CF_3	498, 506
p-CF_3	504
o-HO	488, 493, 507
m-HO	488, 492
p-HO	488
o-MeO	493
m-MeO	493
p-MeO	493, 498, 506
o-EtO	488
p-EtO	488, 508
m-Ac	491
p-Ac	490
o-CO_2H	488, 493
m-CO_2H	488, 493
p-CO_2H	490
o-CO_2Et	507
p-CO_2Et	507
o-HS	495
p-MeS	505
o-H_2N	490, 509
p-H_2N	490
m-Me_2N	505
p-Me_2N	491
p-AcNH	506
o-NO_2	506, 509
m-NO_2	488, 493
p-NO_2	488, 493
o-Cl	488, 493, 508
m-Cl	488, 493
p-Cl	488, 491, 493
2-Cl-4-EtO	508
m-Br	488
p-Br	488, 502, 510

TABLE 2.41. 1-ARYL-2,5-DIMETHYLPYRROLES

1-Aryl Group	Ref.
2-MeO-1-naphthyl	511
12-Hexyl-6-chrysyl	512
2-Pyridyl	505, 507
3-Me-2-pyridyl	491
4-Me-2-pyridyl	491
6-Me-2-pyridyl	502
2-NH_2-6-pyridyl	513
6-MeO-3-pyridyl	513
2-Triazolyl	514
5-Pyrazolyl	515
1-Me-5-pyrazolyl	515
2-Me-5-pyrazolyl	515
1,3,4-Triazolyl	516
1-(2-Pyrrolidonyl)	517

TABLE 2.42. 1-ALKYL-2,5-DISUBSTITUTED- AND 2,5-DISUBSTITUTED PYRROLES

1-Alkyl Group	2-Substituent	5-Substituent	Ref.
H	Me	*t*-Bu	518
H	*t*-Bu	*t*-Bu	519, 520
H	C_6F_5	C_6F_5	470
H	*p*-Tol	*p*-Tol	485
H	*p*-ClC_6H_4	*p*-ClC_6H_4	480
H	*s*-Bu	H	484
Me	*i*-Pr	*i*-Pr	454
Me	*t*-Bu	*t*-Bu	454
Me	*p*-TolCO	CH_2CO_2Me	521
Me	Me	CH_2CO_2Et	473
Et	*i*-Pr	*i*-Pr	454
Et	*t*-Bu	*t*-Bu	454
i-Pr	Et	Et	454
i-Pr	*i*-Pr	*i*-Pr	454
t-Bu	Et	Et	454
$PhCH_2$	*i*-Pr	*i*-Pr	454
$PhCH_2$	*t*-Bu	*t*-Bu	454
$PhCH_2$	Me	CO_2Me	478
$HO-(CH_2)_2-$	Ph	Ph	522
$HO-(CH_2)_2-$	Me	C_9H_{19}	495
$HO-(CH_2)_3-$	Ph	Ph	522
$HO-(CH_2)_3-$	Me	C_9H_{19}	495
$HO-(CH_2)_3-$	Me	CO_2Me	478
$HO-(CH_2)_3-$	*n*-Bu	CO_2Me	478
$HO-CH_2CHOHCH_2-$	Ph	Ph	522
$H_2N-(CH_2)_2-$	Ph	Ph	522
$H_2N-(CH_2)_3-$	Ph	Ph	522
$H_2N-(CH_2)_4-$	Ph	Ph	522
$Me_2N-(CH_2)_2-$	Ph	Ph	522
$Me_2N-(CH_2)_3-$	Ph	Ph	522
$Et_2NCH_2CHOHCH_2-$	Ph	Ph	522
4-Morph-$(CH_2)_2-$[a]	Ph	Ph	522

[a] Morph = morpholino.

TABLE 2.43. 1-ARYL-2,5-DISUBSTITUTED PYRROLES

Substituent on 1-Aryl group	2-Substituent	5-Substituent	Ref.
o-HO	Me	Ph	507, 523
o-HO	Ph	Ph	507, 523
o-HO	Me	*p*-Tol	511
o-MeO	Me	*p*-Tol	511
2,5-diHO	Me	Ph	511
2,5-diMeO	Me	Ph	511
o-Tol	*p*-$MeOC_6H_4$	$CH_2CH_2CO_2Et$	524–527
p-NH_2	Ph	Ph	528
m-HO_2C	Me	Ph	529
o-NH_2	Ph	Ph	530, 531
2,6-diMe	*p*-$MeOC_6H_4$	CH_2CH_2COOH	524, 525, 527
o-MeO	*p*-$MeOC_6H_4$	CH_2CH_2COOH	524
p-F	*p*-$MeOC_6H_4$	CH_2CH_2COOH	524, 527
o-F	*p*-$MeOC_6H_4$	CH_2CH_2COOH	525, 527
o-Me	*p*-$MeOC_6H_4$	CH_2CH_2COOH	524, 527
o-Cl	*p*-HOC_6H_4	CH_2CH_2COOH	525, 526
p-Cl	*p*-HOC_6H_4	CH_2CH_2COOH	525, 526
o-MeO	*p*-HOC_6H_4	CH_2CH_2COOH	525–527
o-Me	*p*-HOC_6H_4	CH_2CH_2COOH	526
p-F	*p*-HOC_6H_4	CH_2CH_2COOH	526
o-F	*p*-HOC_6H_4	CH_2CH_2COOH	526

TABLE 2.44. 1-METHYL-2,3,5-TRISUBSTITUTED- AND 2,3,5-TRISUBSTITUTED PYRROLES

1-Substituent	2-Substituent	3-Substituent	5-Sbstituent	Ref.
H	Me	PhCO	Ph	216, 471
H	Me	Ac	Ph	216, 471
H	Me	2-NO_2-3-ClC_6H_3	Me	532
H	Me	CO_2Et	Ph	474
H	CO_2Et	2-NO_2-3-ClC_6H_3	Me	483
H	CO_2Et	CO_2Et	Me	533, 472
H	CO_2Et	CH_2CO_2Et	Ph	479
H	Ph	PhCO	Ph	216, 471
H	Ph	Ph	Ph	29
H	Ph	CH_2CO_2H	Ph	534
H	Ph	Ph	2-Naphthyl	481
H	Ph	Ph	*p*-$MeOC_6H_4$	481
H	*p*-ClC_6H_4	*p*-ClC_6H_4	Ph	481
H	Ph	Ph	2-Naphthyl	481
H	*p*-Tol	Ph	2-Naphthyl	481
H	*p*-Tol	Me	*p*-Tol	485
H	*p*-Tol	Ph	*p*-Tol	485
H	Ph	*p*-$Me_2NC_6H_4$	2-Naphthyl	481
H	Ph	*p*-$Et_2NC_6H_4$	2-Naphphyl	481
H	Ph	Ph	1-Naphthyl	480
H	Ph	Ph	*p*-ClC_6H_4	480
H	Ph	Ph	*p*-$MeSOC_6H_4$	480

TABLE 2.44. (*Contd.*)

1-Substituent	2-Substituent	3-Substituent	5-Sbstituent	Ref.
H	Ph	Ph	*p*-$AcNHC_6H_4$	480
H	Ph	Ph	*p*-$CH_2{=}CHC_6H_4$	480
H	Ph	Ph	*p*-$PhSOC_6H_4$	480
H	$-(CH_2)_3-$		Me	535
Me	Me	CO_2Et	Ph	474
Me	Me	Ac	*o*-$NO_2C_6H_4$	536
Me	Et	2-Pyridyl	Ph	475
Me	Me	3-Pyridyl	Ph	475
Me	Et	3-Pyridyl	Ph	475
Me	*n*-Pr	3-Pyridyl	Ph	475
Me	*n*-Pr	2-Furyl	Ph	475
Me	*n*-Pr	Ph	2-Furyl	475
Me	*n*-Pr	Ph	3-Pyridyl	475
Me	*i*-Pr	CO_2Et	Me	476
Me	*n*-Bu	CO_2Et	Me	476
Me	Ph	2-Furyl	Ph	475
Me	Ph	2-Furyl	3-Pyridyl	475
Me	Ph	3-Pyridyl	Ph	475
Me	Ph	Ph	3-Pyridyl	475
Me	Ph	22-Chinolyl	Ph	475
Me	3-Pyridyl	2-Furyl	Ph	475
Me	3-Pyridyl	2-Furyl	2-Furyl	475
Me	3-Pyridyl	2-Furyl	3-Pyridyl	475
Me	3-Pyridyl	3-Pyridyl	3-Pyridyl	475
Me	2-Pyridyl	H	Me	475
Me	2-Pyridyl	H	Ph	475
Me	Me	CO_2Et	Me	473
$PhCH_2$	Me	Ac	2-$NO_2C_6H_4$	536
$(CH_2)_2OH$	Me	CO_2Et	Ph	474
CH_2CO_2Me	Me	CO_2Et	Ph	474
CH_2CO_2Et	Me	CO_2Et	2-Naphthyl	457

be used to prepare pyrroles having a vacant 5 position **495** (Eq. 151).[486]

2.7.1.2. From Derivatives of Succinaldehyde

2.7.1.2.1. Open-Chain Acetals

Succinaldehyde should react with primary amines to furnish pyrroles substituted only at position 1. However, as succinaldehyde is unstable, the diacetal or dichloro derivatives are utilized as protected derivatives. Thus, the diacetal **497**,

TABLE 2.45. 1-PHENYL- AND SUBSTITUTED 1-PHENYL-2,3,5-TRISUBSTITUTED PYRROLES

Substituent on 1-Phenyl Group	2-Substituent	3-Substituent	5-Substituent	Ref.
H	Ph	Ph	Ph	537
H	Me	Ac	*m*-$NO_2C_6H_4$	538
H	Me	PhCO	Ph	539
H	Me	Ac	2-Naphthyl	536
H	*p*-ClC_6H_4	CO_2H	*p*-ClC_6H_4	534
H	H	*s*-Bu	H	484
p-NO_2	H	CO_2Et	H	540
p-HO	H	CO_2Et	H	540
p-CO_2H	H	CO_2Et	H	540
p-NO_2	CO_2Et	CO_2Et	H	540
p-MeO	CO_2Et	CO_2Et	H	540
p-CO_2Et	CO_2Et	CO_2Et	H	540
o-Me	Me	Ac	*m*-$NO_2C_6H_4$	538
m-Me	Me	Ac	*m*-$NO_2C_6H_4$	538
p-Me	Me	Ac	*m*-$NO_2C_6H_4$	538
p-Ac	Me	Ac	*m*-$NO_2C_6H_4$	538
p-CO_2Et	Me	Ac	*m*-$NO_2C_6H_4$	538
m-NO_2	Me	Ac	*m*-$NO_2C_6H_4$	538
p-Me	Me	CO_2Et	*p*-$MeOC_6H_4$	456
p-MeO	Me	CO_2Et	*p*-$MeOC_6H_4$	456
p-NO_2	Me	CO_2Et	*p*-$MeOC_6H_4$	456
p-Cl	Me	CO_2Et	*p*-$MeOC_6H_4$	456

TABLE 2.46. 2,3,4,5-TETRASUBSTITUTED- AND 1-ALKYL-2,3,4,5-TETRASUBSTITUTED PYRROLES

1-Substituent	2-Substituent	3-Substituent	4-Substituent	5-Substituent	Ref.
H	*t*-Bu	CO_2Et	CO_2Et	*t*-Bu	541
H	Ph	Me	Ph	*p*-HOC_6H_4	472
Me	Me	CO_2Me	Me	Et	476
i-Pr	Me	CO_2Et	CO_2Et	Me	454
i-Pr	Me	CH_2OH	CH_2OH	Me	454
$PhCH_2$	Me	Me	Me	Me	542, 461
$PhCH_2$	Me	Et	Et	Me	461
$PhCH_2$	Me	*i*-Pr	*i*-Pr	Me	461
$PhCH_2$	Me	Ph	Ph	Me	461
$PhCH_2$	H	CO_2Et	CO_2Et	H	543
$PhCH_2$	Me	CO_2Et	CO_2Et	Me	494
$H_2NCOC_2CH_2$	Me	Me	Me	Me	498
$NCCH_2CH_2$	Me	Me	Me	Me	498

TABLE 2.47. 1-PHENYL- AND SUBSTITUTED 1-PHENYL-2,3,4,5-TETRASUBSTITUTED PYRROLES

Substituent on 1-Phenyl Group	2-Substituent	3-Substituent	4-Substituent	5-Substituent	Ref.
H	Me	Me	Me	Me	542
H	Me	Ac	Ph	2-Thienyl	476
p-NH_2	Me	Me	Me	Me	482
p-MeO	Me	CO_2Me	Ph	2-Thienyl	476
p-HN_2SO_2	Me	CO_2Et	CO_2Et	Me	544

TABLE 2.48. 1-AMINO-2,5-DISUBSTITUTED PYRROLES AND RELATED COMPOUNDS

1-Substituent	2-Substituent	5-Substituent	Ref.
NH_2	Me	Me	545[a], 546
NH_2	CH_2CO_2Et	CH_2CO_2Et	547[b]
NHPh	Me	Me	493
NH-*o*-Tol	Me	Me	493
NH-*m*-Tol	Me	Me	493
NH-*p*-Tol	Me	Me	493
NH-*o*-$NO_2C_6H_4$	Me	Me	493
NH-*p*-$NO_2C_6H_4$	Me	Me	493
NH-2,4-di$NO_2C_6H_3$	Me	Me	493
NHAc	Me	Me	522
$NHCONH_2$	Ph	Ph	548
$NHCOCH_2NMe_2$	Me	Me	549
$NHCOCH_2CN$	Me	Me	550
NHCO-*p*-$MeOC_6H_4$	Me	Me	550
NHCO-2-furyl	Me	Me	550
$NHCOCH_2CN$	Me	Ph	550
NHCO-4-pyridyl	Me	Ph	550
NHCO-*p*-$MeOC_6H_4$	Me	Ph	550
NHCO-2-furyl	Me	Ph	550
$NHCOCH_2CN$	Me	*p*-PhC_6H_4	550
NHCO-4-pyridyl	Me	*p*-PhC_6H_4	550
NHCO-*p*-$MeOC_6H_4$	Me	*p*-PhC_6H_4	550
NHCO-2-furyl	Me	*p*-PhC_6H_4	550
$NHCO_2t$-Bu	Ph	Ph	548
$NHSO_2Ph$	Ph	Ph	548
$NHSO_2Ph$	Ph	$CH_2CH_2CO_2H$	551
$NHSO_2Me$	Ph	$CH_2CH_2CO_2H$	551
Morpholino	Me	Me	552
Piperidino	Me	Me	552
N-Mepyridazyl	Me	Me	552

[a] From *N*-aminophthalimide.
[b] Pyridazine also formed.

TABLE 2.49. OTHER 1-AMINOPYRROLES

1-Substituent	2-Substituent	3-Substituent	4-Substituent	5-Substituent	Ref.
NH_2	Ph	Ph	Ph	Ph	553
NH_2	Et	CO_2Et	Me	H	476
NH_2	Me	CO_2Et	2-Furyl	2-Thienyl	476
NH_2	Me	CO_2Me	2-Thienyl	2-Thienyl	476
NH_2	$-CHMeCH(CO_2H)CH_2-$		H	Ph	554
$NHCONH_2$	Me	CO_2Et	H	Ph	555, 556
NHCOPh	Me	CO_2Et	H	Me	494
NH–DNP[a]	Me	CO_2Et	CO_2Et	Me	557
Morpholino	Me	CO_2Et	CO_2Et	Me	552
Morpholino	Ph	Ph	H	Ph	552
Piperidino	Me	CO_2Et	CO_2Et	Me	552
N-Mepiperidino	Me	CO_2Et	CO_2Et	Me	552
N-Mepiperidino	Ph	Ph	H	Ph	552

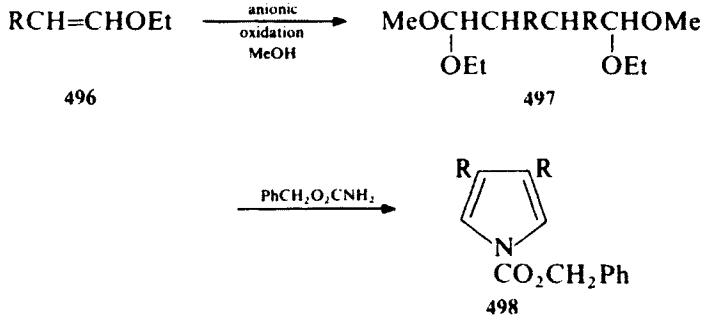
[a]DNP = $2,4\text{-di}NO_2C_6H_4$

TABLE 2.50. 1-HYDROXYPYRROLES

2-Substituent	3-Substituent	4-Substituent	5-Substituent	Ref.
Me	CO_2Et	CO_2Et	Me	541
Me	CO_2Et	Ac	Me	558
Me	PhCO	PhCO	Ph	559
Me	Ac	Ac	Me	560[a]
t-Bu	H	H	*t*-Bu	541
t-Bu	CO_2Et	H	*t*-Bu	541
t-Bu	CO_2Et	CO_2Et	Me	541
Ph	Ph	Ph	Ph	541
CO_2Me	PhCO	H	Ph	561

[a]As monooxime.

produced by the anionic oxidation of vinyl ethers **496**, can be used to prepare the pyrrole **498**:[562]



(153)

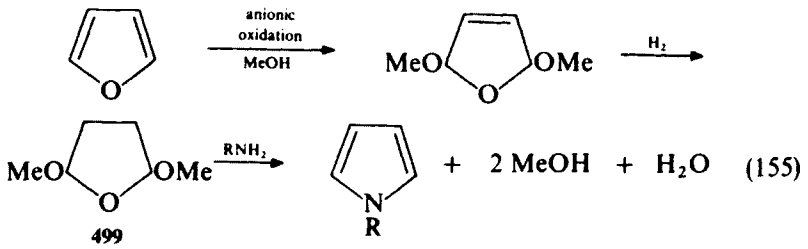
Dimethoxytetrahydrofuran (**499**) reacts with trimethylsilyl chloride to give the dimethoxydichlorobutane **500**, from which 1-substituted pyrroles **501** can be prepared:[563,564]

499 500 501

R = CH_2CO_2Et, CH_2Ph, $CH(CO_2Et)CH_2Ph$, Ac, or COPh (154)

2.7.1.2.2. Dialkoxy- and Dihalotetrahydrofurans

In 1952, Clauson-Kass reported the preparation of 2,5-dimethoxytetrahydrofuran (**499**) by the anionic oxidation of furan, followed by the hydrogenation of the resulting dihydrofuran.[565,566] As a cyclic acetal of succinaldehyde, a facile method for the preparation of 1-substituted pyrroles (Eq. 155) was thus available.



499 (155)

Since then, the reaction of **499** with primary amines has been the method of choice for the preparation of 1-substituted pyrroles, as can be seen in Tables 2.51 and 2.52.

TABLE 2.51. 1-ALKYLPYRROLES FROM 2,5-DIALKOXYTETRAHYDROFURANS

1-Alkyl Group	Ref.
Me	566
Et	566
n-Bu	566
n-C_5H_{11}	566
$PhCH_2$	566, 567
CH_2CH_2CN	568
CH_2COPh	499
CH_2CO-*p*-Tol	499
CH_2CO-*p*-$NO_2C_6H_4$	499
CH_2CO-*p*-Ac-C_6H_4	499
$CPh(CONH_2)(CH_2)_2NMe_2$	569
$CH_2PO(OEt)_2$	570
$CHPhPO(OEt)_2$	570

TABLE 2.52. 1-ARYLPYRROLES FROM DIALKOXYTETRAHYDROFURANS

1-Aryl Group	Ref.
Ph	566
o-Tol	566
p-Tol	566
o-$NH_2C_6H_4$	571
o-$MeO_2CC_6H_4$	568
p-$PhOC_6H_4$	572
p-$HO_2CCH_2C_6H_4$	573
p-$HO_2C(CH_2)_3C_6H_4$	574
p-$HO_2C(CH_2)_4C_6H_4$	574
2-Me-3-$NO_2C_6H_3$	575
3,4-diMe-2-$NO_2C_6H_2$	576
2-PhCO-4-ClC_6H_3	577
2-(8-Nitro)naphthyl	578
2-Thienyl	579
2-Cyclopenta[b]thienyl	579
2-Pyridazinyl	580
9-Acridinyl	581
2,4-diMe-2-pyrimidinyl	581
4,6-diMe-2-pyrimidinyl	581
3-(2-Carbethoxy)benzothienyl	582
3-(2-Carbethoxy)benzofuryl	582

In a similar manner, the reaction of **499** with benzenesulfonamide will give 1-benzenesulfonylpyrrole,[583,584] while 1-aminopyrrole can be prepared from *N*-aminophthalimide followed by hydrolysis.[545,585] The 1-tosylaminopyrrole results from the reaction with tosylhydrazine.[586,587]

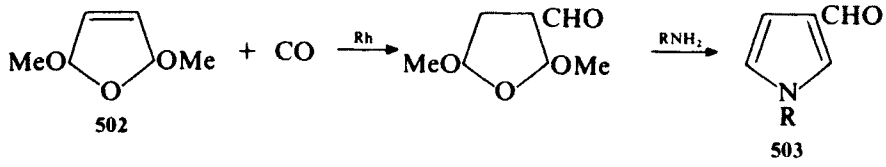
TABLE 2.53. 1,2-DISUBSTITUTED PYRROLES FROM 2-SUBSTITUTED 2,5-DIALKOXYTETRAHYDROFURANS

1-Substituent	2-Substituent	Ref.
H	Et	566
Ph	Me	566
o-Tol	Me	566
p-Tol	Me	566
H	CHO[a]	566
H	CO_2Me	566
Ph	CO_2Me	588
Ph	CO_2Et	589
o-ClC_6H_4	CO_2Me	588
o-$NO_2C_6H_4$	CO_2Me	588
o-$PhCH_2O_2CC_6H_4$	CO_2Me	588
2,5-di$MeOC_6H_3$	CO_2Me	588
2,6-di$NO_2C_6H_3$	CO_2Me	588
p-$MeOC_6H_4$	CO_2Et	589
$PhCH_2$	CO_2Et	589

[a]As acetal.

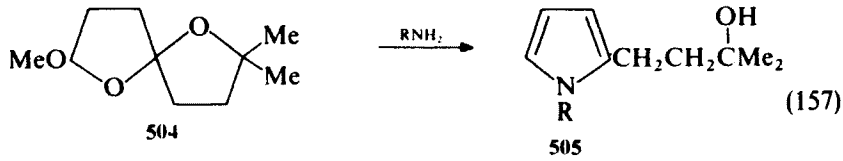
The conversion of substituted furans into their dialkoxytetrahydro derivatives provides a route to 1-substituted pyrroles having substituents at other ring positions (e.g., alkyl, carbalkoxy, and formyl; see Table 2.53).

The 3-carboxaldehyde **503** can be prepared by carbonylation of the dihydrofuran **502**:[583,584,590,591]



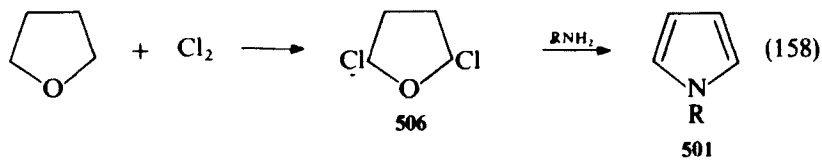
502 **503** (156)

The reaction of amines with the spirocompound **504** produces the 1-substituted-2-(3-hydroxypropyl)pyrroles **505**:[592]



504 **505** (157)

The chlorination of tetrahydrofuran results in the 2,5-dichloro compound **506**, which reacts with primary amines in a manner analogous to the dimethoxy compound and a number of 1-substituted pyrroles **501** have been prepared in this manner:[593–595]

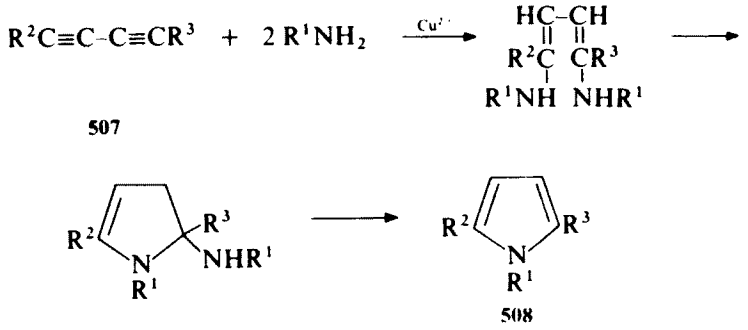


506 **501** (158)

2.7.1.3. From Other 4-Carbon Units of Same Oxidation State as Pyrrole

2.7.1.3.1. Dialkynes

The addition of primary amines to a 1,3-diyne **507**, which probably occurs through a double Michael addition and is often catalyzed by copper salts, has been used to prepare a number of both symmetrical and nonsymmetrical 2,5-disubstituted pyrroles **508** (Eq. 159). In many cases the yields exceed 80%.



(159)

The need for the catalyst is evident since, when the addition of benzylamine to 1,4-diphenyl-1,3-butadiyne is carried out in the absence of the copper salts, the major product is the 2,3,6-triphenylpyridine, instead of the 1,2,5-triphenylpyrrole.[596] Table 2.54 lists the pyrroles that have been produced by the reaction of amines with dialkynes.

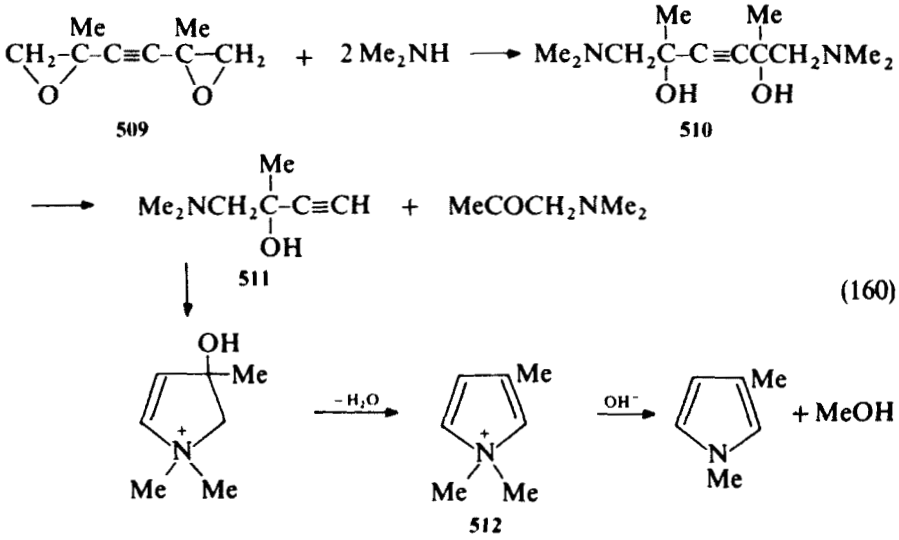
TABLE 2.54. 1,2,5-TRISUBSTITUTED PYRROLES FROM PRIMARY AMINES (R^1NH_2) AND DIALKYNES ($R^2C{\equiv}C{-}C{\equiv}CR^3$)

R^1	R^2	R^3	Ref.
H	H	H	597
H	Ph	Ph	597
Me	Me	Me	597
Me	Ph	Me	597
Me	Ph	Ph	597
n-Bu	Ph	Ph	597, 599
Ph	Ph	H	597
Ph	Ph	Ph	597, 599
p-Tol	Ph	Ph	597
p-$MeOC_6H_4$	Ph	Ph	597
p-ClC_6H_4	Ph	Ph	597
p-HOC_6H_4	Ph	Ph	597
p-$NO_2C_6H_4$	Ph	Ph	597
2-Pyridyl	Ph	Ph	597, 598
2-Pyridyl	Ph	Me	598
2-Naphthyl	Et	Me	597
p-$EtOC_6H_4$	Et	Et	597
Ph	Ph	CH_2CH_2	600
Ph	$PhOCH_2$	$PhOCH_2$	601, 602
Ph	*p*-$NO_2C_6H_4OCH_2$	*p*-$NO_2C_6H_4OCH_2$	601
Ph	*p*-$ClC_6H_4OCH_2$	CH_2OH	603
Ph	2-Naphthyl-OCH_2	CH_2OH	604

2.7.1.3.2. Bisepoxides

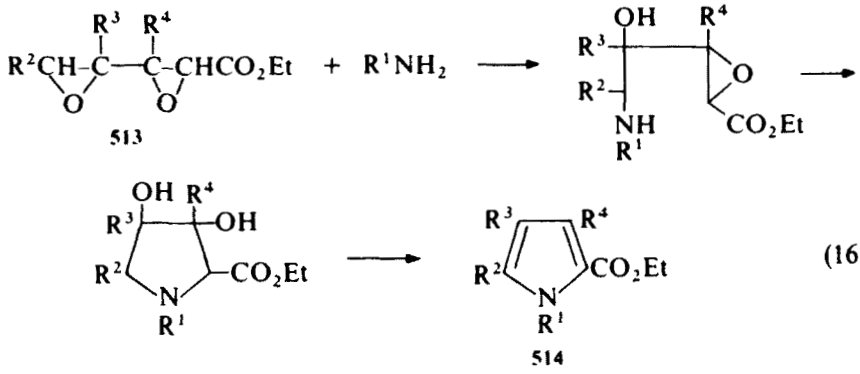
Perveev and Statsevich have found that the reaction of dimethylamine with the bisepoxyalkyne **509** produces 1,3-dimethylpyrrole. They have proposed that

there is cleavage of the product **510**, formed by the addition of the amine to both epoxy functions[605], to give 1-dimethylamino-3-butyn-2-ol (**511**), which then closes to the quaternary compound **512**. Subsequent attack by hydroxide ion leads to the loss of a methyl group as methanol. In a similar manner, but without the last step, **509** reacts with butylamine.[606]



(160)

The reaction of amines with the bisepoxypentanoate **513** yields the substituted pyrrole-2-carboxylates **514**:[607]



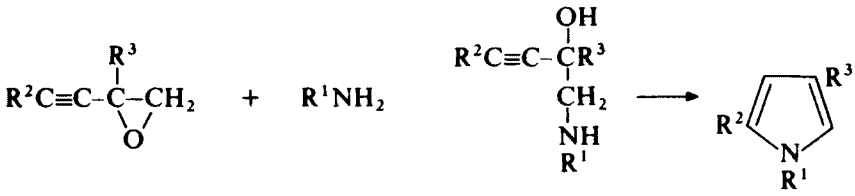
(161)

R^1	R^2	R^3	R^4
Me	Me	Me	Me
$PhCH_2$	Ph	H	Ph

2.7.1.3.3. Epoxyalkynes or Ketones

Perveev and co-workers have published a number of papers reporting the reaction of 2-methyl-1,2-epoxy-3-alkynes **515** (R^3 = Me) with primary amines,

which initially produces the 2-methyl-2-hydroxy-1-amino-3-alkyne **516** (R^3 = Me) that cyclizes to the 2-substituted-4-methylpyrrole **517** (R^3 = Me) (Eq. 162). The reaction also occurs with secondary amines with the subsequent loss of the alkyl group as the alcohol.[608]



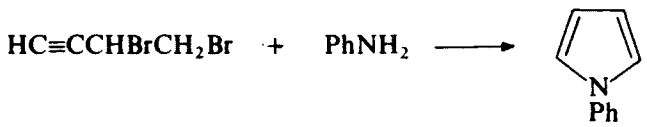
515 **516** **517**

(162)

R^1	R^2	R^3	Ref.
H	Me	H	609
H	Ph	H	609
H	*i*-Pr	H	610
H	*t*-Bu	Me	611
H	CH_2=CH	H	609, 612
Me	Me	H	609, 613
Me	Ph	H	608, 614, 615
Me	CH_2=CH	H	609, 612
Me	H	HC≡C	616
Me	Me	MeC≡C	616
Me	Ph	PhC≡C	616
Et	H	Me	617
Et	Ph	H	609
Et	CH_2=CH	H	609, 612, 615
Et	cyclo-C_6H_{11}	H	609
n-Pr	Me	H	613[a]
n-Bu	Me	H	613[a]
CH_2CH_2OH	Me	H	609
CH_2CH_2OH	Ph	H	609
$PhCH_2$	Me	H	609
$PhCH_2$	Ph	H	609
Ph	Me	H	609
$PhCH_2CHCO_2H$	Ph	Me	618

[a] R_2NH used.

A simple method for the preparation of 1-substituted pyrroles is the reaction of 1,2-dibromobut-3-yne with amines:[619]

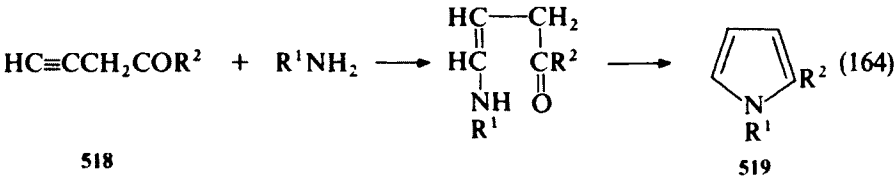


(163)

2.7.1.3.4. Alkynediols or Ketones

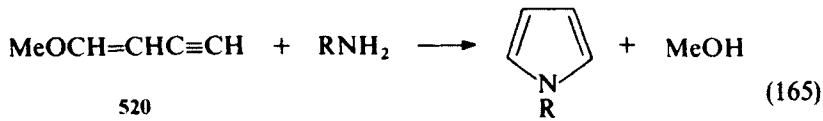
Pyrrole itself can be prepared by the vapor-phase reaction of 2-butyne-1,4-diol with ammonia over aluminum oxide.[620] At the same oxidation level are the acetylenic ketones **518**, which react with amines, probably via an initial

condensation at the carbonyl group followed by a Michael-type addition to the triple bond and thence to the pyrrole **519**:[621,622]



518 **519** (164)

In a similar manner, two patents have reported that the reaction of the acetylenic enol ether **520** leads to the pyrrole **521**:[623,624]

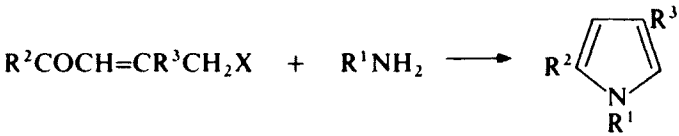


520 **521** (165)

R = Me or *n*-Bu

2.7.1.3.5. 1-Haloalk-2-en-3-ones

A number of papers have described the preparation of 1-haloalk-2-en-3-ones, which, on treatment with primary amines, undergo conversion into pyrroles in good yield.

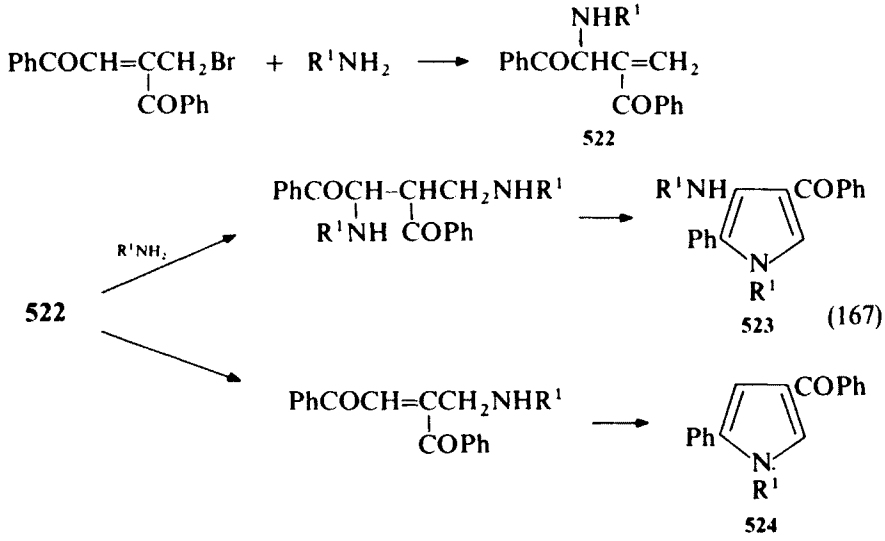


(166)

R^1	R^2	R^3	X	Ref.
H	Me	H	Cl	625
H	*n*-Bu	H	Cl	625
H	Ph	H	Cl	625
H	Me	Me	Cl	625
H	Et	H	Cl	626
H	*n*-Pr	H	Cl	626
H	cyclo-C_5H_9	H	Cl	626
H	cyclo-C_6H_{11}	H	Cl	626
Me	Me	H	Cl	626
Me	Et	H	Cl	626
Me	*n*-Pr	H	Cl	626
Me	cyclo-C_5H_9	H	Cl	626, 627
Me	cyclo-C_6H_{11}	H	Cl	626, 627
Me	Me	Me	Cl	625
Me	Ph	Ph	Br	628
Et	Me	H	Cl	625
n-Bu	cyclo-C_6H_{11}	H	Cl	626
t-Bu	Ph	Ph	Br	628, 629
cyclo-C_5H_9	cyclo-C_6H_{11}	H	Cl	626
cyclo-C_6H_{11}	Ph	Ph	Br	628
allyl	Me	H	Cl	626
Ph	Ph	Ph	Br	629
$PhCH_2$	Ph	Ph	Br	629
$PhCH_2CH_2$	Ph	Ph	Br	629

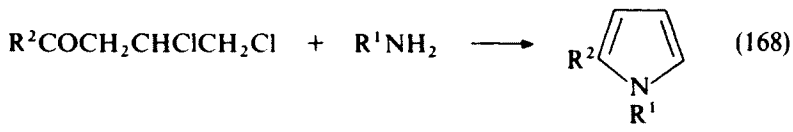
The requisite halobutenones, utilized in Eq. 166, can be prepared by the halogenation of the chalcones[629,630] or the acylation of allylic halides.[625]

When the reaction of halo enediones with amines is carried out in a polar solvent, a 3-aminopyrrole **523** is obtained. The expected product **524** is formed in nonpolar solvents, and it is believed that both pyrroles result from an initial S_N2' reaction to form **522**, which leads to the monoamino and diamino-intermediates.[631]



(167)

The reaction of a 3,4-dichloroketone with a primary amine is analogous to the reaction of the chlorobutenones and yields 1,2-disubstituted pyrroles:[632]



(168)

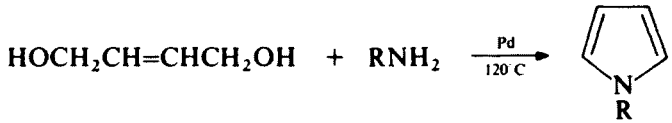
R^1	R^2
Me	H
Et	Ph
allyl	cyclo-C_5H_9
allyl	cyclo-C_6H_{11}

Three patents utilize variations of these methods for the synthesis of pyrrolonitrin analogs.[633–635]

2.7.1.4. From Other 4-Carbon Units of Lower Oxidation State than Pyrrole

As indicated in Section 2.7.1.3.4, the reaction of ammonia with 2-butyne-1,4-diol produces pyrrole. In a similar manner the reaction of amines with 2-butene-

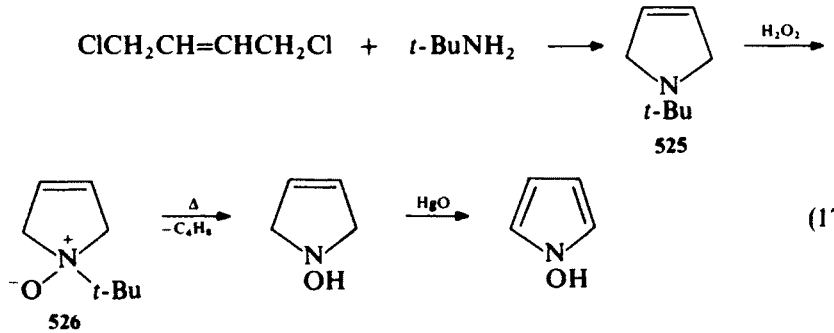
1,4-diol will give 1-substituted pyrroles when palladium is present as a dehydrogenation catalyst:[636]



(169)

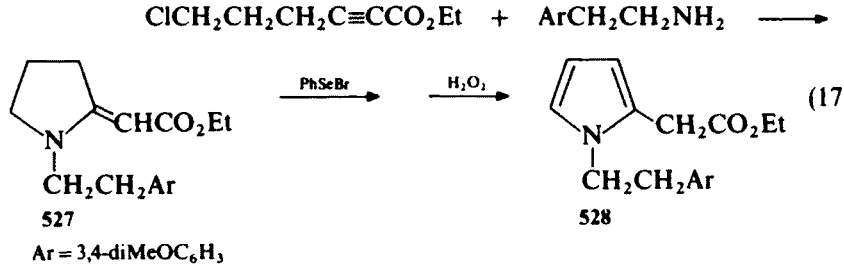
R = *n*-Bu, Ph, cyclo-C_6H_{11}, or CH_2CH_2OH

The Δ^3-pyrroline **525**, which results from the reaction of 1,4-dichlorobut-2-ene with *t*-butylamine, has been converted into 1-hydroxypyrrole by an interesting series of reactions. Formation of the *N*-oxide **526** is followed by thermolysis, which results in the elimination of isobutylene by a Cope-type reaction and the production of 1-hydroxy-Δ^3-pyrroline. Oxidative aromatization by mercuric oxide gives 1-hydroxypyrrole:[637]



(170)

The combined Michael addition and displacement of the halogen by a primary amine from ethyl 6-chlorohex-2-ynecarboxylate produces the exocyclic pyrroline **527**, which has been converted into the pyrrolylacetate **528** by reaction with phenylselenyl bromide followed by oxidation with peroxide:[638]



(171)

2.7.1.5. From Butadienes

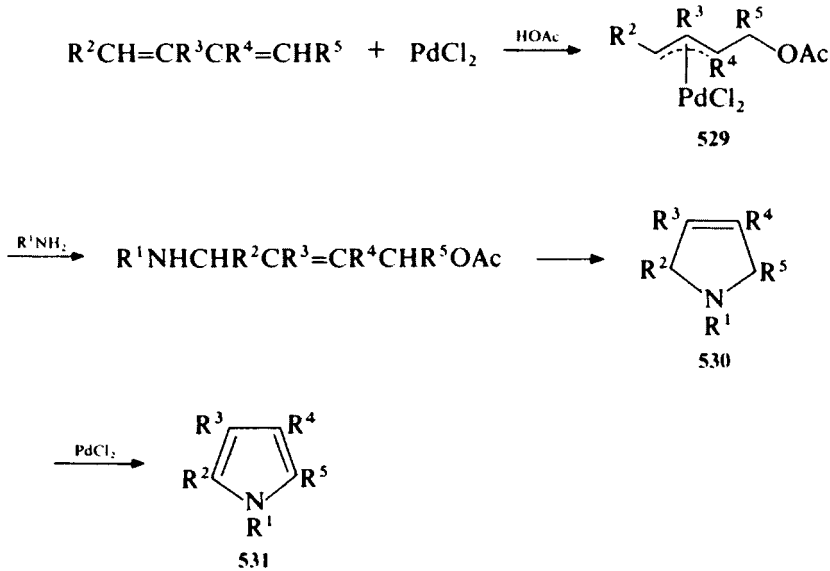
Pyrrole has been formed by the reaction of butadiene with "active nitrogen" produced by microwave discharge.[639,640] The vapor-phase reaction of ammonia and butadiene over alumina can also be utilized for the industrial

production of pyrrole.[641] It has been reported that 1-alkylpyrroles can be formed by the reaction of 1,4-dibromobuta-1,2-diene and amines:[642]

$$BrCH{=}C{=}CHCH_2Br + RNH_2 \longrightarrow \underset{R}{\overset{N}{\langle\!\rangle}} \qquad (172)$$

R = Et, *n*-Pr, *n*-Bu, or cyclo-C_6H_{11}

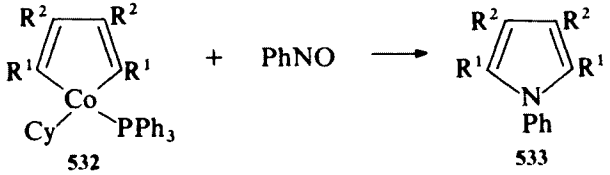
The addition of amines to buta-1,3-dienes, catalyzed by palladium(II) chloride in acetic acid, apparently occurs via a π-complex of the acetate **529**, and the resulting pyrroline **530** is aromatized by oxidation by the palladium(II). The pyrroles **531** are obtained in 15–50% yields (Scheme 30).[643]



R^1	R^2	R^3	R^4	R^5
Et	H	H	H	H
$PhCH_2$	H	H	H	H
Et	H	Me	H	H
$PhCH_2$	H	Me	H	H
$PhCH_2$	H	Me	Me	H
$PhCH_2$	Me	H	H	Me
$PhCH_2$	Me	H	H	H

Scheme 30

Attack by nitrosobenzene on the dimerization product **532** of alkynes by the σ-complex of cyclopentadienyl cobalt leads to approximately 35% yields of the 1-phenylpyrroles **533**.[644]

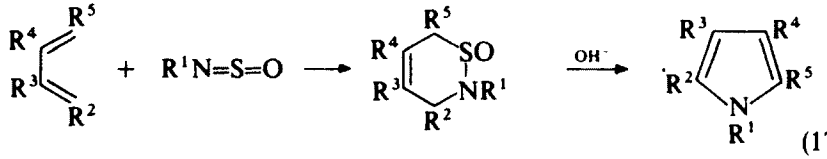


532 533 (173)

R^1	R^2
Ph	Me
Ph	Ph

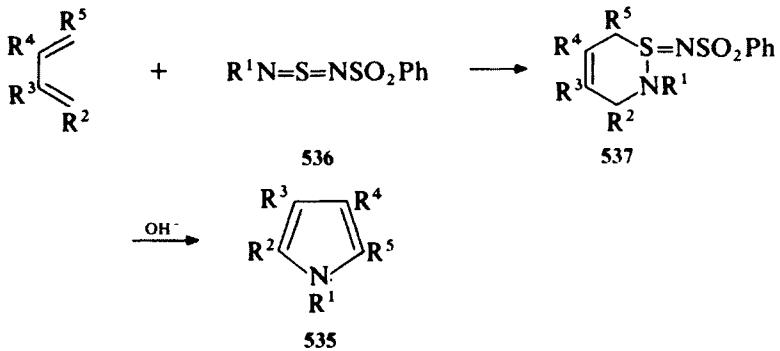
2.7.1.5.1. With Thiazines and Sultams

N-Sulfinamides behave as dienophiles and undergo a Diels–Alder cycloaddition with buta-1,3-dienes to give the 1,2-thiazine oxides **534**. Treatment of these adducts with a strong base produces a ring contraction with the loss of sulfur mono-oxide to produce the pyrrole **535** (Eq. 174).[645] Yields often are in excess of 80%.



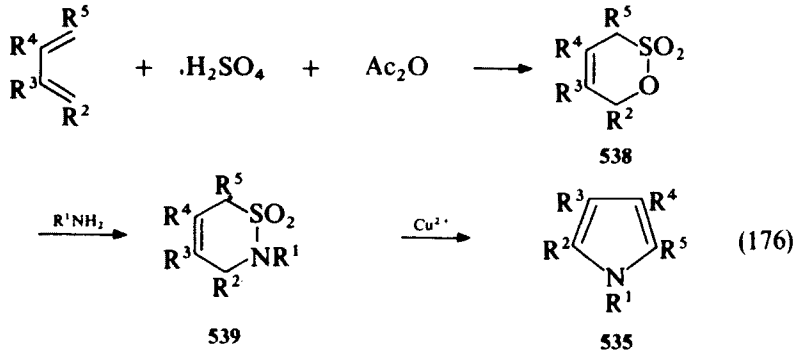
534 535 (174)

Similarly, the addition of sulfondiimides **536** to dienes yield *S*-substituted 1,2-thiazines **537**, which can be converted into pyrroles **535**:



536 537 535 (175)

The analogous sultams or thiazine dioxides **539** can be formed by the reaction of an amine with the corresponding sultones **538**, which are produced by the reaction of butadienes with sulfuric acid. Treatment of the sultams with copper salts cause ring contraction and production of the pyrroles **535**:



(176)

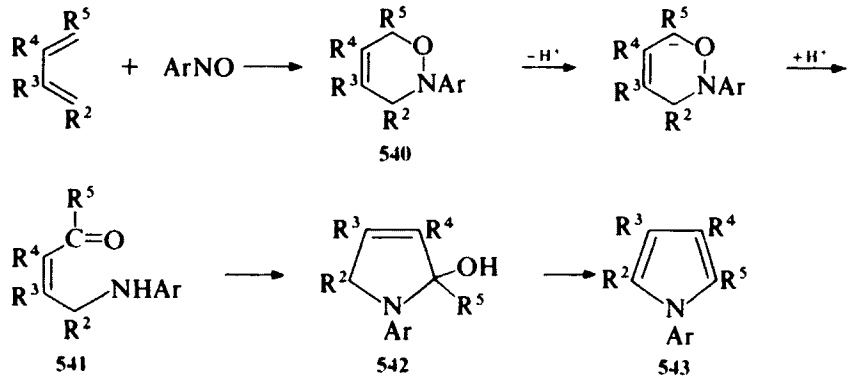
TABLE 2.55. PYRROLES FROM 1,2-THIAZINES

R^1	R^2	R^3	R^4	R^5	Z	Ref.
H	H	Me	H	H	O	646[a]
H	H	Me	Me	H	O	646[a], 647[a]
Ph	H	Me	H	H	NSO_2Ph	648
Ph	H	Me	Me	H	NSO_2Ph	648
p-Tol	H	Me	Me	H	NSO_2Ph	648
m-$NO_2C_6H_4$	H	H	H	H	NSO_2Ph	648
p-$NO_2C_6H_4$	H	H	H	H	NSO_2Ph	648
m-$NO_2C_6H_4$	H	Me	H	H	NSO_2Ph	648
p-$NO_2C_6H_4$	H	Me	H	H	NSO_2Ph	648
p-$NO_2C_6H_4$	Me	H	H	H	NSO_2Ph	648
o-$NO_2C_6H_4$	H	Me	Me	H	NSO_2Ph	648
p-$NO_2C_6H_4$	H	Me	Me	H	NSO_2Ph	648
Ph	Me	H	Me	H	O_2	649[b]
Ph	*n*-C_7H_{15}	H	Me	H	O_2	650[b]
$PhCH_2$	Me	H	Me	H	O_2	649[b]
$PhCH_2$	Me	Me	H	Me	O_2	650[b]
p-Tol	Me	Me	Me	H	O_2	650[b]
p-Tol	H	Me	Me	H	O_2	651
p-$MeOC_6H_4$	Me	H	Me	Me	O_2	650[b]
p-$NO_2C_6H_4$	H	Me	Me	H	O_2	652
p-ClC_6H_4	H	Me	Me	H	O_2	652
p-BrC_6H_4	H	Me	Me	H	O_2	651, 652
o-HOC_6H_4	Me	H	Me	H	O_2	653[b]
o-$MeO_2CC_6H_4$	H	Me	Me	H	O_2	654[b], 655
m-$Me_2NC_6H_4$	Me	Me	Me	H	O_2	649[b]
$PhSO_2$	H	H	H	H	Ph	656
$PhSO_2$	H	Me	Me	H	Ph	656

[a]From the *N*-carbethoxy compound.
[b]Through the sultone.

2.7.1.5.2. With Oxazines

A number of papers, particularly those by Kresze and Firl,[659–661] have reported the 1,4-cycloaddition of nitrosobenzene to a variety of buta-1,3-dienes to give the 1,2-oxazine **540**, which can be converted into 1-phenylpyrroles **543** in excellent yields (> 90%). The mechanism for the conversion of the oxazine into the pyrrole, which is often carried out by passing a solution of the oxazine over basic alumina, may occur by deprotonation followed by ring opening to the aminoketone **541**, which then ring closes to **542** and subsequent dehydration leads to **543** (Scheme 31).[657]



Scheme 31

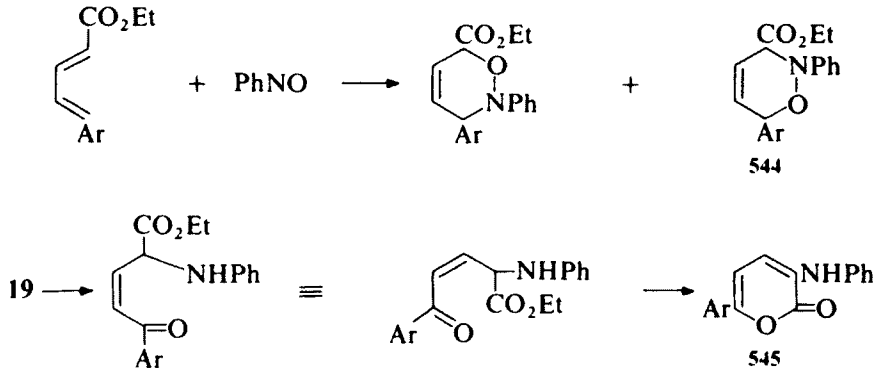
TABLE 2.56. 1-ARYLPYRROLES (**543**) FROM 1,2-OXAZINES

Ar	R^2	R^3	R^4	R^5	Ref.
Ph	H	Me	Me	H	658[a]
Ph	Me	H	H	CO_2Me	659
p-ClC_6H_4	H	H	H	CO_2Me	659
p-ClC_6H_4	Me	H	H	CO_2Me	659
p-ClC_6H_4	Ph	H	H	CO_2Me	659
p-ClC_6H_4	Me	Br	H	CO_2Me	659
p-ClC_6H_4	Me	H	H	CO_2Me	660
Ph	H	H	H	2-Pyridyl	661[a]
Ph	H	H	H	3-Pyridyl	661[a]
Ph	H	H	H	4-Pyridyl	661[a]
Ph	Me	H	H	2-Pyridyl	661[a]
Ph	Ph	H	H	COPh	657
Ph	2-Furyl	H	H	2-ThienylCO	657
Ph	Ph	H	H	*t*-BuCO	657

[a]Dehydrated in acidic media.

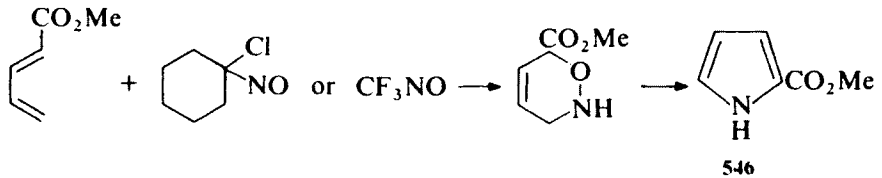
When R^2 is an alkoxycarbonyl group and either R^5 is an aryl group or the nitrosoarene is substituted by an electron-withdrawing group, there may be some reversal of orientation in the cycloaddition due to the shift in charge

density in the diene and/or dienophile. The alternate oxazine **544** may ring-open and reclose to the 3-aminopyrone **545** as shown in Scheme 32. Similarly, electron-withdrawing groups on the aryl group of R^5 increases the formation of **545**.[662,663]



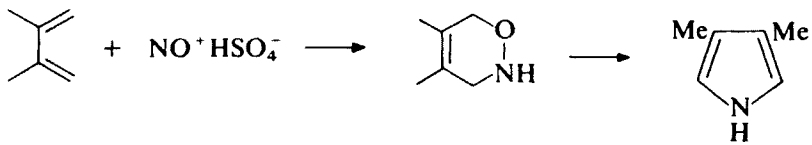
Scheme 32

If 1-chloro-1-nitrosocyclohexane or trichloronitrosomethane is used in place of nitrosobenzene, it is possible to produce 1-unsubstituted pyrroles (e.g. **546**).[659,661]



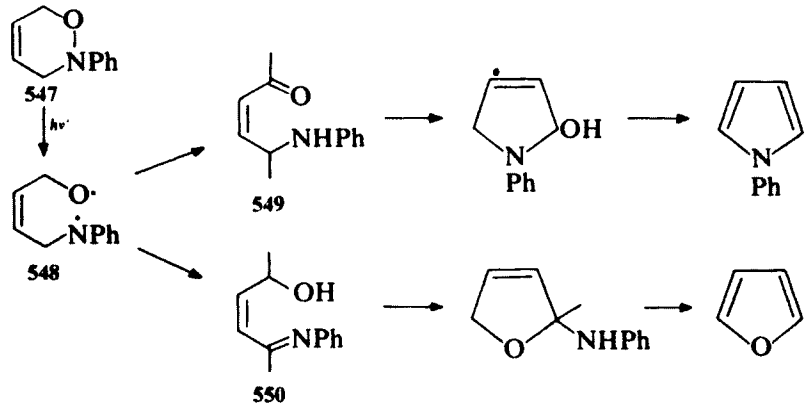
(177)

Likewise, the reaction of nitrosyl sulfuric acid gives the *N*-unsubstituted oxazine, and subsequently the 1-unsubstituted pyrrole (Eq. 177).[664]



(178)

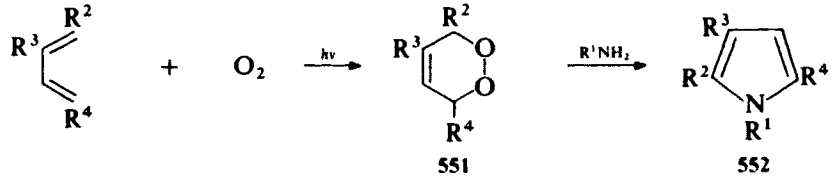
Photolysis of the *N*-aryl-1,2-oxazines **547** also leads to the formation of pyrroles, with furan as a minor product. The oxazine opens to the diradical **548** in which hydrogen migration can give either the aminoketone **549**, which leads to the pyrrole, or the imino alcohol **550** which produces furan (Scheme 33).[665,666]



Scheme 33

2.7.1.5.3. With Dioxines

3,6-Dihydro-1,2-dioxines **551**, produced by the photochemical addition of oxygen to butadienes, react with primary amines to give pyrroles **552** in yields of 50–90%:[667–669]



(179)

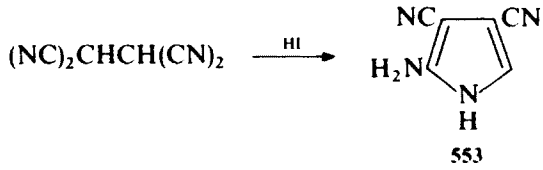
TABLE 2.57. PYRROLES (**552**) FORMED FROM 1,2-DIOXINES[668]

R^1	R^2	R^3	R^4
H	H	Ph	H
H	Ph	H	Ph
Et	Ph	H	Ph
Et	H	*t*-Bu	H
Ph	H	Me	H
Ph	H	*t*-Bu	H
Ph	H	Ph	H
Ph	Ph	Ph	H
$PhCH_2$	H	*t*-Bu	H
$PhCH_2$	H	Ph	H
$PhCH_2$	Ph	Ph	H

2.7.2. From 4-Carbon Units Containing Nitrogen

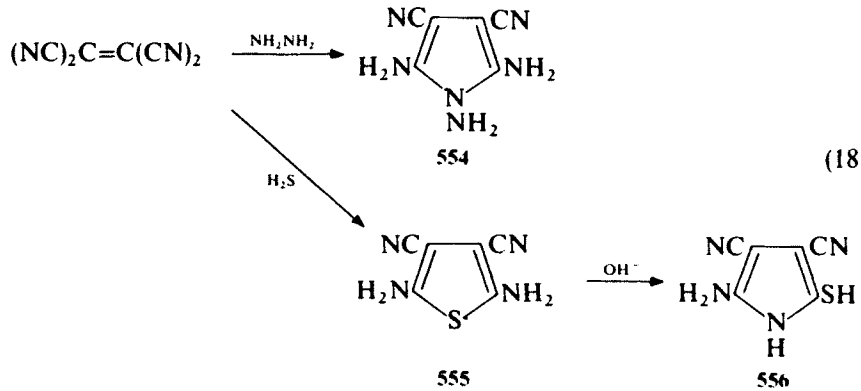
2.7.2.1. Succinonitriles

Tetracyanoethane undergoes a ring closure, when treated with hydriodic acid, resulting in the 2-aminopyrrole **553** (Eq. 180). The stoichiometry indicates that the hydriodic acid must also function as a reducing agent.[670]



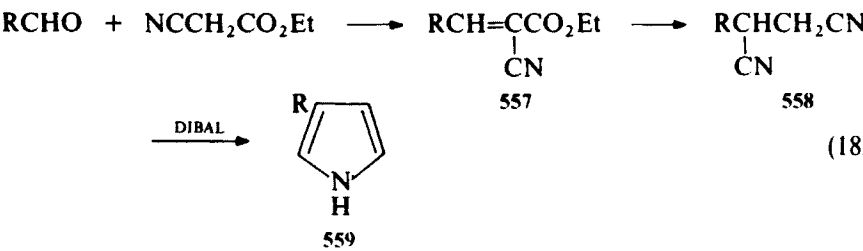
553 (180)

Tetracyanoethane, on the other hand, undergoes two quite different ring closures. In the first case, the addition of hydrazine results in the 1,2,5-triaminopyrrole **554**, in which excess hydrazine must act as a reducing agent.[671] The second type of reaction involves an interesting ring transformation of the initially formed aminothiophene **555** into the mercaptopyrrole:[672]



(181)

A more useful synthesis leading to 3-substituted pyrroles **559** utilizes the preparation of the requisite succinonitrile **558** by the addition of hydrogen cyanide to the Knoevenagel product **557**. Reduction of **558** by DIBAL gives



(182)

R = *i*-Pr, *n*-Bu, or Ph

good yields of **559** (Eq. 182).[673] Since 3-substituted pyrroles are usually difficult to prepare, this method should be exploited.

2.7.2.2. γ-Nitro- and Aminoketones

Reduction of **560**, formed by the condensation of an aryl methyl ketone with 1-nitro-2-dimethylaminoethene, is reported to give the 2-arylpyrroles:[269,674]

$$ArCOCH_3 + Me_2NCH{=}CHNO_2 \xrightarrow{OEt} \underset{\mathbf{560}}{ArCOCH{=}CHCH{=}NO_2^-} \xrightarrow{S_2O_4^{2-}} \text{2-Arylpyrrole} \qquad (183)$$

Ar = Ph, *p*-$MeOC_6H_4$, or *p*-BrC_6H_4

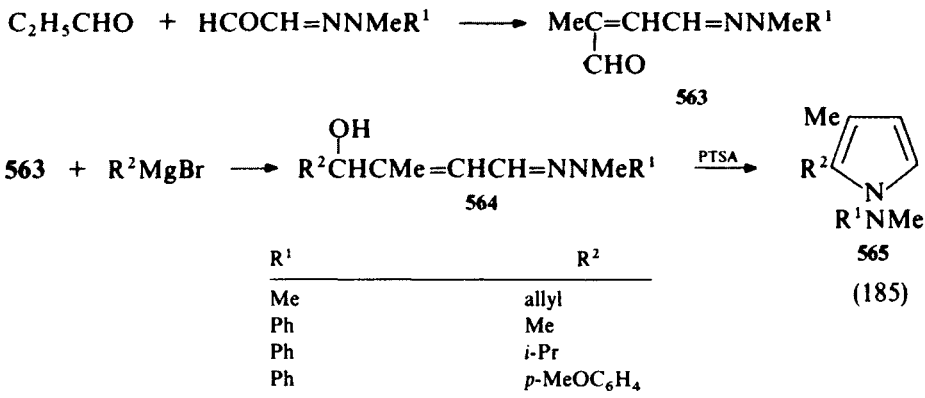
A versatile preparation of the trisubstituted pyrrole **562** involves the Michael condensation of a nitroalkene with a chalcone or vinyl ketone. Subsequent reduction of the resulting nitroketone **561**, either in one step or through the *N*-oxide, results in good yields of the pyrroles:[675–678]

$$R^1CH_2NO_2 + R^2CH{=}CHCOR^3 \longrightarrow$$

$$\underset{\mathbf{561}}{R^1CH(NO_2)CHR^2CH_2COR^3} \xrightarrow{\text{reduction}} \underset{\mathbf{562}}{\text{2,3,5-Trisubstituted pyrrole}} \qquad (184)$$

R^1	R^2	R^3
Me	Ph	Me
Me	Ph	Ph
CO_2Et	Ph	Ph
Et	4-Pyridyl	Ph

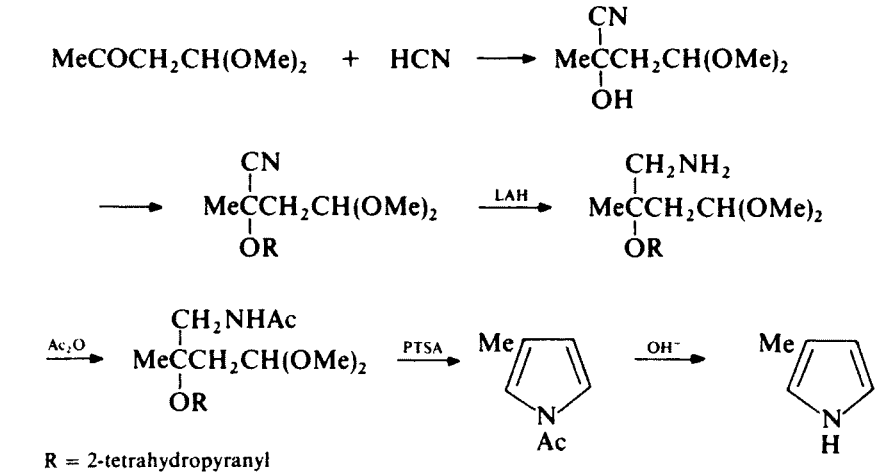
An interesting sequence of reactions was used in the preparation of the 2,3-disubstituted 1-aminopyrroles **565**. It involved the condensation of an aldehyde with the hydrazone of glyoxal to form the ketoaza-alkene **563**. Reaction with a Grignard reagent converts **563** into the hydroxyaza-alkene **564**, which undergoes ring closure with acid (Eq. 185). Yields in this reaction range from 45 to 75%.[679]



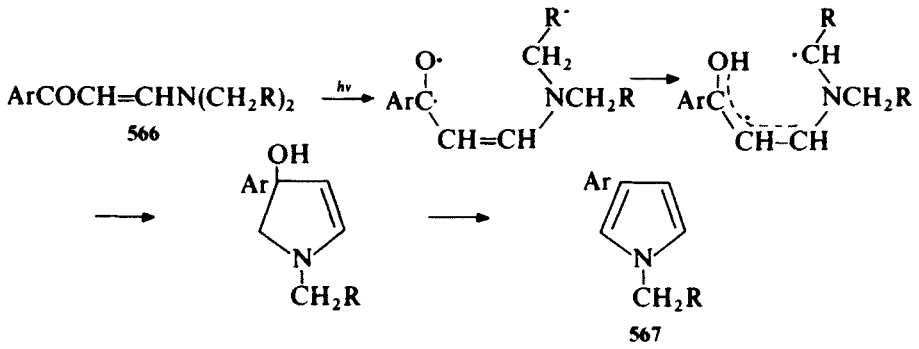
R^1	R^2
Me	allyl
Ph	Me
Ph	*i*-Pr
Ph	*p*-$MeOC_6H_4$

(185)

A specific synthesis of 3-methylpyrrole, which results in about 20% overall yield starting with the dimethylacetal of 3-oxobutanal, is outlined in Scheme 34.[680,681]



Scheme 34

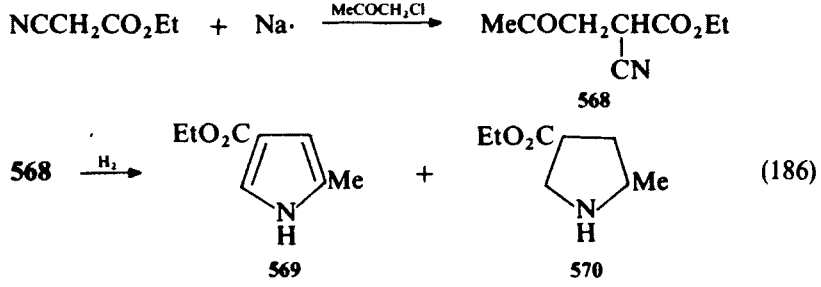


Scheme 35

Photolysis of the dialkylamino ketone **566** is believed to involve a Norrish-type 2 rearrangement. Subsequent ring closure gives the 4-hydroxy-2-pyrroline, which leads to the pyrrole **567** (Scheme 35). The yields are poor when R = H.[682–684]

2.7.2.3. β-Cyanoketones

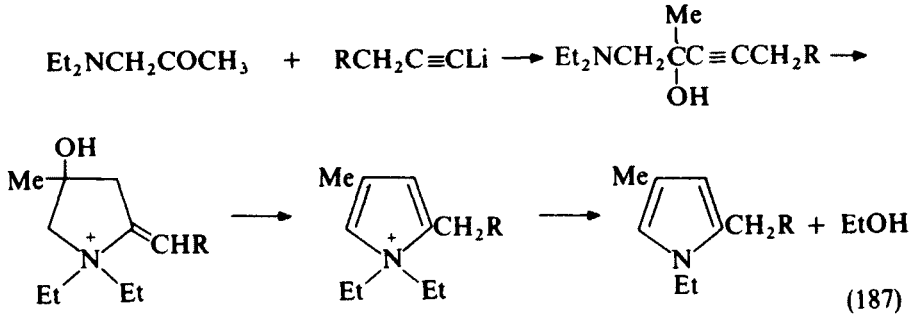
Hydrogenation of the cyanoketone **568**, produced by the alkylation of ethyl cyanoacetate with chloroacetone, produces both the pyrrole **569** and the pyrrolidine **570**:[685,686]



(186)

2.7.2.4. 4-Aminobutynols

As discussed in section 2.7.1.3, addition of an amine to an epoxyalkyne yields an aminobutynol, which ring-closes to the pyrrole (Eq. 187). Aminobutynols can also be prepared by the addition of a lithium alkyne to an α-aminoketone.[687]



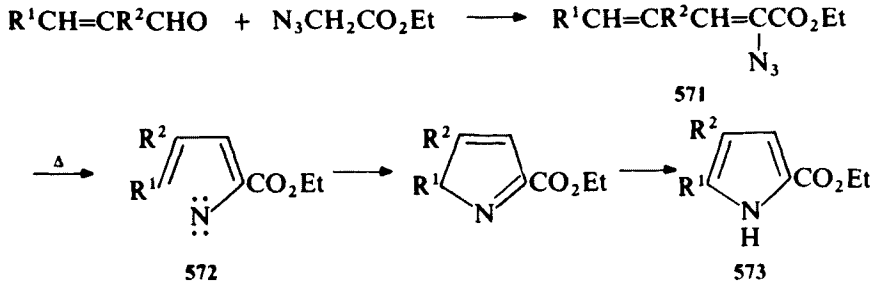
(187)

R = H or *n*-Pr

2.7.2.5. Azidobutadienes

Hemetsberger[688] has developed a synthesis of pyrroles utilizing the condensation of ethyl azidoacetate with an unsaturated aldehyde to produce an

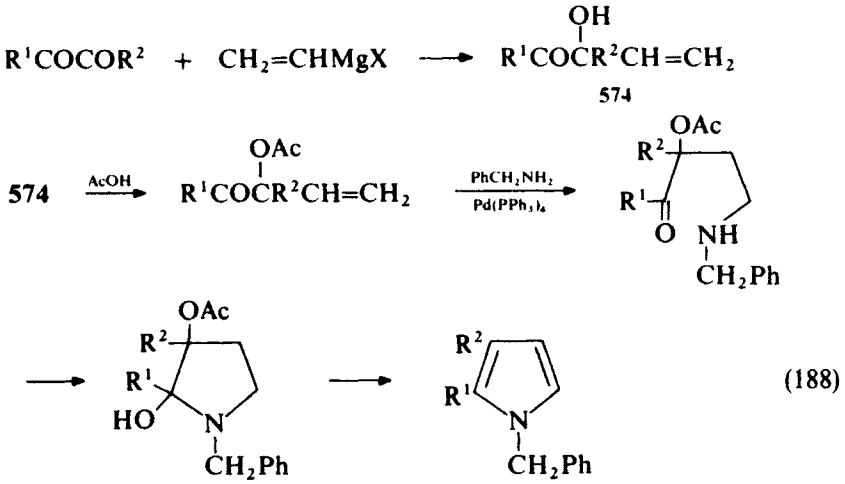
azidobutadiene **571**, which on heating gives an excellent yield of pyrroles (**573**) via an intermediate nitrene **572** (Scheme 36). (See Table 2.58).



Scheme 36

2.7.3. Miscellaneous Reactions

2,3-Disubstituted pyrroles can be prepared from the corresponding α-diketone. Treatment with vinylmagnesium halide gives the unsaturated hydroxyketone **574**, which is converted into the acetate and reacted with benzylamine in the presence of tetrakis(triphenylphosphine)palladium to produce the pyrrole **575**.[690]



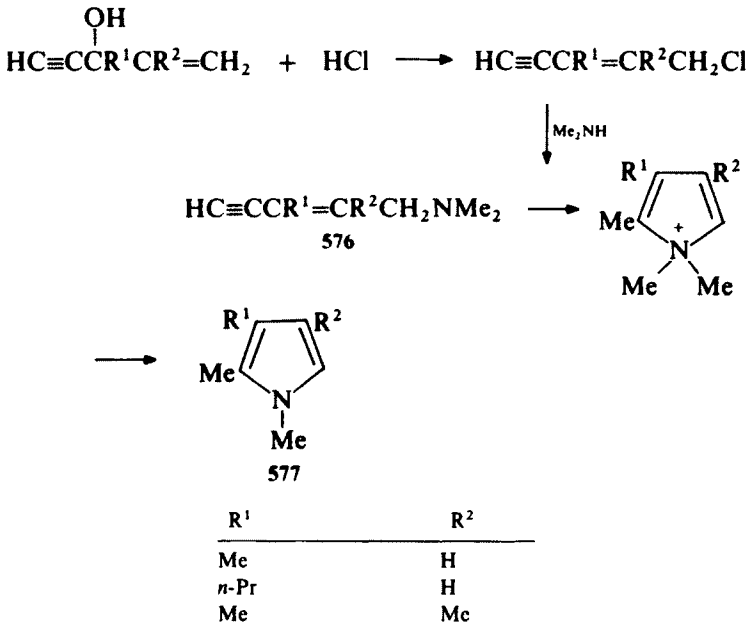
(188)

R^1	R^2
Me	Me
Ph	Ph
Ph	H
$-(CH_2)_4-$	

TABLE 2.58. PYRROLES (573) FORMED FROM AZIDOBUTADIENES

R^1	R^2	Ref.
H	Ph	688
H	*p*-Tol	688
H	*p*-ClC_6H_4	688
H	*p*-BrC_6H_4	688
Ph	Ph	688
Ph	H	688, 689
Me	Ph	688
2-Furyl	H	689
3-Furyl	H	689
2-Thienyl	H	689
3-Thienyl	H	689

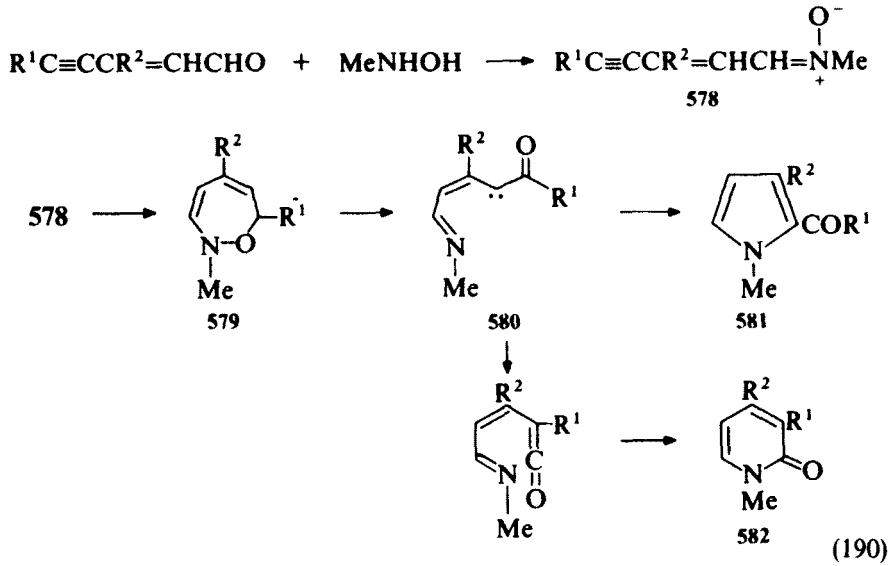
Allylic substitution converts the pent-1-en-4-yn-3-ol into the 1-chloro-2-penten-4-yne, which reacts with dimethylamine to yield the 1-dimethylamino compound **576**. Cyclization and thermal loss of a methyl group produces the 1,2,3,4-tetrasubstituted pyrrole **597** (55–60%):[691]



(189)

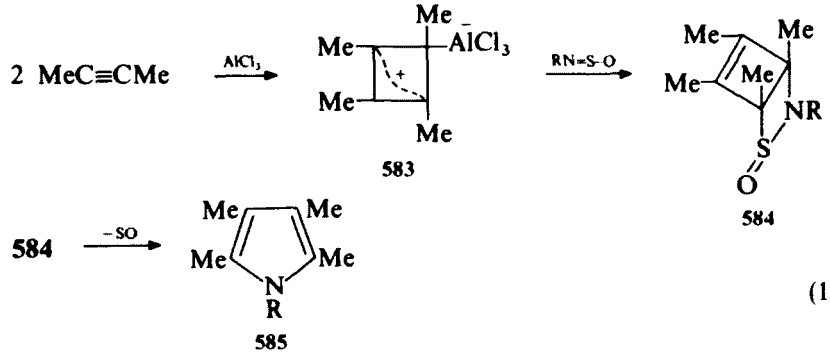
R^1	R^2
Me	H
n-Pr	H
Me	Me

Addition of *N*-methylhydroxylamine to the pent-2-en-4-ynal produces the butenynyl nitrone **578**, which is presumed to ring-close on heating to the 1,2-oxazepine **579**. When R^1 and R^2 are *t*-butyl groups, the 2-acylpyrrole **581** is produced, but with smaller groups a pyridone **582** results. It is proposed that the oxazepine opens to a carbonyl carbene **580**, which may recyclize to the pyrrole or, via the ketene, produces the pyridone:[692]



(190)

But-2-yne forms a cyclobutadiene complex **583**, when treated with aluminum chloride. Reaction of the complex with *N*-phenylsulfinylamine produces the 2,3,4,5-tetramethyl-1-phenylpyrrole (**585**, R = Ph) via the initial formation of the bicyclic sulfinylamine **604**:[693] The corresponding 1-*t*-butyl derivative (**585**, (R = *t*-Bu) has also been obtained.



(191)

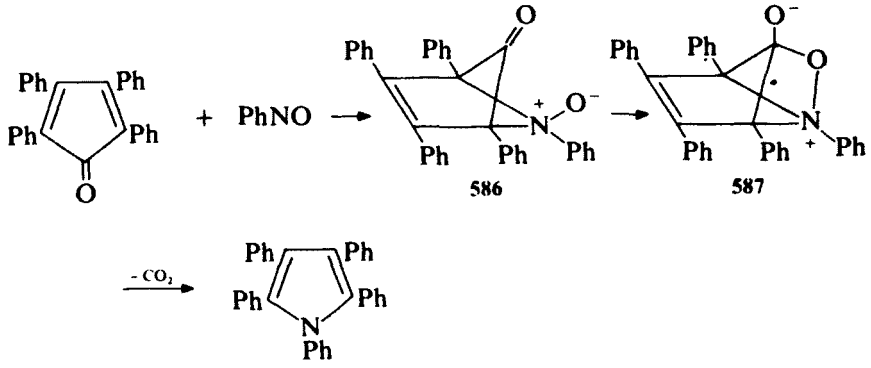
2.8. FORMATION OF PYRROLES VIA RING TRANSFORMATIONS

2.8.1. From 5-Membered Rings

2.8.1.1. Cyclopentanes

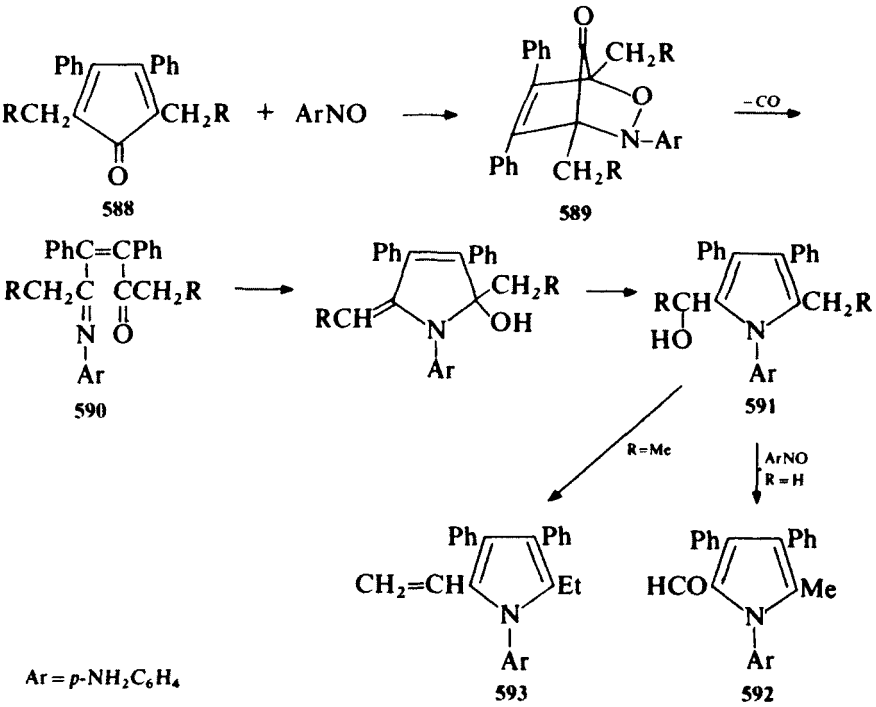
There are two reports of the conversion, with loss of the carbonyl group, of cyclopentadienones into 1-arylpyrroles by the reaction with nitrosobenzenes. In

the first instance tetraphenylcyclopentadienone is reported to give the pentaphenylpyrrole.[694] It was suggested that the initial step was the addition of the nitroso group to form an azobicyclo[2.2.1]heptene system **586**, which rearranged to a tricyclic system **587** (Scheme 37).



Scheme 37

However, a more recent paper has described the reaction of 2,5-dialkylcyclopentadienones **588** with *p*-nitrosodimethylaniline.[695] The products depend on the nature of the alkyl groups. A methyl group is converted into a formyl group



Scheme 38

leading to the formylpyrrole **592**, whereas the 2-vinylpyrrole **593** is obtained from the ethylcyclopentadienone. The proposed mechanism invokes the initial formation of an azabicyclo[2.2.2]octene **589** (Scheme 38). Loss of carbon monoxide (not carbon dioxide, as reported earlier) and ring opening produces the anil of a diketone **590**. Ring closure to the alcohol **591**, which may undergo either dehydration or oxidation to the formyl group, leads to the two products. This mechanism can also be used to explain the formation of the pentaphenylpyrrole shown in Scheme 37.

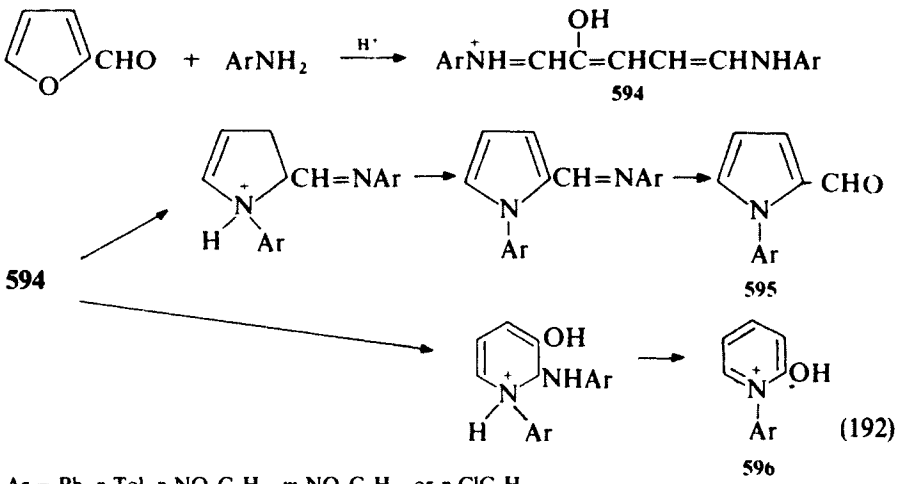
2.8.1.2. Furans

Pyrrole can be commercially prepared by the gas-phase reaction of furan with ammonia. A number of papers and patents have described conditions for the reactions.[696-701]

Although water is produced in the reaction, the injection of steam into the system increases the yield of pyrrole.[702] Aluminosilicate or zeolite catalysts have been found to be more effective than the aluminum oxide used in earlier work.[703-705] An increase in the reaction temperature favors the formation of indole, carbazole, and the isomeric pyrrocoline.[699,700] Likewise, the vapor-phase reaction of 2-methylfuran with ammonia produces some of the isomeric 3-methylpyrrole as well as the 2-methylpyrrole.[706]

In a similar manner, 1-substituted pyrroles have been prepared by the reaction of furan, furfural, and acetylfuran with primary amines.[707-711] However, methyl furoate is decarboxylated under these conditions.[712] In the competitive reaction of furan with aniline and ammonia, the product was almost exclusively the 1-phenylpyrrole.[713]

Under acidic conditions, furfural undergoes a ring opening with aryl amines to form the so-called Stenhouse salts **594**, which can ring-close to give either the pyrrole **595** or the 3-hydroxypyridinium salt **596**:[714]

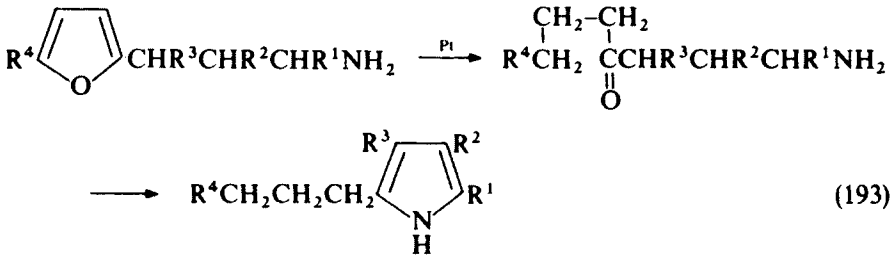


(192)

Ar = Ph, *p*-Tol, *p*-$NO_2C_6H_4$, *m*-$NO_2C_6H_4$, or *p*-ClC_6H_4

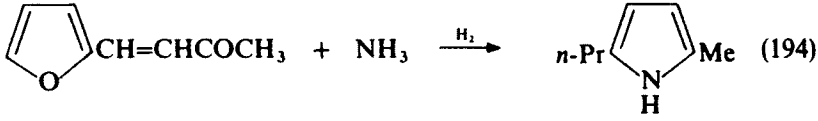
Pyrrole formation is aided by electron-withdrawing groups, whereas **596** is the major product with electron-releasing groups. It has been reported that the Stenhouse salts were not intermediates when alcohols were used as the solvent.[715]

In a number of papers, Belskii and co-workers have described the conversion of 2-(3-aminopropyl)furans into 2-alkylpyrroles:



(193)

Depending on how strenuous the conditions are, fragmentation of the *n*-propyl side chain may occur to give ethyl and methyl pyrroles as well. The requisite aminofurans are conveniently prepared via the chalcones, which are reductively aminated:



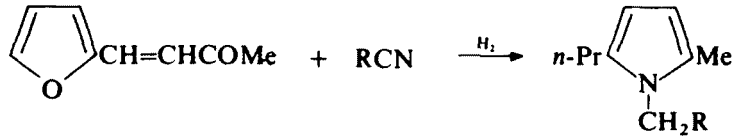
(194)

TABLE 2.59. 2-PROPYLPYRROLES FROM 2-(3-AMINOPROPYL)FURANS (Eq. 193, R^4 = H)

5-Substituent	4-Substituent	3-Substituent	Ref.
H	H	H	716–718[a]
Me	H	H	716, 718–721[a]
n-Pr	H	H	716, 720[a]
Et	H	H	718–721[a]
H	Me	H	722[a], 723
n-Bu	H	H	724[a]
C_6H_{13}	H	H	724[a]
Et	Et	H	723
Me	H	Et	725[a]
Me	H	*n*-Pr	725[a]
Me	*n*-Pr	H	718[a]

[a]From amination of chalcone.

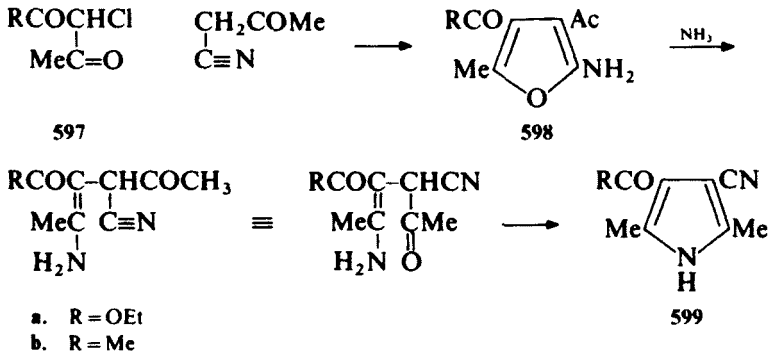
If nitriles are used in place of ammonia, the 1-substituted pyrroles are produced by the hydrogenation of the nitrile to the corresponding primary amine:[726]



(195)

R = Me, Et, *n*-Pr, or *i*-Bu

The 2-aminofuran **598**, obtained by the reaction of cyanoacetone with either the chloroacetoacetate or chloropentanedione **597**, undergoes an interesting ring opening and reclosure, when treated with ammonia, to yield the cyanopyrrole **599**:[727]

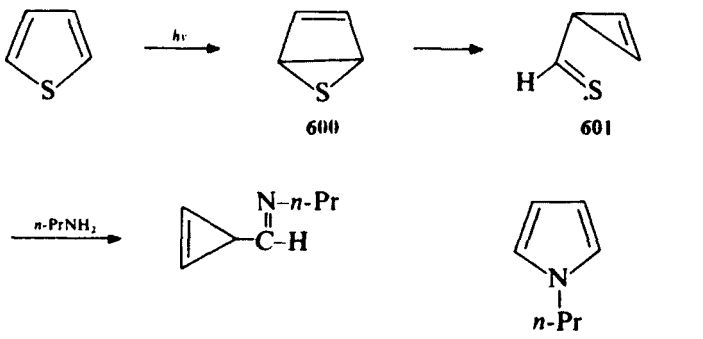


(196)

a. R = OEt
b. R = Me

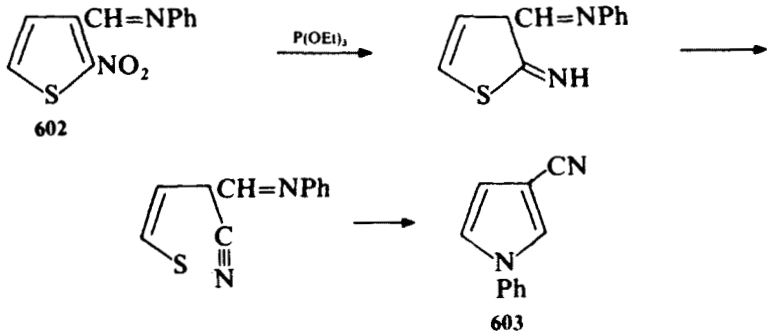
2.8.1.3. Thiophenes

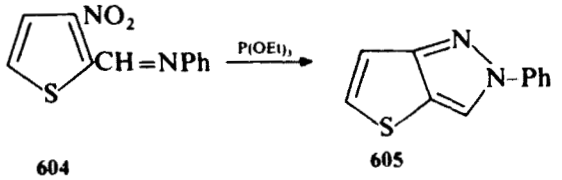
The photolysis of thiophene in the presence of *n*-propylamine yields 1-*n*-propylpyrrole and sulfur. However, the reaction is not the simple replacement of the sulfur since 2-methylthiophene gives a 5:1 mixture of 1-*n*-propyl-2- and 3-methylpyrroles. The suggested mechanism involves the initial formation of the valence isomer **600**, which rearranges to the cyclopropenylthioaldehyde (**601**), with loss of identity of positions 2 and 3. Exchange with the amine and ring closure produces the 1-substituted pyrroles:[728]



(197)

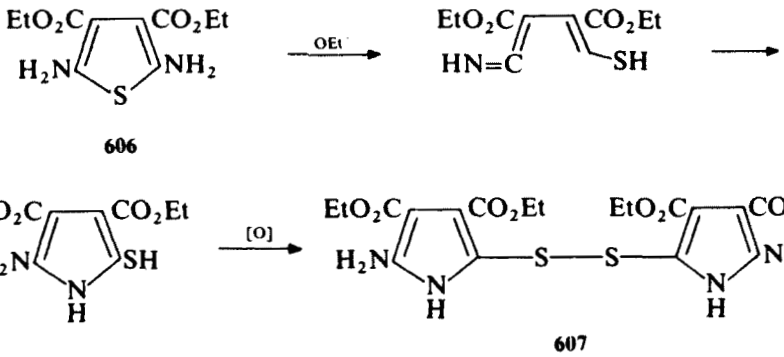
Reduction of the anil of 3-formyl-2-nitrothiophene **602** with triethyl phosphite produces the pyrrole-3-carbonitrile **603**. With the reverse orientation of substituents, as in **604**, however, a thieno[3,2-*c*]pyrazole **605** results:[729,730]





(198)

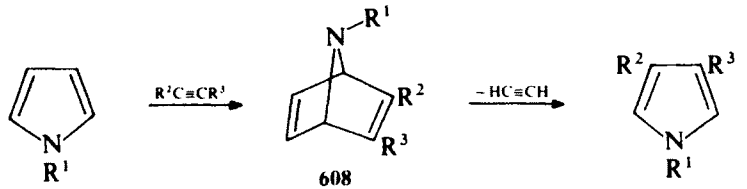
Treatment of the diaminothiophene **606** with base gives the bis(2-amino-5-pyrrolyl)disulfide **607**:[731]



(199)

2.8.1.4. Pyrroles

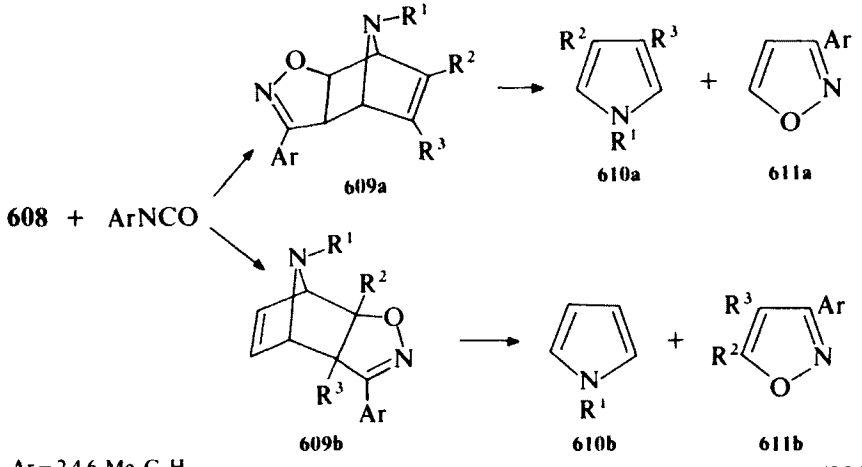
Although 1-alkylpyrroles generally undergo Michael addition reactions with dimethyl acetylenedicarboxylate,[732] pyrroles having an electron-withdrawing group at the 1 position undergo a Diels–Alder cycloaddition. The bicyclo[2.2.1]azaheptadiene **608** undergoes a retro-Diels–Alder reaction with loss of acetylene (Eq. 200).[17,733–735] Other alkynes used in the initial cycloaddition include ethyl phenylpropiolate (for the preparation of a pyrrolnitrin precursor)[736] and di(trifluoromethyl)ethyne.[737,738]



(200)

R^1	R^2	R^3
CO_2Et	CO_2Me	CO_2Me
CO_2t-Bu	CF_3	CF_3
CO_2Et	m-$NO_2C_6H_4$	CO_2Me

Incorporation of the extruded acetylene in an aromatic system assists the retro-reaction, since only gentle heating of the cycloadducts **609** leads to reversion to the pyrrole **610** and isoxazole **611**:[738,739]

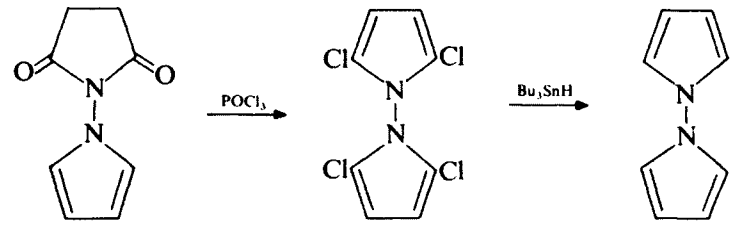


(201)

R^1	R^2	R^3
CO_2Et	CO_2Me	CO_2Me
CO_2t-Bu	CF_3	CF_3

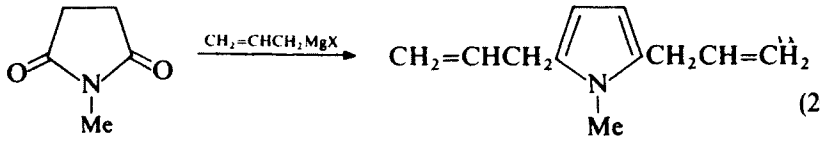
2.8.1.4.1. Succinimide

The reduction of succinimides can lead to the pyrroles. Thus, chlorination of *N*-(1-pyrrolyl)succinimide yields 2,2′5,5′-tetrachloro-1,1′-bipyrryl, which on reduction with the tributyltin gives 1,1′-bipyrryl:[740]



(202)

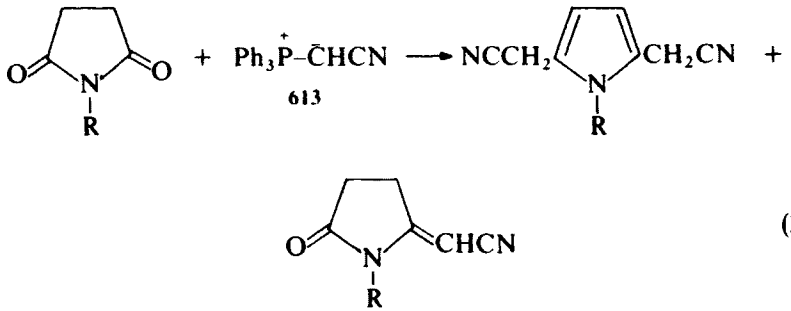
The reaction of *N*-methylsuccinimide with the allyl Grignard reagent yields the 2,5-diallylpyrrole **612**:[741]



(203)

612

Reaction of the phosphorane **613** with the *N*-substituted succinimides produces a mixture of the 2,5-di(cyanomethyl)pyrrole and the pyrrolidone **614** (Eq. 204). When R is an aryl group, the pyrrole predominates.[742]



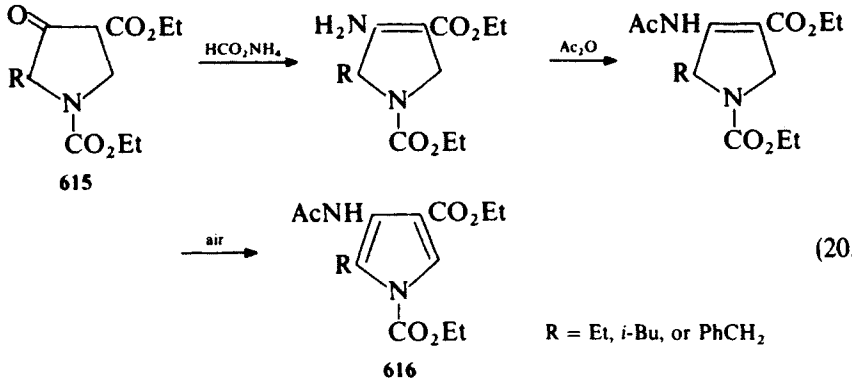
(204)

R = H, Me, or Ph

614

2.8.1.4.2. Pyrrolidines and Pyrrolines

A number of methods for the conversion of pyrrolines into pyrroles have been developed. In many cases, air oxidation is sufficient since, as mentioned earlier, whereas the stoichiometry of many reactions indicates that a pyrroline should result, it is the pyrrole which is isolated. A specific example is illustrated by the conversion of the pyrrolidone **615** into the 3-acetamidopyrrole **616**:[743]

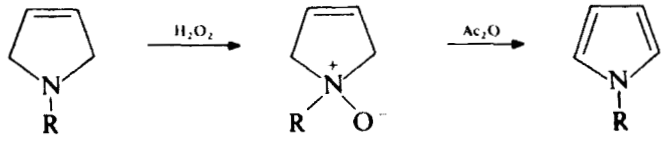


(205)

R = Et, *i*-Bu, or $PhCH_2$

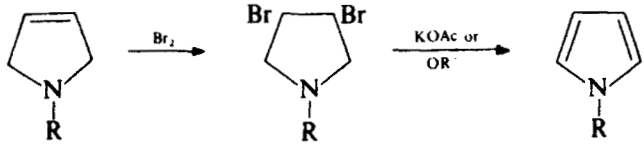
615 **616**

Nickel(IV) oxide has been used to aromatize Δ^3-pyrrolines[744] and treatment of Δ^3-pyrrolines **617** with acetic anhydride produces the pyrrole **618**:[745]

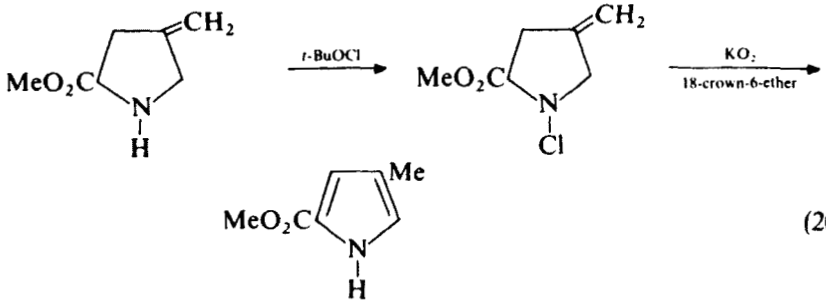


617 **618** (206)

Halogenation-dehydrohalogenation reactions have been utilized on several occasions to convert pyrrolines into pyrroles:[746–748]

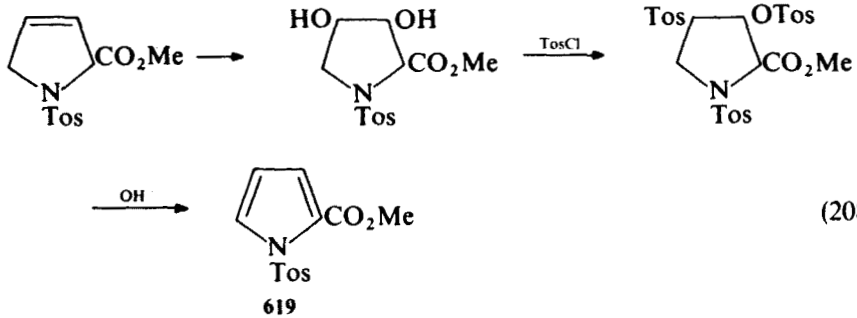


R = $PhCH_2$ or $PhSO_2$



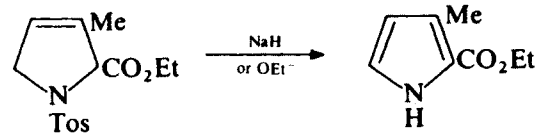
(207)

In a similar manner, the sequence of glycol formation, ditosylation, and treatment with base has been used in the preparation of the pyrrole **619**:[749]



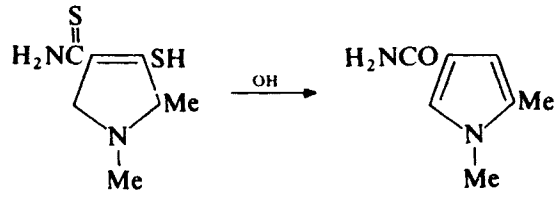
619 (208)

A number of papers have reported the conversion of the readily available 1-arenelsulfonylpyrrolines **620** into pyrroles **621** through elimination of the sulfonyl group on treatment with base:[750–753]



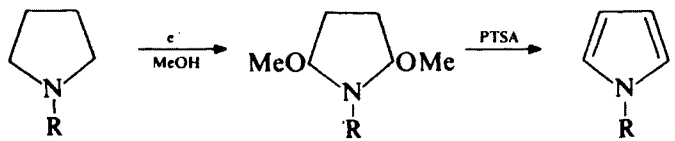
620 621 (209)

There is one report of aromatization through the loss of sulfide from the 3-mercaptopyrroline **622**:[754]



622 (210)

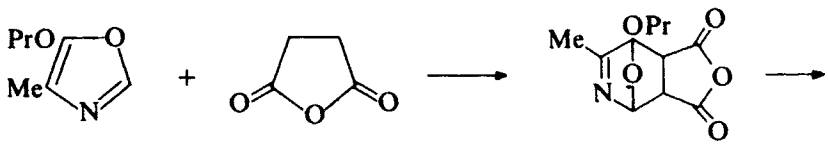
Catalytic dehydrogenation of pyrrolidines can be utilized for their conversion into the corresponding pyrroles.[755] Also, the electrolytic oxidative methoxylation of pyrrolidines has been reported.[756] Treatment of the 2,5-dimethoxypyrrolidines with acid eliminates two molecules of methanol with the formation of the pyrroles **623**:



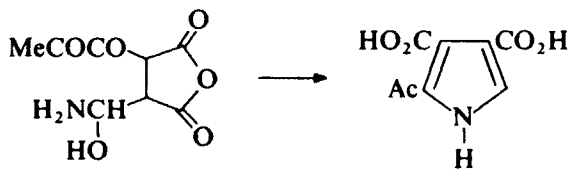
623 (211)

2.8.1.5. Oxazoles and Isoxazoles

Ring opening of the Diels–Alder cycloadduct **625**, derived from the oxazole **624** and maleic anhydride, followed by reclosure, yields the 2-acylpyrrole **626**:[757]

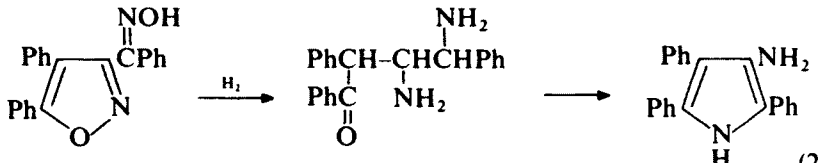


624 625



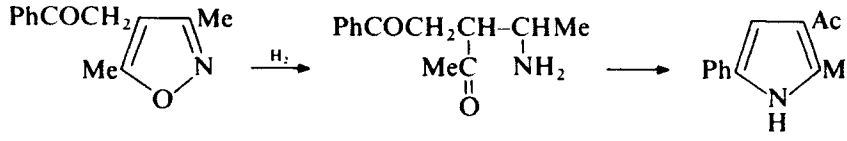
626 (212)

Hydrogenation of the oxime of the 3-benzoylisoxazole **627** gives the 3-aminopyrrole **629**, presumably through ring opening to **628** and then closure on the alternate nitrogen atom:[758]



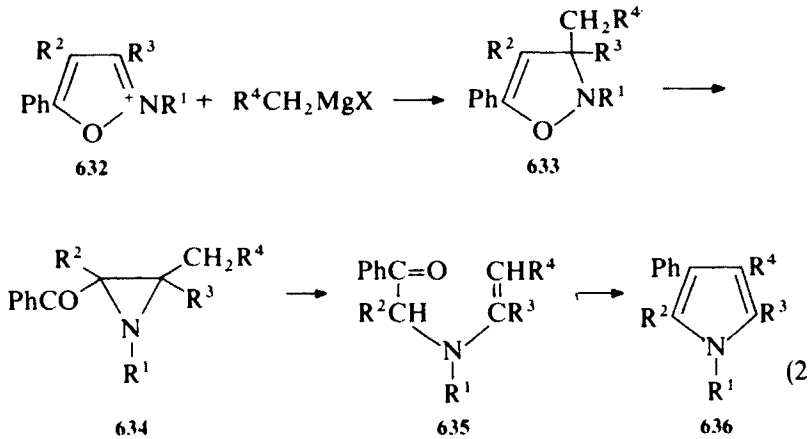
627 628 629 (213)

Likewise, the isoxazole **630** is transformed into the 3-acetylpyrrole **631**:[758]



630 631 (214)

The reaction of a Grignard reagent with isoxazolium salts **632** produces 3-substituted pyrroles **636** (Eq. 215).[759,760] It was suggested that the intermediate isoxazolidone **633** initially rearranges to the aziridine **634**, which then opens to the enamine **635**, analogous to that postulated as an intermediate in the Knorr synthesis (see Table 2.60).

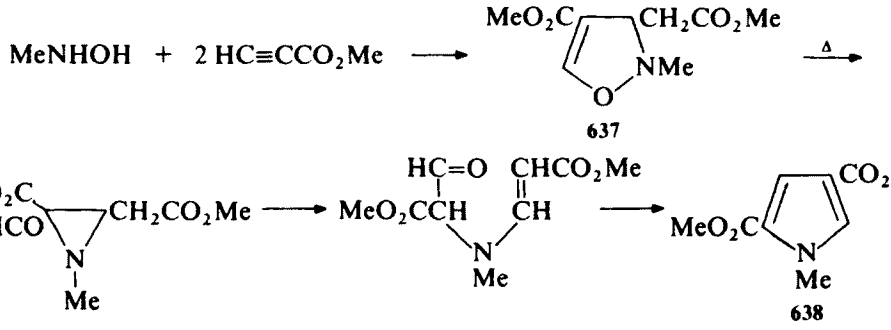


632 633 634 635 636 (215)

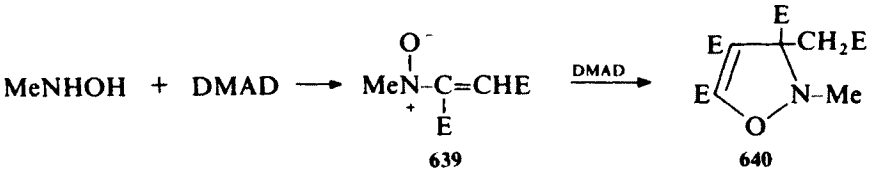
In a similar manner, isoxazolidine **637**, formed by the reaction of *N*-methylhydroxylamine with two molecules of methyl propiolate, rearrange to the pyrrole **638**:[761]

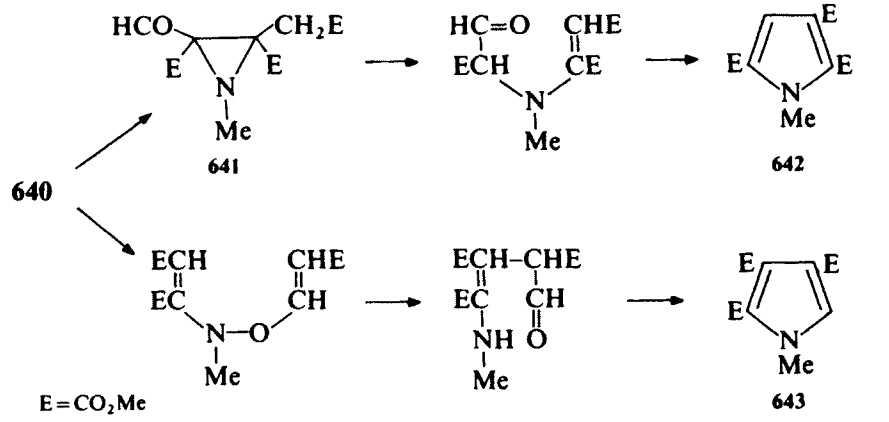
TABLE 2.60. PYRROLES (636) FORMED FROM ISOXAZOLIUM SALTS

R^1	R^2	R^3	R^4	Ref.
Me	Me	H	Ph	759, 760
Me	H	H	Ph	759, 760
Me	H	H	*p*-Tol	759, 760
Me	H	H	*p*-ClC_6H_4	759, 760
Me	H	Me	Ph	759
Me	Me	Me	Ph	759
Me	H	H	H	759
Ph	Me	H	Ph	759
Me	Me	H	Ph	759



(216)





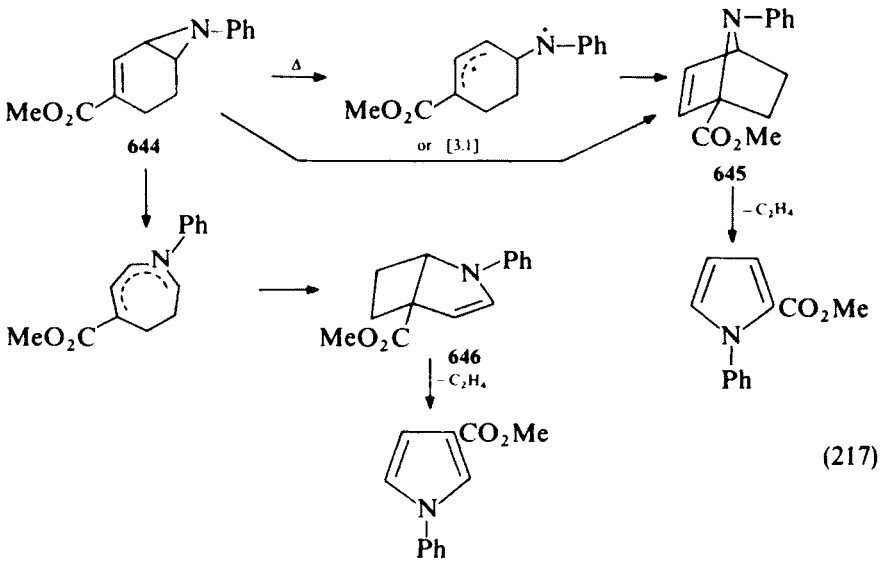
Scheme 39

The addition of the nitrone **639** to DMAD produces an isoxazoline **640**, which rearranges on heating into a mixture of the two isomeric pyrroletricarboxylates **642** and **643**, one through the aziridine **641** and the other by a Piloty-type rearrangement (Scheme 39).[762]

2.8.2. From 6-Membered Rings

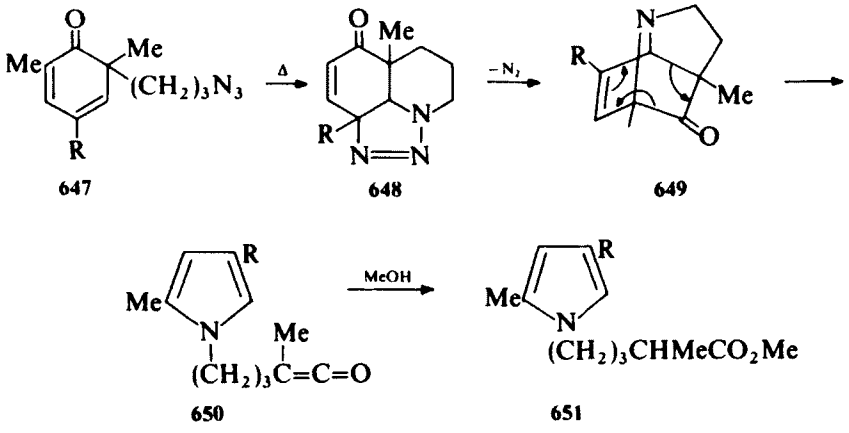
2.8.2.1. Cyclohexanes

There are two reports of pyrroles being derived from the cyclohexyl series. In the first, thermolysis of **644** produces a 3 : 2 mixture of methyl 1-phenylpyrrole-2- and -3-carboxylates (Eq. 217).[763] It has been proposed that the 2-isomer is formed through the formation of the 7-azabicyclo[2.2.1]heptene **645**, through either a diradical process or a sigmatropic shift, followed by elimination of ethene in a retro-Diels–Alder reaction. The formation of the 3-isomer could result from the opening of the aziridine system and subsequent ring closure to the 2-azabicyclo[3.1.1]heptene **646**.



(217)

In the second example, thermolysis of the azidopropylcyclohexadienone **647** produces the pyrrole **651**, which has the 6-carbon unit attached to the 1 position.[764] The mechanism is assumed to involve the initial formation of the reduced triazolopyridine **648**, which on loss of nitrogen rearranges to the tricyclic compound **649**. A retro-Diels–Alder reaction would form the pyrrole derivative **650**, and reaction of the ketene with the alcoholic solvent yields **651**:



647 648 649 650 651

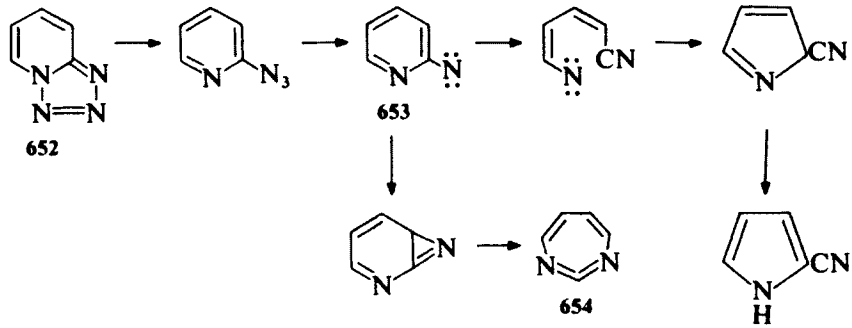
R = CO_2Me or CH_2OAc

(218)

2.8.2.2. Pyridines

2.8.2.2.1. Pyridines

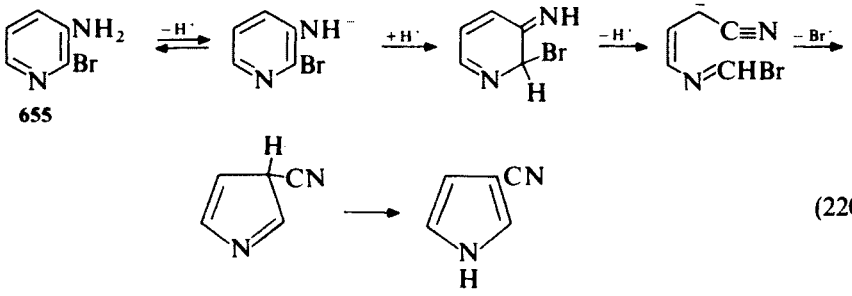
Gas phase thermolysis of the triazolopyridine (**652**) produces about equal amounts of the 2-cyanopyrrole and the cyclic carbodiimide **654** (Eq. 219).[765] Presumably, the nitrene **653**, formed from 2-azidopyridine, ring-opens and then recloses to give the pyrrole. The carbodiimide may result from insertion of the nitrene and opening of the azirine.



652 653 654

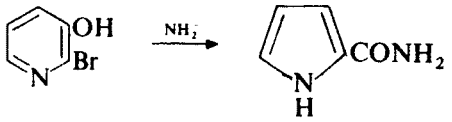
(219)

3-Cyanopyrrole can be formed from the 2-bromo-3-aminopyridine (**655**) on treatment with sodamide (Eq. 220).[766] This reaction is specific since the other isomers of **655** simply undergo nucleophilic substitution of the halogen.



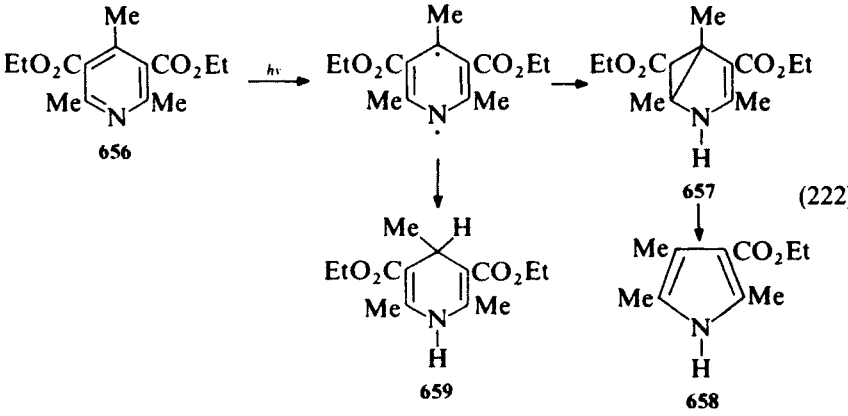
(220)

In contrast, 2-bromo-3-hydroxypyridine produces pyrrole-2-carboxamide:[767]



(221)

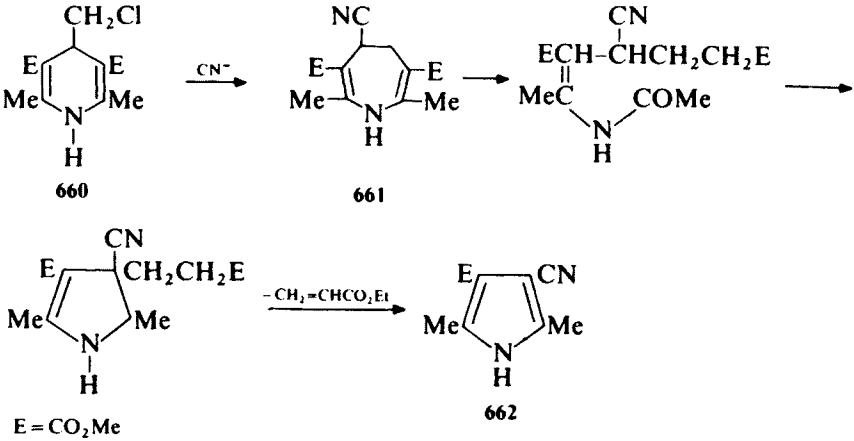
Photolysis of the symmetrical diester **656** produces both the dihydropyridine **659** and pyrrole-3-carboxylate **658** in an approximately 2 : 1 ratio (Eq. 222).[768] It is suggested that the pyrrole results from extrusion of methoxycarbonylcarbene from the photochemically produced homopyrrole **657**.



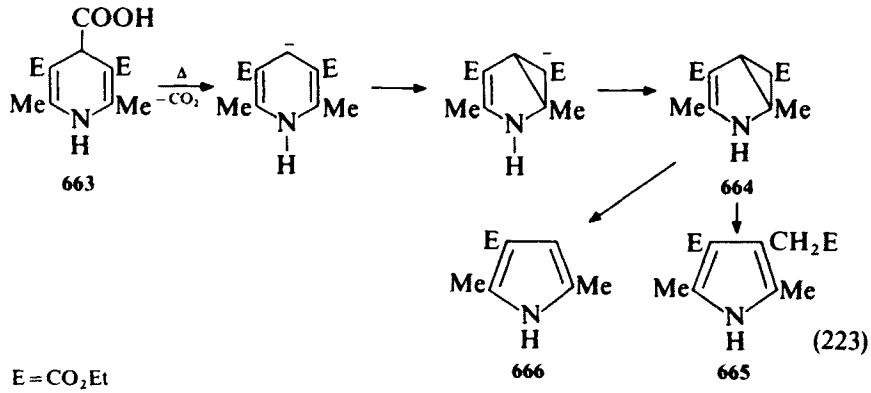
(222)

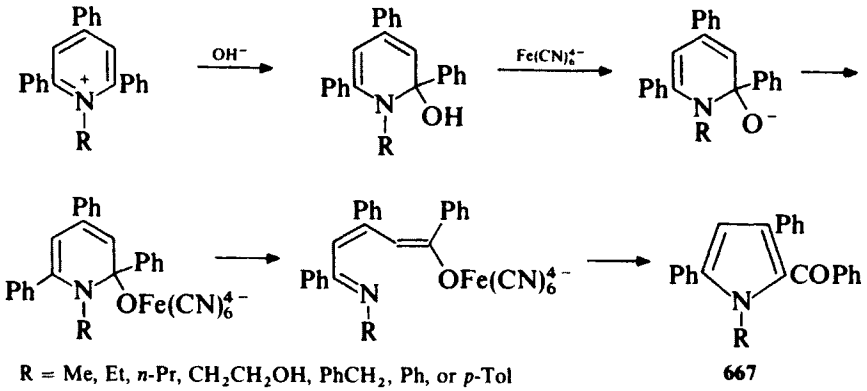
Several papers have discussed the transformation of 4-(chloromethyl)-1,4-dihydropyridine **660** into the 3-cyanopyrrole **662** through the action of cyanide ion.[769–771] The suggested mechanism involving an azepine intermediate **661** and loss of methyl acrylate is shown in Scheme 40.

The decarboxylation of the 1,4-dihydropyridine-4-carboxylic acid **663** gives only a small amount of the expected pyridine but produces about equal amounts of the two pyrroles **665** and **666** (Eq. 223).[772,773] It has been proposed that the homopyrrole **664** is formed on the loss of carbon dioxide and can either open to the 3-pyrrolylacetate **665** or lose the methoxycarbonyl carbene to produce **666**.



Scheme 40



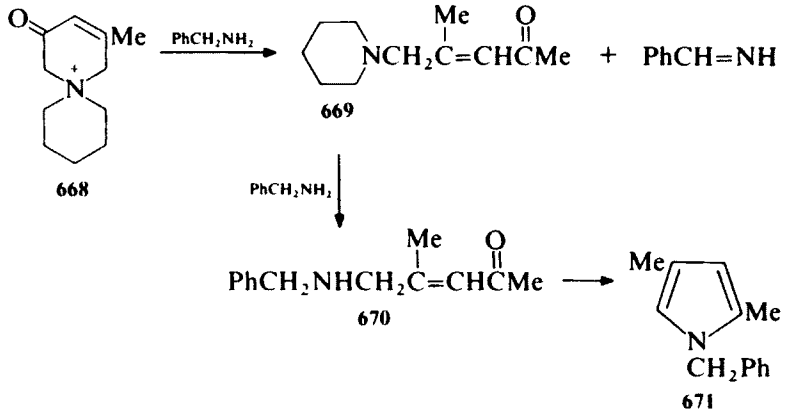


Scheme 41

2.8.2.2.2. Pyridinium Ions

Oxidation of the *N*-substituted 2,4,6-triphenylpyridinium ions by the ferricyanide ion leads to the benzoylpyrrole **667** in 65–97% yields.[774] The mechanism proposed for this transformation is given in Scheme 41.

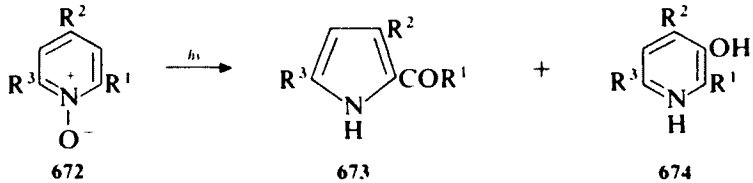
Treatment of the quaternary salt **668** with benzylamine produces the 1-benzylpyrrole **671** (Eq. 224).[775] It is suggested that reduction of **668** by hydride transfer from the amine causes ring opening to the 5-amino-3-penten-2-one **669**, which undergoes transamination to **670** and then ring closure to the pyrrole.



(224)

2.8.2.2.3. Pyridine 1-Oxides

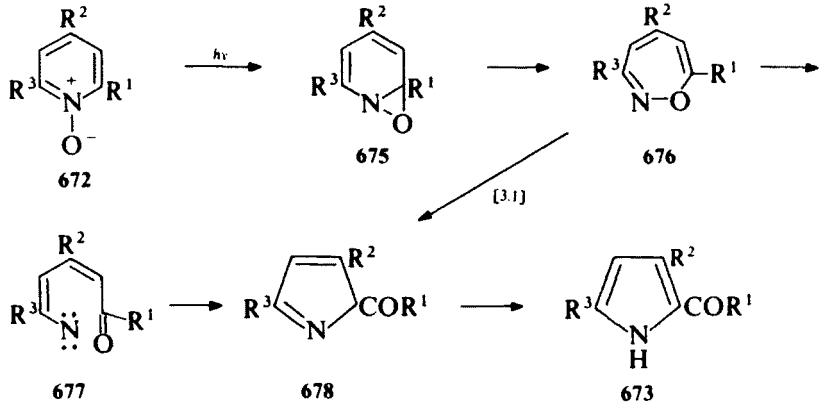
Photolysis of pyridine 1-oxides **672** in an inert solvent simply produces deoxygenation,[776,777] but in a polar solvent ring contraction occurs to yield 2-acylpyrroles **673**, together with the 3-hydroxypyridines **674**. For example, pyridine 1-oxide gives the 2-formylpyrrole.



(225)

As shown in Scheme 42, the mechanism for the reaction is believed to involve the initial excitation of the 1-oxide and formation of **675**, followed by opening to the 1,2-oxazepine **676**. Conversion into the pyrrole may involve the nitrene **677**, which ring-closes, or, alternatively, via a direct [3.1] sigmatropic shift from **676** to **678**.[778]

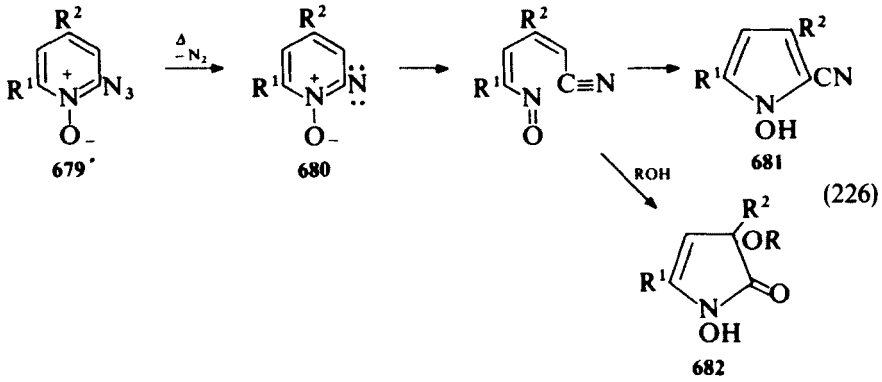
In the early studies, the yield of pyrroles was poor (1–5%), but Streith has found that the addition of copper salts to the photolysis medium raised the yields to about 40%.[779] It has been suggested that the copper ion acts in a reversible electron transfer process.[780] When there are substituents at position 2 of the pyridine ring, it is possible for oxaziridine formation to occur in either



Scheme 42

direction. In some cases both products are observed, while in other reactions the substituent is found to be attached only to the carbonyl group. For example, 2-aminopyridine 1-oxide yields pyrrolylcarboxamides,[781] and 2-cyanopyridine 1-oxides produce the acyl nitriles.[782] In contrast, a 2-methylpyridine 1-oxide yields both 2-acetyl and 2-formyl-5-methyl pyrroles[783] (see Table 2.61).

Abramovitch has found that the thermolysis of 2-azidopyridine 1-oxides **679** produces the 2-cyano-1-hydroxypyrroles **681** via the nitrenes **680**.[786]



(226)

R^1	R^2	Ref.
H	H	786–788
Me	H	786, 788, 789
H	Me	786–789
Me	Me	789

When there is a substituent at position 3, a 2*H*-pyrrole is formed.[790] If alcohols are used as the solvent instead of benzene or other inert solvent, the 3-methoxypyrroline **682** is isolated.[787,789]

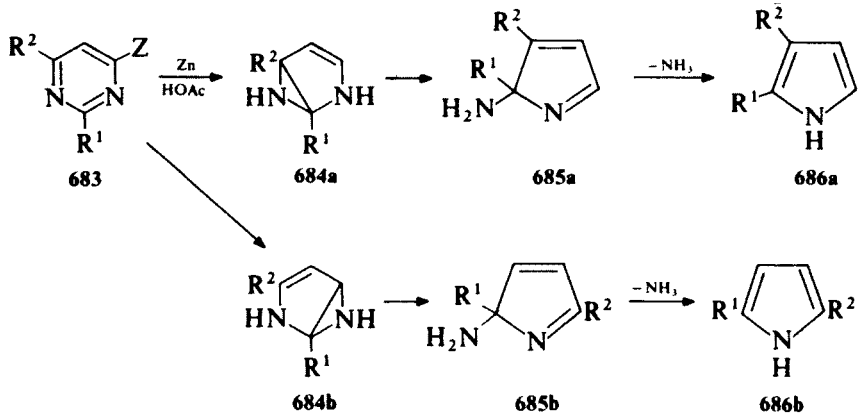
TABLE 2.61. PYRROLES (673) FORMED BY PHOTOLYSIS OF PYRIDINE 1-OXIDES

R^1	R^2	R^3	Ref.
H	H	H	779, 783
H	H	Me	783
Ph	Ph	Ph	784
CN	H	CN	782
Me	Me	Me	785
NH_2	H	H	781
H	Me	H	778–780
H	MeO	H	778–780
H	Ph	H	778–780
H	Cl	H	778–780
H	CN	H	778–780

[a]With Cu^{2+}.

2.8.2.3. *Pyrimidines*

The reduction of the 4-substituted 2-arylpyrimidines **683** by zinc in acetic acid leads to the formation of the 2,3- and 2,5-pyrroles **686**.[791,792] Although the 6-chloro derivative was used in some instances, this is unnecessary and is apparently reductively removed in the initial steps. As indicated in Scheme 43, the suggested mechanism involves the formation of the bridged species **684a** or **b**, which ring-opens to yield the aminopyrrolines **685**. Subsequent loss of ammonia produces the two pyrrole systems.



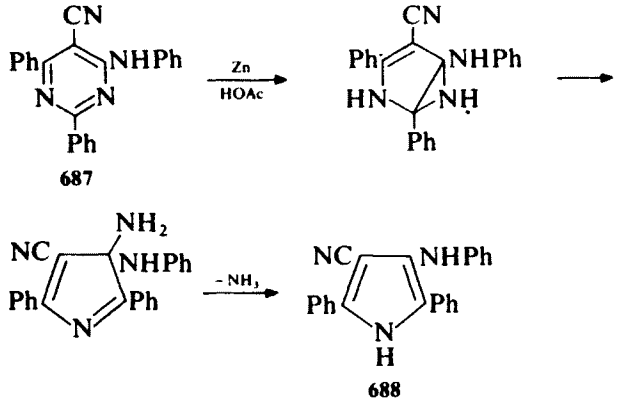
683 684a 685a 686a

684b 685b 686b

R^1	R^2	Z
Ph	Me	Cl
Ph	Me	H
Ph	Cl	Cl

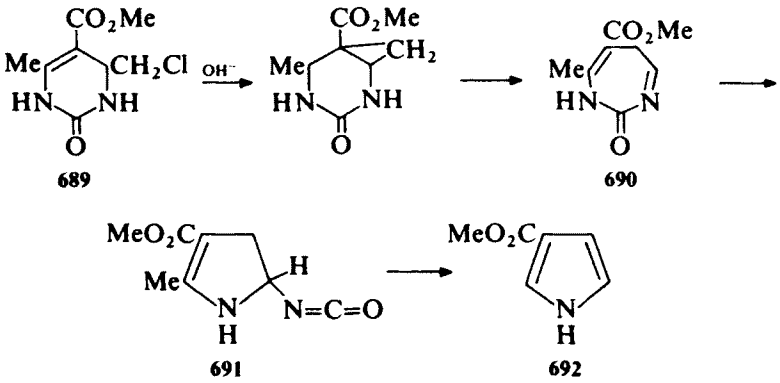
Scheme 43

Reduction of the 4-anilinopyrimidines **687** occurs in a similar manner, although the initial bridging apparently occurs in only one direction leading to the 3-anilinopyrrole **688** as the sole product (Eq. 227) (50–80%).[793–795] Also, only ammonia is eliminated in the last step.



687 688 (227)

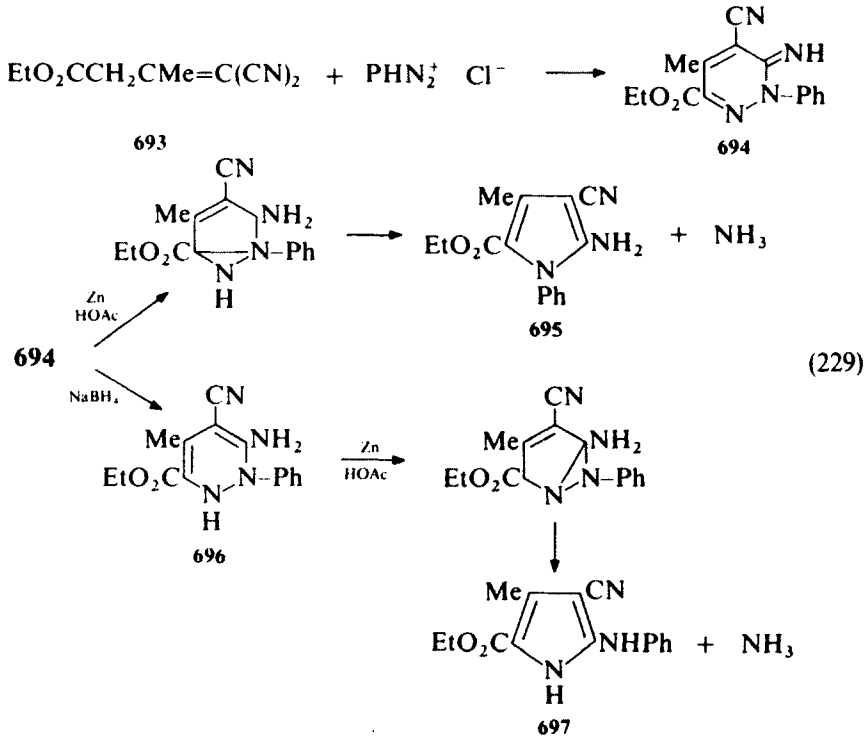
Treatment of the 4-chloromethyldihydropyrimidone **689** with base causes a ring contraction with loss isocyanate (Eq. 228).[796] The proposed mechanism involves an initial cyclopropane ring formation, followed by a ring opening to the diazepine **690**. A sigmatropic shift leads to the pyrroline **691**, which then loses HCNO to form the pyrrole **692**.



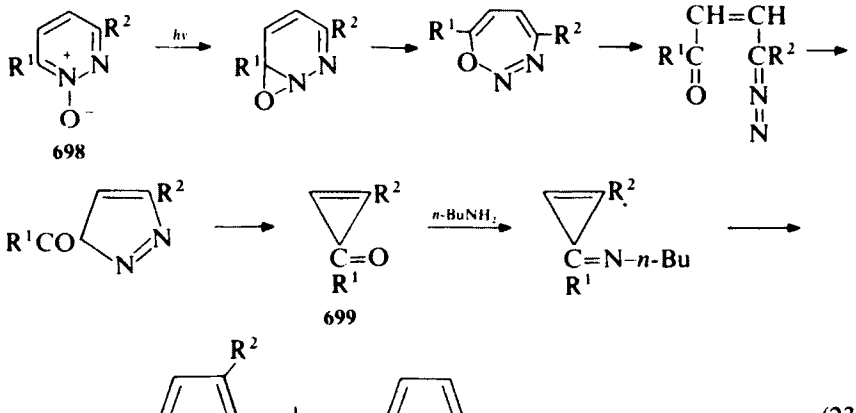
689 690 691 692 (228)

2.8.2.4. Pyridazines

Zinc reduction of the dihydropyridazines **694**, produced by the reaction of diazonium salts with the dinitrile **693**, causes ring contraction to the 1-phenyl-2-aminopyrrole **695** (Eq. 229). If sodium borohydride is initially used as the reducing agent, however, the resulting dihydropyridazine **696** can be further reduced by zinc to give the 2-anilinopyrrole **697** with incorporation of the alternate nitrogen atom.[797,798]



(229)

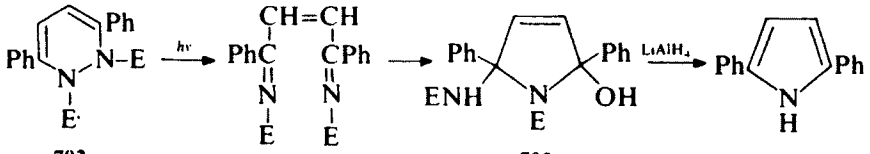


(230)

R^1	R^2
H	H
Me	H
Me	Me

In the presence of a primary amine, photolysis of the pyridazine 1-oxide **698** apparently occurs via the cyclopropenyl ketone **699**, since both isomers **700** and **701** are formed.[799,800]

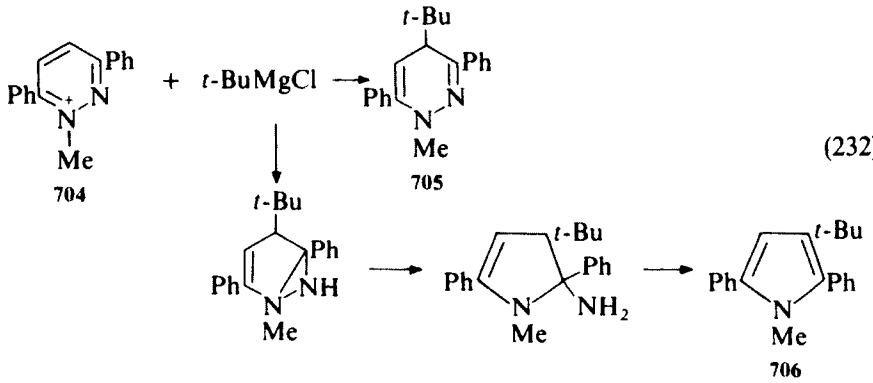
Photolysis of the dihydropyridazine **702** yields the Δ^3-pyrroline **703**, which is converted into 2,5-diphenylpyrrole by reduction with lithium aluminum hydride:[801]



702 **703**

E = CO_2Et (231)

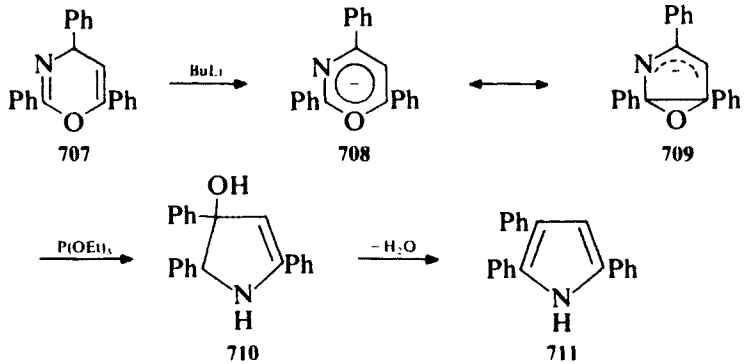
The pyridazinium ions **704** react with the Grignard reagent to give a mixture of the dihydropyridazine **705** and the pyrrole **706**.[802]



704 **705** **706** (232)

2.8.2.5. Oxazines

There is one report of the conversion of the 4*H*-1,3-oxazine **707** into the pyrrole **711** through the anion **708** for which the epoxide structure **709** is a

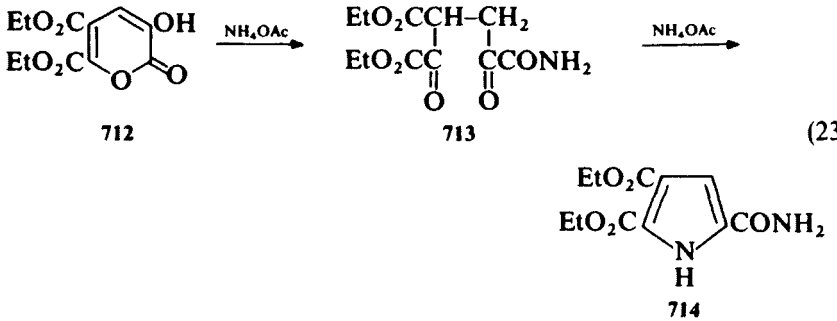


707 **708** **709** **710** **711** (233)

possible valence isomer. Reduction of **708** with triethyl phosphite gives the hydroxypyrroline **710**, which on loss of water yields **711**.[803]

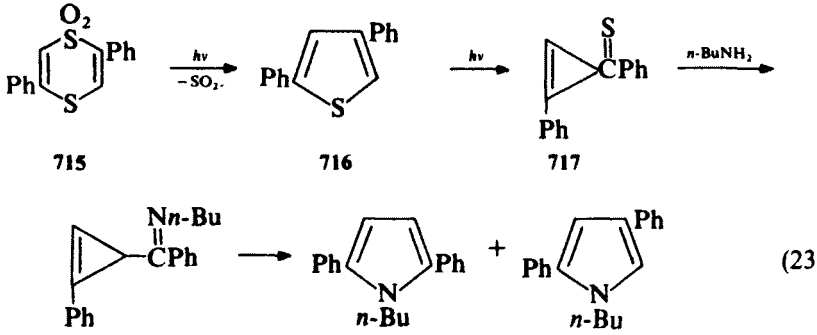
2.8.2.6. Other 6-Membered Ring Systems

The reaction of the 3-hydroxypyr-2-one **712** with ammonium acetate gives the 2-pyrrolylcarboxamide **714** via the intermediate 1,4-dione **713**:[804]



712 **713** **714** (234)

Photolysis of the 1,4-dithiin-1,1-dioxide **715** in the presence of *n*-butylamine gives 2,5-diphenyl- and 2,4-diphenyl-1-*n*-butylpyrrole via the initial transformation into the thiophene **716** and subsequent rearrangement to the cyclopropenylthioaldehyde **717**, as described in Section 2.8.1.3 leads to the two pyrroles:[805]

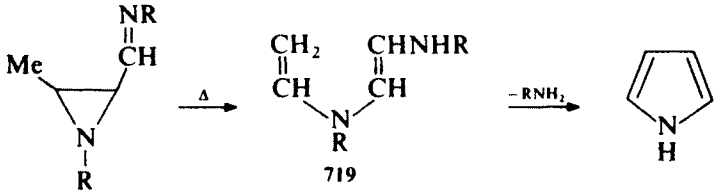


715 **716** **717** (235)

2.8.3. From Other Ring Systems

2.8.3.1. 3-Membered Rings

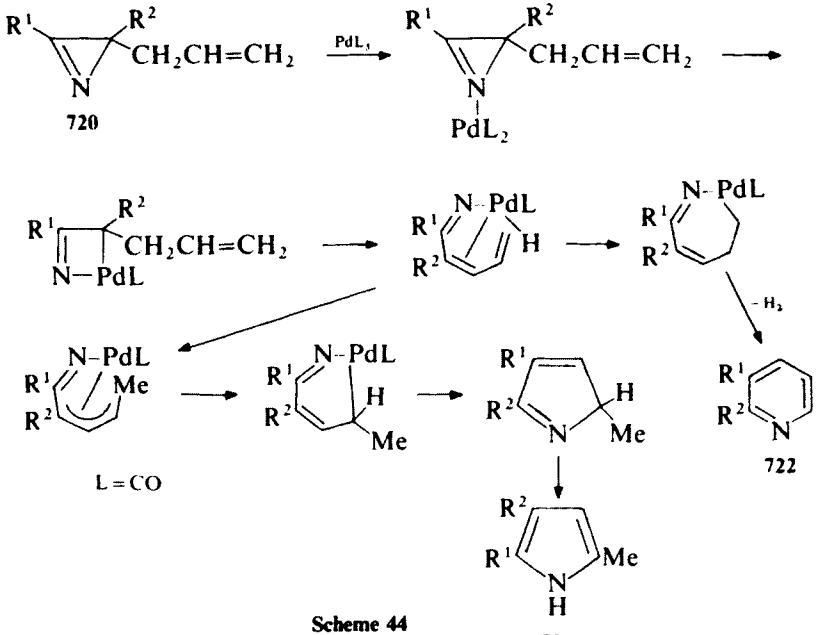
1-Alkylpyrroles result from the thermolysis of **718** via a [1,5] *H*-sigmatropic shift with C_2–C_3 bond breaking to give the divinylamine **719**, which ring-closes with loss of amine: [806]



(236)

R = Et, *i*-Pr, or *t*-Bu

Under the influence of palladium(0) complexes, 2-allylazirines **720** undergo a ring enlargement to give the pyrrole **721** and the pyridine **722**. The suggested mechanism is shown in Scheme 44.[807]

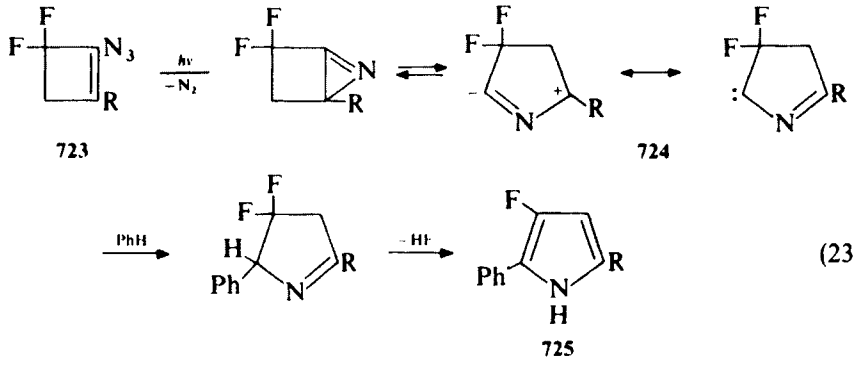


Scheme 44

R^1	R^2	721 (%)	722 (%)
Ph	Me	20	18
Me	Ph	18	10
Ph	H	14	45

2.8.3.2. 4-Membered Rings

Internal insertion of the nitrene, produced by the photolysis of the azidocyclobutene **723** in benzene, leads to the formation of the carbene **724**, which adds to the benzene and produces the pyrrole **725** in 90% yield:[808]

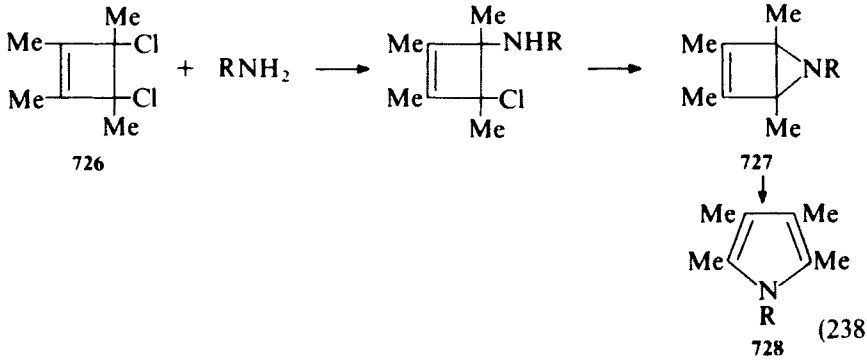


723 724 725

(237)

R = CO_2Me or CN

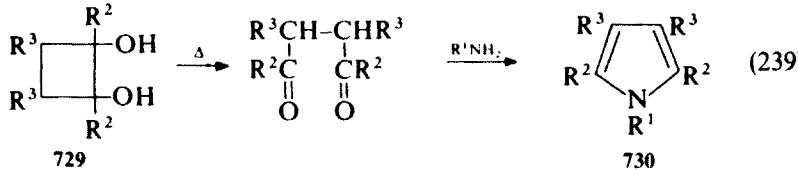
Reaction of an amine with the dichlorocyclobutene **726** produces the pyrrole **728**, possibly by way of the "Dewar-type" pyrrole **727**:[809]



726 727 728

(238)

In a somewhat similar reaction, thermal ring opening of the diol **729** to the diketone has been suggested as the route to the pyrrole **730**:[810]

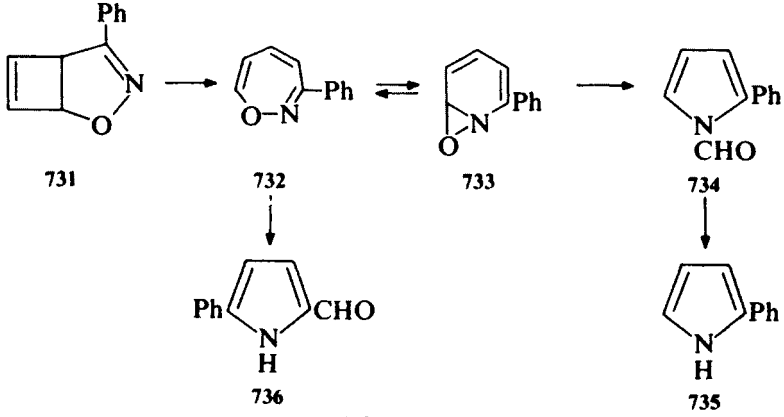


729 730

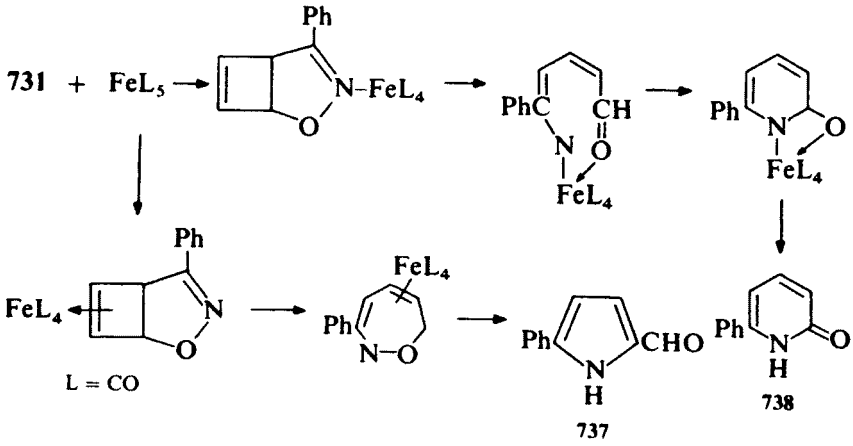
(239)

A number of papers have described the conversion of the 2-oxa-3-azabicyclo[3.2.0]heptadiene **731** into pyrroles **734**, **735**, and **736**. The reaction presumably involves the intervention of the oxazepines **732** and **733** (Scheme 45).[811–813] More recently the reaction of **731** with iron pentacarbonyl has been reported to produce **737** and the pyridone **738**. The two products result from different sites for complex formation (Scheme 46).[814]

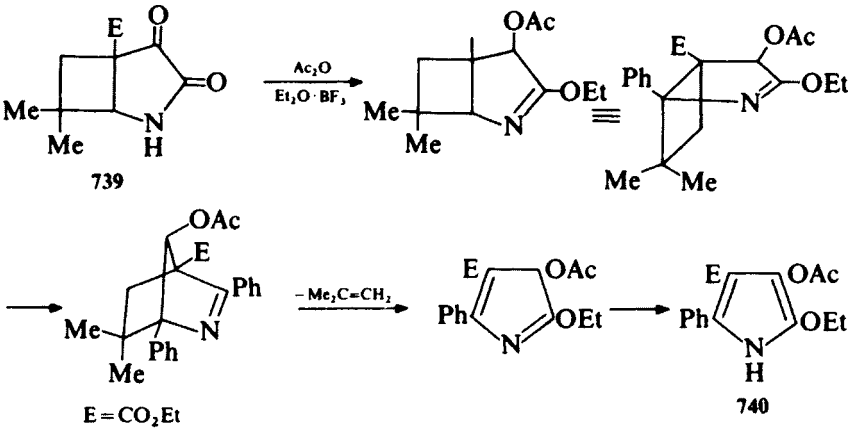
The azabicyclo[3.2.0]heptanedione **739** is converted into the pyrrole **740** via a sequence of steps including a retro-Diels–Alder reaction (Scheme 47).[815]



Scheme 45

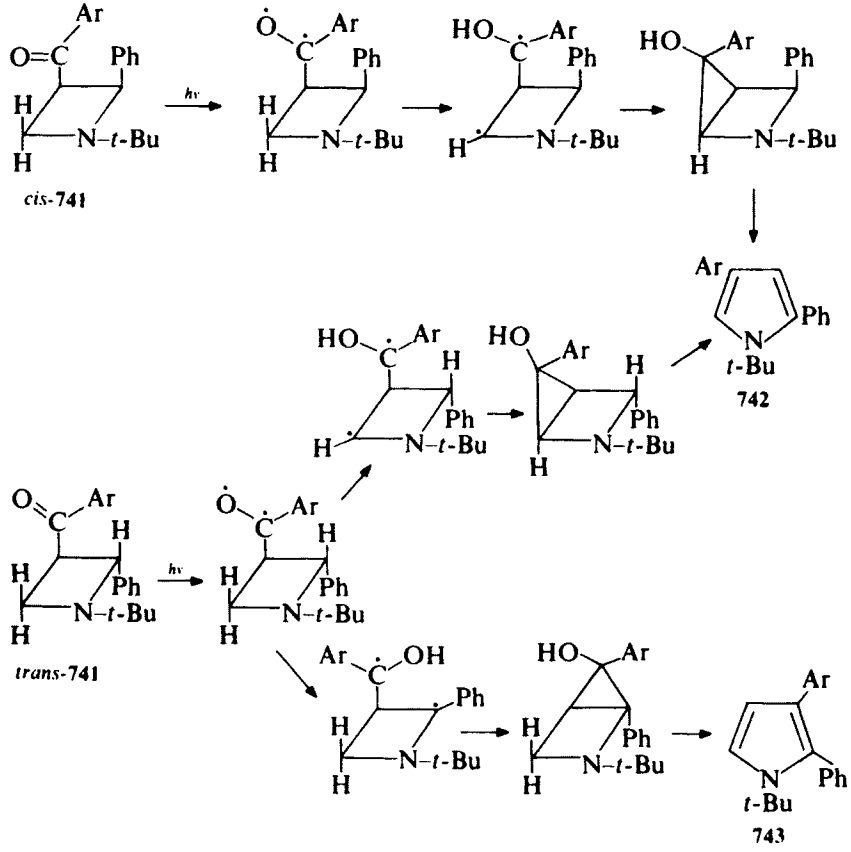


Scheme 46



Scheme 47

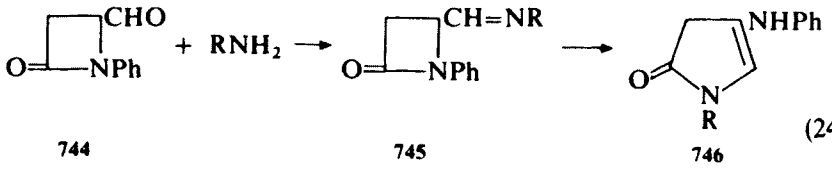
The photochemical ring expansion of the cis- and trans-isomers of 1-alkyl-3-aroyl-2-phenylazetidines **741** yields different diarylpyrroles; the cis-isomer gives the 2,4-diaryl pyrrole **742**, whereas both the 2,3- and 2,4-diarylpyrroles **743** and **742** are obtained from the trans-isomer. With the cis-isomer, proton abstraction by the initially formed excited triplet state can only occur with the hydrogen at position 4, whereas in the trans-isomer either the 2- or 4-proton can be abstracted, leading to both products (Scheme 48).[816–820]



Scheme 48

Azetidinones (β-lactams) can be considered as C–C–N–CO synthons. The reaction of primary amines with the 4-formyl-1-phenylazetidin-2-one **744** leads to the 4-amino-2-pyrrolidones **746**. The reaction sequence probably involves the initial formation of the imine **745**, which attacks the lactam linkage:[821]

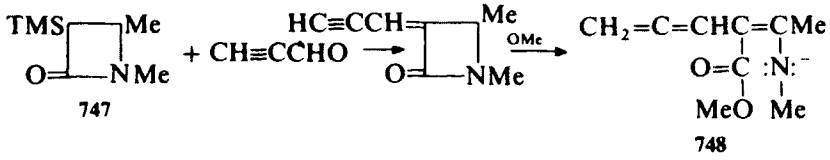
In another reaction, when the trimethylsilyl derivative of the azetidinone **747** is allowed to condense with the propynal, ring expansion via the allene **748** produces methyl 1,2,5-trimethylpyrrole-3-carboxylate (Scheme 49).[822]



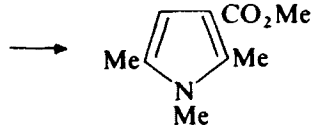
744 745 746

R = *n*-Bu, *i*-Bu, or $PhCH_2CH_2$

(240)



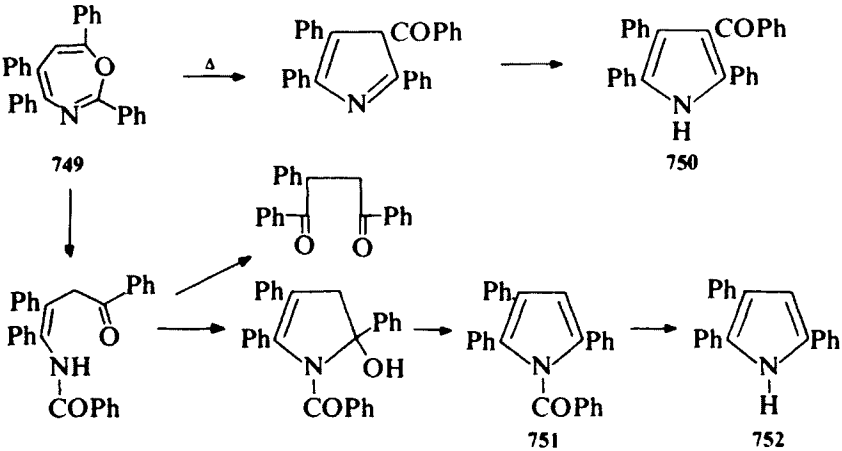
747 748



Scheme 49

2.8.3.3. 7-Membered Rings

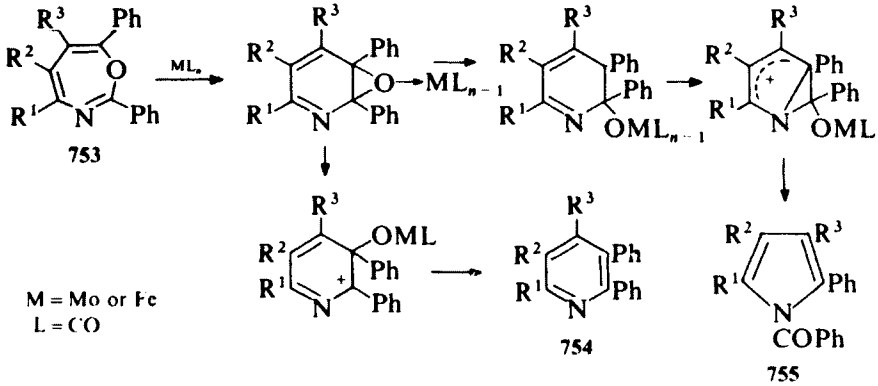
Thermolysis of the 1,3-oxazepine **749** results in the formation of an almost quantitative yield of the 3-acylpyrrole **750**. The same pyrrole is also produced together with 1,2,4-triphenylbutan-1,4-dione by base-catalyzed hydrolysis. Acid-catalyzed hydrolysis also gives **750** together with the 2,3,5-triphenylpyrroles **751** and **752** (Scheme 50).[823]



749 750 751 752

Scheme 50

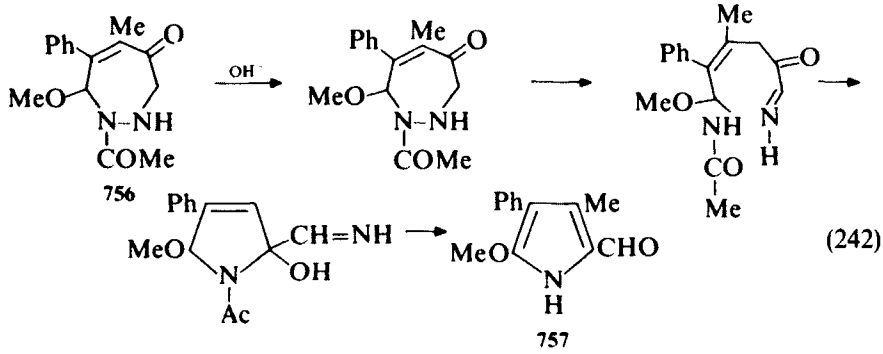
The use of molybdenum or iron carbonyl causes the transformation of the oxazepine **753** into the pyridine **754** and 1-benzoylpyrrole **755**:[824]



(241)

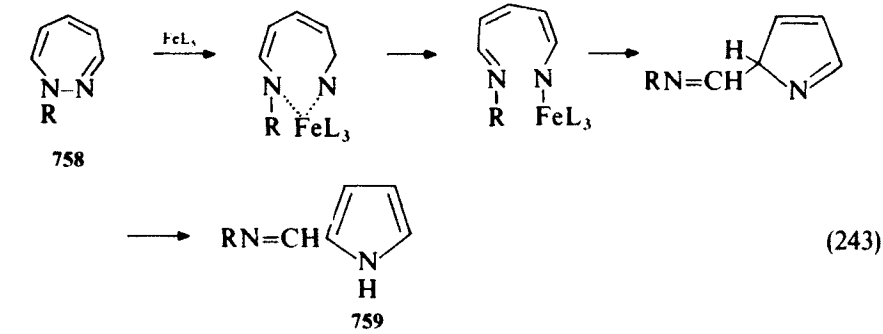
R^1	R^2	R^3	Ratio (754 : 755)
Ph	H	Ph	0.33 : 1
H	Ph	H	4 : 1
H	H	H	14 : 1

Treatment of the tetrahydro-1,2-diazepin-4-one **756** with base yields the anil of the 2-formylpyrrole **757**:[825]



(242)

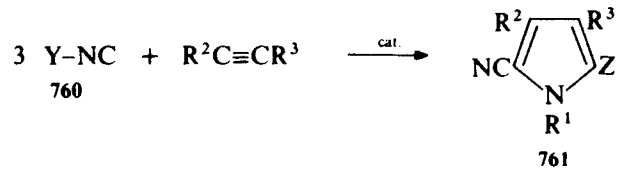
A similar reaction is observed with iron pentacarbonyl and the diazepine **758** to give an anil **759**:[826]



(243)

2.9. MISCELLANEOUS METHODS

The nickel- or palladium-catalyzed reaction of three molecules of either the *t*-butyl or trimethylsilylisocyanide (**760**) with an alkyne can lead to the formation of a 5-amino-2-cyanopyrrole **761** with yields in excess of 85% (Eq. 244). It has been suggested that the reaction occurs via a metal–isocyanide complex, similar to a carbene-metal complex.[827] Although the nickel-catalyzed reaction is non-regiospecific (e.g., the reaction with phenylacetylene gives a 1 : 1 mixture of the regioisomers), palladium catalysis yields the isomer with the smaller group adjacent to the nitrile group. In the case of the trimethylsilyl compound, the very labile TMS group migrates to the 2-amino group from the ring nitrogen atom.



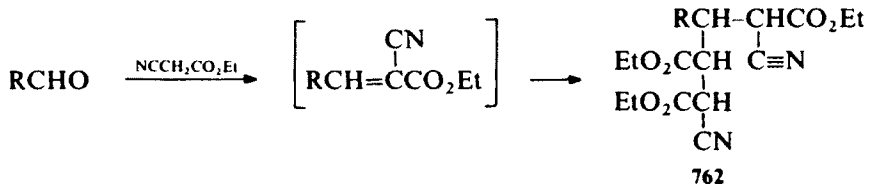
(244)

Y	R^1	R^2	R^3	Z	Cat.	Ref.
t-Bu	*t*-Bu	H	H	NH*t*-Bu	$NiCl_2$	828
t-Bu	*t*-Bu	CO_2Me	CO_2Me	NH*t*-Bu	$NiCl_2$	829
t-Bu	*t*-Bu	H[a]	CO_2Me	NH*t*-Bu	$NiCl_2$	828
t-Bu	*t*-Bu	H[a]	*n*-Bu	NH*t*-Bu	$NiCl_2$	828, 829
t-Bu	*t*-Bu	H[a]	Ph	NH*t*-Bu	$NiCl_2$	828
t-Bu	*t*-Bu	H[a]	$MeOCH_2$	NH*t*-Bu	$NiCl_2$	828, 829
t-Bu	*t*-Bu	Ph	Ph	NH*t*-Bu	$NiCl_2$	829
t-Bu	*t*-Bu	Ph[a]	CN	NH*t*-Bu	$NiCl_2$	829
TMS	H	Ph	Ph	$N(TMS)_2$	$PdCl_2$	830
TMS	H	*p*-$MeOC_6H_4$	*p*-$MeOC_6H_4$	$N(TMS)_2$	$PdCl_2$	830
TMS	H	*p*-ClC_6H_4	*p*-ClC_6H_4	$N(TMS)_2$	$PdCl_2$	830
TMS	H	Ph	*p*-$MeOC_6H_4$	$N(TMS)_2$	$PdCl_2$	830
TMS	H	2-Thienyl	2-Thienyl	$N(TMS)_2$	$PdCl_2$	830
TMS	H	Ph	TMS	$N(TMS)_2$	$PdCl_2$	827
TMS	H	TMSC C	TMS	$N(TMS)_2$	$PdCl_2$	827
TMS	H	C_6H_{13}	TMS	$N(TMS)_2$	$PdCl_2$	830

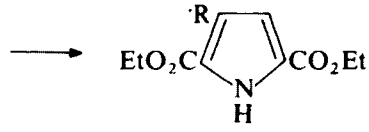
[a] Mixture of isomers.

A patent has described a potentially convenient method for the preparation of 3-substituted pyrrole-2,4-dicarboxylates **763** by the base-catalyzed condensation of an aldehyde with two molecules of ethyl cyanoacetate.[831] Presumably, an initial aldol-like condensation of the aldehyde and ester is followed by the Michael addition of the second molecule of the ester to give **762** (Eq. 245). However, the subsequent steps are unclear.

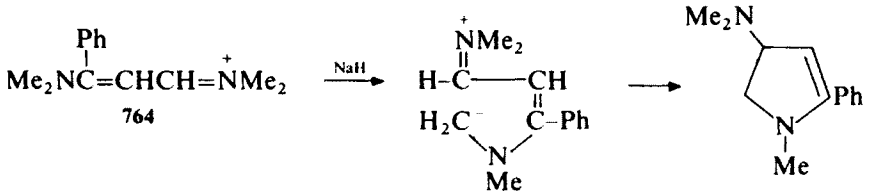
Cyclization of the 1-phenylpentamethinium salt under the influence of a strong base leads to the formation of 1-methyl-2-phenylpyrrole:[832]



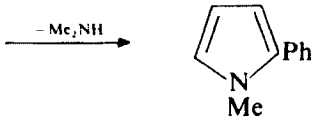
762



763 (245)

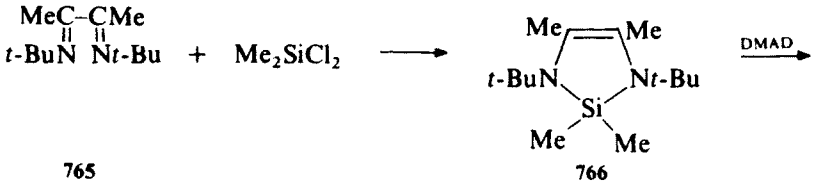


764

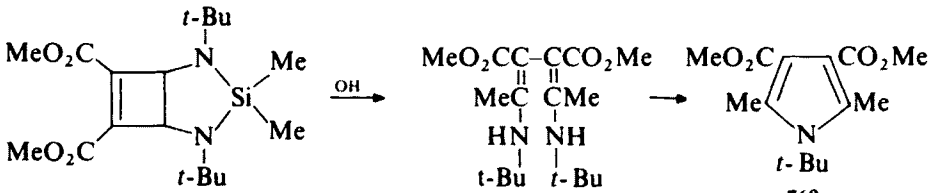


(246)

The double silylation of the diimine **765** by dimethyldichlorosilane gives the diazasilacyclopentene **766**, which can undergo cycloaddition with DMAD. Hydrolysis of the resulting bicyclic compound (**767**) results in the loss of the silyl group and an electrocyclic ring opening of the cyclobutene system. The subsequent ring closure of the diaminobutadiene **768** with the loss of amine leads to the pyrrole **769**:[833]

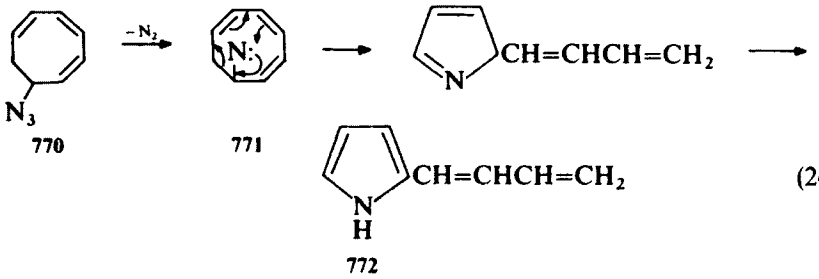


765 766



767 768 769 (247)

The nitrene **771**, obtained from the azide of cyclooctatriene **770**, undergoes an intramolecular insertion with concurrent ring opening to give 1-(2-pyrrolyl)buta-1,3-diene (**772**):[834]



770 **771** **772** (248)

2.10. REFERENCES

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CHAPTER 3

Reactivity of the 1*H*-Pyrrole Ring System

3.1. INTRODUCTION

Anthony H. Jackson

School of Chemistry and Applied Chemistry
University of Wales, College of Cardiff
Cardiff CF1 3TB, UK

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3.1.1. Aromaticity

Pyrrole is a "π-excessive" (electron-rich) 5-membered heterocycle with six π-electrons delocalized over the ring. It undergoes electrophilic substitution much more readily than benzene; substitution normally occurs preferentially at the 2 (or α) position.[1-4] Nucleophilic substitution is virtually unknown in pyrrole, although nucleophilic addition reactions do occur to protonated forms of pyrrole, such as in the reactions of pyrrole with hydroxylamine and sodium hydrogen sulfite (see Section 3.6.1). Chemical evidence for aromaticity is provided by the high predominance of electrophilic substitution versus addition reactions and the tendency of the ring system to survive reactions in which side chains are degraded. The very low basicity compared with typical secondary amines is also evidence for the delocalization of the lone pair of electrons on nitrogen. Several different types of theoretical and physical criteria have also been cited in support of the aromaticity of pyrroles (see Chapter 1).

The resonance energy of pyrrole has been estimated by several different authors from thermochemical data and also by using equilibrium data[1-5] as, for example, the comparison of the free-energy change resulting from protonation at positions 2 and 3 of the pyrrole ring with that for the corresponding

protonation of model dihydropyridines and dihydropyrroles. The average of the values obtained[2] is about 100 kJ mol^{-1}, which agrees with calculations[6] of the resonance energy obtained by the valence-bond method (103 kJ mol^{-1}). This is somewhat less than the value for benzene (130–140 kJ mol^{-1}) and accords with the accepted view that pyrrole is less aromatic than benzene. Resonance energy determinations of the related 5-membered aromatic heterocycles, thiophen and furan, give the order of aromaticity: benzene > thiophen > pyrrole > furan.[5]

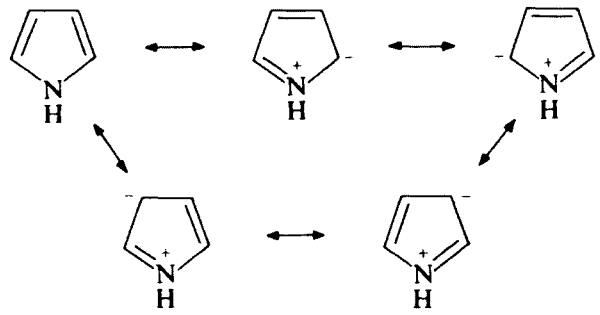
Further physical evidence suppporting delocalization of the π-electrons of pyrrole is provided by bond-length measurements and dipole moments. Electron diffraction, and microwave, spectroscopic measurements, show that the C_2–C_3 bond (133.2 pm) is slightly longer, the C_3–C_4 bond (141.7 pm) slightly shorter, and the N–C_2 bond (137.0 pm) much shorter than the corresponding bonds in cyclopentadiene (134, 147, and 151 pm, respectively). Comparisons with the bond lengths in benzene, thiophen, and furan again lead to the relative order of reactivity benzene > thiophen > pyrrole > furan, on the basis of the criterion that the more aromatic the ring, the closer are the C_2–C_3 and C_3–C_4 bond lengths.

The dipole moment of pyrrole varies with the conditions under which it is determined; it ranges from about 1.55D in the neat liquid up to about 3.0D in solvents to which it can hydrogen-bond.[2] However, the dipole is directed into the ring, whereas in the saturated analog the dipole (1.57D) is directed toward nitrogen, thus providing further evidence for partial delocalization of the lone pair of electrons on the nitrtogen over the whole ring.[2]

The other, and more recently accepted, criterion for aromaticity is the induced ring current observed in the NMR spectra of aromatic compounds. The 2- and 3-protons of pyrrole resonate at δ6.33 and δ6.14, respectively,[7] that is, at lower field than those of olefinic protons, but not as low as those of benzene (δ7.27). Comparisons with the NMR spectra of thiophen and furan again lead to the relative order of aromaticity benzene > thiophen > pyrrole > furan. On the basis of ring current criteria, Elvidge suggested that pyrrole had 59% of the aromatic character of benzene, and this accords qualitatively with resonance energy and bond measurement data. However, other authors disagreed with the quantitative aspects.[2,5]

3.1.2. Theoretical Calculation of Reactivity

Valence-bond representations of the structure of pyrrole include the four zwitterionic resonance forms shown in Scheme 1.1. One can argue that the forms in which the negative charge is located at either of the two α positions are the most stable because they are fully conjugated whereas in those with a negative charge located on the β positions, delocalization occurs over only three atoms of the ring system. This accords with the observed preference for electrophilic substitution at the α position in most of the reactions of pyrrole.



Scheme 1.1

Calculations of reactivity have also been carried out by a wide range of molecular orbital methods from simple Hückel theory to ab initio LCGO–SCF, details of which have been discussed by Jones and Bean,[1] Gossauer,[2] and Chadwick[3]. These calculations have enabled estimates to be made of π-electron densities and of the π-bond orders in the ring. Thus the calculated π-electron densities for both the α- and β-carbon atoms are in the range 1.0–1.1 and on nitrogen 1.6–1.8, whereas the π-bond orders are estimated as 0.42, 0.81, and 0.42 for the N–C, C_2–C_3, and C_3–C_4 bonds, respectively.

3.1.3. Reactivity of 1*H*-Pyrrole towards Electrophiles

Pyrrole reacts very readily with a wide range of electrophiles, and even with such weak reagents as molecular iodine and aryl diazonium salts, giving the 2-substitution product.[1,2,4] Many of these electrophilic substitution reactions may be carried out without the need for Brønsted or Lewis acid catalysts. Indeed, strong acids should be avoided, as they cause polymerization. Thus, for example, nitration and sulfonation can only be carried out under very mild and carefully controlled conditions (see Section 3.3).

The higher reactivity of the pyrrole ring in electrophilic substitution reactions, compared with benzene, may be explained by its lower resonance energy, and the enamine/dienamine-like character engendered by the nitrogen atom. Kinetic studies of electrophilic substitution in pyrrole and its derivatives have been fewer than similar studies in benzene or its 5-membered ring analog, thiophen, but these include protonation, bromination, diazonium coupling, and acylation.[5] The general mechanism of the reactions is the same as that for benzene; that is, the rate-determining step is the formation of the σ (or Wheland)-type intermediate. In a more recent example, it has been observed that there is no primary isotope effect when the rates of diazonium coupling with pyrrole and its perdeuterio derivative were compared.[8] Indeed, the ease of reaction of pyrrole with such weak electrophiles as diazonium salts, iodine, and similar compounds has led many authors to compare its reactivity with those of aniline and phenol (especially in the older literature and text books).

Some attempts have been made to compare the relative reactivities of benzene and the three 5-membered aromatic heterocycles, pyrrole, thiophen, and furan, but this is difficult because of the very wide range of reactivity.[5] For example, kinetic studies of protodetritiation of the four compounds have been carried out, but at different acidities, so direct-rate ratios could not be calculated. However, the relative rate for pyrrole versus furan was estimated to be about 10^5, and the reactivity sequence was benzene < thiophen < furan < pyrrole.[3] Similarly, bromination of pyrrole itself led to decomposition, but, by comparing the rate of brominations at the 5 position of the 2-methoxycarbonyl derivatives of the three heterocycles, the relative reactivities of pyrrole, furan, and thiophen were estimated[9] to be $5.9 \times 10^8 : 1.2 \times 10^2 : 1$. Competitive measurements of the uncatalyzed acylation of the parent heterocycles with trifluoroacetic anhydride led to the reactivity ratios $5.3 \times 10^7 : 1.4 \times 10^2 : 1$ for pyrrole, furan, and thiophen,[10] in good agreement with the data obtained from the bromination reactions. This reactivity sequence also correlates well with the molecular ionization potentials[11] (obtained by electron-impact measurements); higher reactivities corresponded to lower ionization potentials (Table 3.1.1).

TABLE 3.1.1. CORRELATION OF REACTIVITY DATA AND IONIZATION POTENTIALS

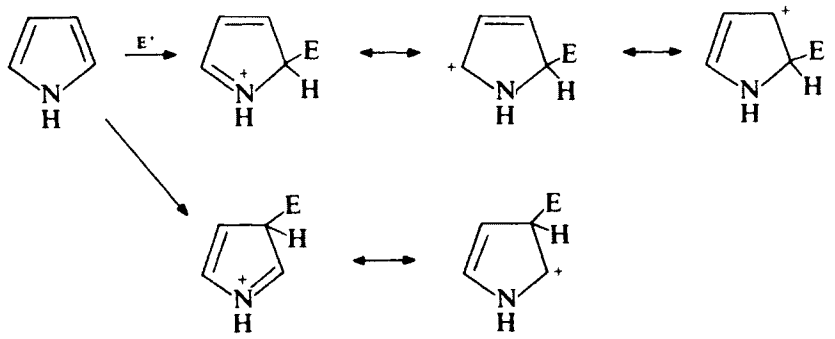
Compound	log k^a	Ionization Potential[b]
Benzene	0	9.53
Thiophen	9.7	9.12
Furan	11.8	8.99
Pyrrole	18.5	8.40

[a] k = Rate of bromination of 2-CO_2Me derivative; see Ref. 9.
[b] Ref. 11.

Although many measurements have been made of the relative reactivities of positions 2 and 3 in thiophen,[3] this has proved almost impossible with pyrrole because of its very high reactivity and the observed preference for 2-substitution. Nitration of pyrrole in acetic anhydride, however, affords both 2- and 3-nitropyrrole, the former being formed in about four times the yield of the latter.[12] With *N*-alkylpyrroles, the yields of the 3-nitro derivative increase somewhat. The partial rate factor for the 2-bromination of pyrrole (3×10^{18}) was calculated from bromination of the methyl pyrrole-2-carboxylate in acetic acid.

The relative reactivities of aromatic compounds have also been determined indirectly from a study of the stabilities of the carbocations generated at a side-chain α position. This was first used by H. C. Brown to determine σ constants for benzene derivatives, and later for thiophen, furan, and other heterocycles. The only data for pyrrole derivatives are given in Marino's review,[5] quoting otherwise unpublished work[13] on the solvolysis of *N*-methylpyrrole-1′-ethyl acetate and -1′-ethyl-*p*-nitrobenzoate, for which the partial rate factors were 5.7×10^{10} and 6.0×10^{10}, respectively.

The greater reactivity of pyrrole ring toward electrophiles, compared with benzene, may be partly due to the fact that the Wheland intermediates (Scheme 1.2) have the same number of double bonds as the starting molecule, as originally suggested by Dewar.[5,14] It is also possible that formation of a π-complex may precede σ-complex formation as pyrroles are strong nucleophiles, and it is conceivable that π-complex formation might even be rate-determining with very powerful electrophiles.



Scheme 1.2

The strong preference for 2-substitution in the normal electrophilic substitutions of pyrrole may be explained qualitatively both by the valence-bond criteria, described above, and by consideration of the resonance forms of the intermediates for 2- and 3-substitution (Scheme 1.2). The intermediate for 2-substitution has three resonance forms, whereas for 3-substitution there are only two resonance structures. There is strong evidence that 2-substitution is thermodynamically preferred. Thus, in strong acid, the 2-protonated form (which corresponds to the Wheland intermediate for 2-substitution) is readily observed by UV and NMR spectroscopy, and, indeed, crystalline salts with this type of structure can be obtained (see Section 3.2.3). On the other hand, in kinetically controlled reactions, substitution may occur preferentially at position 3.[1,2,15] The 3 position may also be favored by reactions in the gas phase,[16,17] as shown by Speranza's recent studies using the ionic species $^3He^3H^+$, $CH_3FCH_3^+$, and $t\text{-}C_4H_9^+$ in the absence of counterions.[18] The products were isolated by gas chromatography and their identities confirmed by mass spectrometry. The results showed that $^3He^3H^+$ was a relatively powerful Brønsted acid, which showed 1.25 : 1 preference for 3- over 2-substitution. With $CH_3FCH_3^+$, the ratios for methylation were 1.4 : 0.4 : 1.0 at positions 3, 2, and 1, respectively, whereas with the *t*-butyl cation there was a very strong preference for 3-substitution and the corresponding ratios were 10.3 : 3.0 : 1.0. These reactions are not of preparative use, but it has been suggested that the degree of solvation of pyrrole, and of the electrophile, in solution may be important factors in determining the site of attack.[18] Furthermore, calculations employing Pearson's hard–soft acid–base theory, lead to the idea that 2-substitution is favored in reactions of

"soft" electrophiles, when attack is frontier-orbital controlled, whereas "hard" electrophiles may attack the 3 position preferentially as the reaction becomes largely charge controlled.[19]

Interestingly, in view of the theoretical studies mentioned above, two groups have reported that 1-benzenesulfonylpyrrole undergoes aluminum chloride-catalyzed acylation specifically at position 3.[20,21] CNDO/3 calculations on ground-state molecular properties, made by Rokach et al.,[21] suggested that the normal regiospecificity of the Friedel–Crafts acylation of the 1-benzenesulfonylpyrrole may be controlled by the "hardness" of the electrophile because of the greater atomic charge of the 3 position. For "softer" electrophiles the 2 position would be more reactive as the reaction becomes "frontier controlled," and Anderson[20] reported that 1-benzenesulfonylpyrrole underwent 2-substitution with the Vilsmeier reagent ($POCl_3$/DMF) and other "softer" electrophiles. A sterically bulkier *N*-substituent may also direct electrophilic substitution toward the 3 position, as, for example, with 1-tri-isopropylsilyl-, 1-*t*-butyl-, or 1-tritylpyrroles.[15,22–24]

Electrophilic substitution at the nitrogen atom of the pyrrole ring normally occurs only under strongly basic conditions, except for proton exchange, which readily occurs under both mildly acidic conditions or in the presence of aqueous base (see Section 3.2.2). The pK_a of the pyrrole NH is 17.5,[25] and so, although proton exchange occurs readily in aqueous base, alkylation (or acylation) can normally be effected only by conversion into the pyrrolyl Grignard or by use of such strong bases as sodamide in liquid ammonia or potassium *t*-butoxide in *t*-butanol or dimethyl sulfoxide (see Section 3.4.2.4). Alkylation on nitrogen can also be effected with aqueous base by the use of phase-transfer catalytic methods and, if electron-withdrawing substituents, such as *C*-acyl groups, are present on the pyrrole ring, the more readily formed *N*-anions can be alkylated under milder basic conditions.

In the reactions of pyrrole Grignard reagents with alkylating or acylating reagents, both 1- and 2-substituted products are formed, together with small amounts of the 3-substituted analogs, whereas the use of pyrrole alkali metal salts strongly favors substitution on nitrogen. The yields of the various products depend on the reaction conditions, but the controlling factor seems to be the ionic character of the "bond" between the metal ion and the *N*-pyrrolyl anion.[26]

Pyrrole is very vulnerable to aerial oxidation, ultimately giving rise to polymeric red tarry materials (see Section 3.5.1). Alkylpyrroles are even more sensitive to oxidation, whereas those with even one electron-withdrawing group (e.g., an acyl or carboxylic group) are relatively stable. Other oxidizing agents, such as peroxide, also afford dark polymeric products, but photooxidation in the presence of a sensitizer affords addition–cleavage products.[27]

The pyrrole ring is not readily reduced chemically except in acidic media, in which the reactive species are protonated forms (see Sections 3.2.2 and 3.5.5). Pyrroles can also be fully reduced to pyrrolidines by catalytic hydrogenation over a wide range of catalysts; more drastic conditions are required for pyrroles bearing electron-withdrawing groups.

The lower aromatic character of pyrrole, compared with benzene or thiophene, is reflected in its facile ability to undergo cycloaddition reactions with carbenes and nitrenes, and Michael-type additions or Diels–Alder reactions with unsaturated esters or other reactive dienophiles. The Diels–Alder reactions occur more readily when the nitrogen is substituted, especially with an electron-withdrawing group.

3.1.4. Substituent Effects on Electrophilic Substitution of 1*H*-Pyrroles

The reactions of electrophiles with pyrroles may be affected by mesomeric, inductive, and steric effcts. Electron-withdrawing substituents have a marked deactivating effect on the reactivity of the pyrrole ring, such as pyrrole carboxylic acids in which the other substituents are alkyl groups decompose very readily on warming, or in the presence of dilute mineral acid, whereas they are much more stable and difficult to decarboxylate thermally if a second electron-withdrawing group (e.g., an acyl or ester group) is present on the ring (see Section 3.2.4). In some electrophilic substitutions, displacement of substituents may also occur; for instance, acyl groups may be substituted by bromine, and carboxylic acid groups are displaced under bromination or iodination conditions. The latter reaction provides a useful preparative route to effect difficult decarboxylations, as the halogen may subsequently be removed by catalytic hydrogenation.[28]

Electron-withdrawing substituents may also change the orientation of substitution on the pyrrole ring; for example, an electron-withdrawing substituent at the 2 position leads to electrophilic substitution at positions 4 and 5, whereas an electron-donating group at position 2 strongly favors electrophilic substitution at position 5. Thus, the reactivity of the 5 position of 2-methylpyrrole is 23.8 times greater than that for the corresponding reaction at the 2 position of the unsubstituted pyrrole ring and, similarly, the rate of proton exchange is 66 times greater.[1] Deactivating substituents at the 3 position inhibit substitution at the neighboring 2 and 4 positions, and substitution tends to occur at the 5 position (which is in a pseudo-"meta" orientation). Electron-donating substituents at the 3 position, on the other hand, activate both the 2 and the 4 positions, with a predominance for the 2 position because of the additional effect of the ring nitrogen atom. The position of electrophilic substitution in pyrroles with two substituents may be qualitatively predicted from considerations on the basis of additivity effects of the two individual substituents.[1,5]

The electronic effects of substituents are probably transmitted largely through the carbon skeleton of the pyrrole ring rather than through nitrogen, and evidence for this view is afforded by correlations of the ionization constants of 4- and 5-substituted pyrrole-2-carboxylic acids with σ_p for the 5-substituent and σ_m for the 4-substituent.[29] The pK_a values of a series of pyrrole carboxylic acids have also been correlated qualitatively with their ease of decarboxylation.[30]

The steric effects of substituents (and of the electrophile) must also be taken into account when predicting the position of substitution, although inhibition of "ortho" substitution is not as pronounced as for benzene derivatives because of the larger angles involved. *N*-Alkyl groups have a rate-enhancing effect on substitution but not as great as that of *C*-alkyl groups. Thus, the rate of protonation at the 2 and 5 positions is only 3.1 times greater, and at the 3 and 4 positions 1.8 times greater, than that for pyrrole itself. On the other hand, bulky substituents on nitrogen tend to promote 3-substitution. This observation has led to new approaches to the synthesis of 3-substituted pyrroles, as these are normally found only as by-products in reactions leading predominantly to 2-substitution. Until recently, 3-substituted pyrroles have been available on a preparative scale by only relatively lengthy indirect methods,[15] but the use of removable bulky 1-substituents now appears to be a promising approach to their direct synthesis.[16] Significantly, the use of the 1-benzenesulfonyl group to direct hard electrophiles, such as acylium ions, into the 3 position is important, and there are also an increasing number of examples of acid-catalyzed rearrangements of 2-substituted pyrroles to 3-substituted pyrroles (see Section 2.3.3).

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3.2. PROTONATION

Anthony H. Jackson

School of Chemistry and Applied Chemistry
University of Wales, College of Cardiff
Cardiff CF1 3TB, UK

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3.2.1. Introduction

Pyrrole is a weak base that undergoes proton exchange at all four carbon atoms and also at nitrogen under mildly acidic conditions. The pK_a for protonation at the 2 position is -3.8, whereas that for the 3 position has been estimated as -5.9. Direct determination of the pK_a for protonation on the nitrogen atom has not been possible, but calculations based on *N*-protonation studies of carbazole lead to an approximate estimate of -10^{14}. Thus, protonation at the 3 position of pyrrole, at equilibrium, is only 1% of that at the 2 position, while protonation at nitrogen is 1 million times less. Molecular orbital calculations using extended Hückel or CNDO/2 methods are also in accord with the basicity order $C_2 > C_3 > N$.[1]

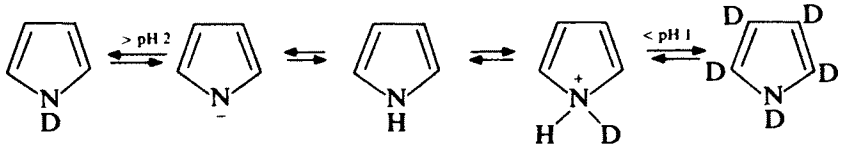
Exchange of the imine proton occurs very rapidly, even under neutral conditions, such as on shaking a deuterochloroform solution of a pyrrole with a little deuterium oxide, the imino proton is exchanged for deuterium, as may readily be observed by loss of the NH resonance at approximately $\delta 8$ ppm in the ^1H NMR spectrum. The rate of imino proton exchange increases both at high and low pH. At high pH, exchange presumably occurs via the pyrrolyl anion 1 and, under these conditions, the protons on carbon are unaffected. Above pH 2, exchange occurs only on nitrogen, but all five hydrogen atoms undergo exchange below pH 1.[2,3] The very high reactivity of pyrrole toward electrophiles is reflected in the overall rate of proton exchange for deuterium in 2,3,4,5-tetradeuteriopyrrole, which is 10^{15} times the rate for deuteriobenzene.[4]

It is impossible to carry out direct selective protonation at the α-carbon atom rather than the β-carbon atom, or vice-versa, but recently this has been carried

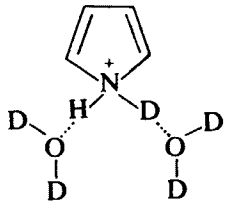
out indirectly by treatment of pyrrolyl lithium derivatives (prepared from the corresponding bromopyrroles) with deuterium oxide.[5]

3.2.2. Protonation on Nitrogen

There is little direct evidence for the mechanism of proton exchange at nitrogen in pyrroles, but under neutral, or acidic, conditions the transient *N*-doubly protonated species **2.2** is presumably involved. The loss of aromaticity and resonance energy involved in formation of such an intermediate presumably accounts for its low stability (as indicated by the estimate of pK_a noted above), but the much higher rate of exchange, compared with that at the 2 and 3 positions, presumably reflects significantly higher rates of protonation and deprotonation. The greater loss of stability on *N*-protonation, compared with that on *C*-protonation, is consistent with estimates of the greater heat of *N*-protonation.[6] The rate of exchange of the imino proton is too fast for study in aqueous solution, but in mixtures of deuterium oxide and an aprotic solvent, such as acetonitrile, the rate is reduced sufficiently to be studied by using the first overtone of the NH stretching mode in the IR spectra. Proton exchange at carbon has been followed by ^1H NMR spectroscopy and was found to be 10–100 times slower than at nitrogen. As the entropies of activation for exchange at nitrogen and carbon are similar ($\Delta S \sim -35\ J\ K^{-1}\ mol^{-1}$), it has been suggested that the NH exchange process requires water molecules in the transition state[3,6] (see **2.3**).



2.1 **2.2**



2.3

At alkaline pH, proton exchange on nitrogen occurs via the anion **2.1**, as mentioned previously. The pK_a of the pyrrole NH is 17.5,[7] so that the concentration of the anion in aqueous base is very low, and, although proton exchange occurs extremely rapidly under these conditions, alkylation on nitrogen can normally be effected only with the aid of strong bases, such as sodamide in liquid ammonia, or potassium *t*-butoxide in *t*-butanol or dimethyl sulfoxide. If

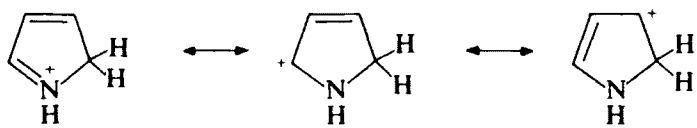
electron-withdrawing substituents, such as *C*-acyl groups, are present on the pyrrole ring, however, the more readily formed *N*-anions are readily alkylated under mildly basic aqueous conditions.

The IR spectra of the solid hydrochlorides of several alkyl pyrroles have been interpreted in terms of *N*-protonated species,[8] but, in solution, there is no doubt that the species observed are *C*-protonated. It has been suggested that the *N*-protonated species dissociate to the free base in solution and then reprotonate on carbon,[8] but a more likely explanation is that the crystalline salts are already protonated on carbon. However, 1-deuteriopyrrole is reported to rearrange to a *C*-deuterium derivative on heating. Pentadeuteriopyrrole is converted into the 2,3,4,5-tetradeuterio NH-pyrrole on being shaken with water.

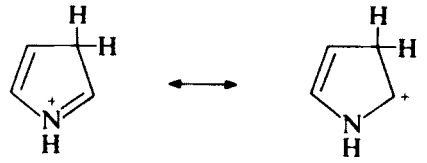
3.2.3. Protonation on Carbon

The formation of salts and other products, on treatment of pyrroles with proton acids or Lewis acids, has now been known for a century. In the case of pyrrole itself, a trimer has been isolated and polymers are also formed. With alkylpyrroles, dimers, and higher oligomers, or polymers are normally observed, although crystalline monomeric salts have been obtained in some cases (see Section 3.2.5). Pyrroles with electron-withdrawing substituents are relatively unreactive toward ring protonation, and protonation generally occurs on the electron-withdrawing group; for instance, IR spectra of the hydrochloride salts of 2- and 3-acetyl and formyl-pyrroles show that protonation occurs on the acyl oxygen atom,[9,10] although there is also evidence for limited protonation at any unsubstitued α position.[11] Polymeric tarry material is also formed from pyrrole and alkylpyrroles when left to stand exposed to air, but these reactions, about which relatively little is known mechanistically, are largely autoxidative in nature (see Section 3.5.1). The acid-catalyzed polymerizations may also involve some degree of oxidation if carried out in air. In subsequent discussion, however, only the anaerobic acid-catalyzed reactions of pyrroles will be considered.

C-Protonation of the pyrrole ring produces resonance stabilized species **2.4** and **2.5**. Direct evidence for the formation of the 2-protonated species **2.4** from pyrrole and of substituted analogs of the 3-protonated species **2.5** has been obtained by ^{1}H NMR spectroscopy in acidic media,[12,13–16] for example, in 12–16 M sulfuric acid or trifluoroacetic acid. Even though these conditions are quite strongly acidic, they may be contrasted with the need to use "superacids" (e.g., SbF_5/FSO_3H or BF_3/HF) to observe the corresponding *C*-protonated species with benzene derivatives.[17]



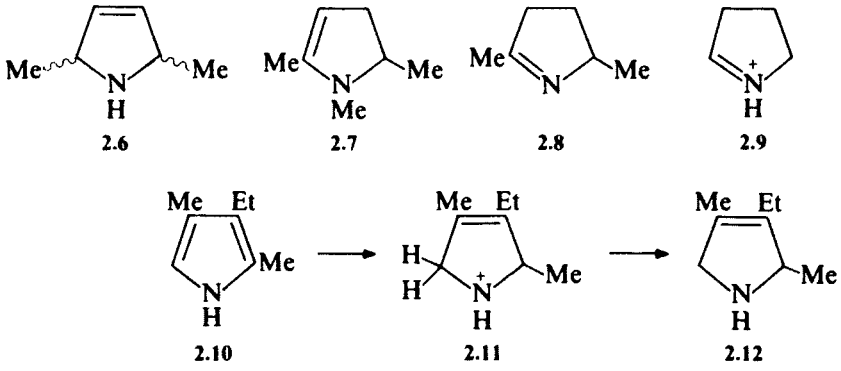
2.4a **2.4b** **2.4c**



2.5a 2.5b

In general, ^{1}H NMR spectroscopic observations show that, at equilibrium, protonation of pyrroles occurs predominantly at the 2 position, unless substituents are present that specifically favor 3-substitution. This is consistent with the well-known predominance of pyrroles for electrophilic attack at the 2 position and is supported by simple theoretical arguments concerning the relative stabilities of the protonated species **2.4** and **2.5**. The positive charge in the 2-protonated form may be delocalized over four atoms in the ring as shown by the three canonical structures **2.4a**, **2.4b**, and **2.4c**, whereas the charge in the 3-protonated form is delocalized over only two atoms, as shown in the two canonical forms **2.5a** and **2.5b**.

The earliest reported studies of exchange reactions in pyrrole were carried out by Koizumi and Tatani some 50 years ago.[2] Their deuterium exchange studies have already been alluded to above and show that deuterium exchange on carbon is rapid at both the 2 and 3 positions, as well as on nitrogen below pH 2. Thus, both the pyrrolenine forms **2.4** and **2.5** must be present in appreciable amounts in 0.1 M acid. There are numerous examples of the chemical reduction of pyrroles to Δ^3-pyrrolines in acidic media,[18] and these can be attributed to reduction of the 2-protonated forms **2.4**. For example, pyrrole itself affords Δ^3-pyrroline and small amounts of pyrrolidine, whereas 2,5-dimethylpyrrole gives a mixture of the *cis*- and *trans*-dimethyl-Δ^3-pyrrolines **2.6** (with the *trans*-isomer predominating), as well as other products arising from acid-catalyzed dimerization, and so on (see Section 3.2.5). Small amounts of Δ^2- and Δ^1-pyrrolines are also formed,[19] such as **2.7** from the reduction of 1,2,5-trimethylpyrrole and **2.8** from 2,5-dimethylpyrrole, while pyrrolidine as well as Δ^3-pyrroline have been found in the reduction of pyrrole by zinc and acetic acid. The Δ^2-pyrrolines



2.6 2.7 2.8 2.9

2.10 2.11 2.12

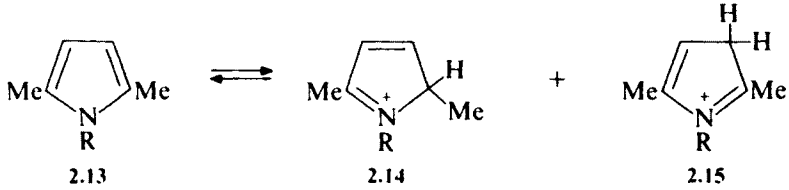
presumably arise via reduction of 3-protonated pyrroles (cf. **2.5**) and the pyrrolidines by 3-protonation of the enamine system in the Δ^2-pyrrolidine to form Δ^1-pyrroline salts (cf. **2.9**), which then undergo further reduction. For a more detailed discussion, see Section 3.5.5.

Catalytic hydrogenation of pyrroles in acidic media often affords oligomeric or polymeric products, and small amounts of pyrrolidines have also been observed. Kryptopyrrole **2.10** is hydrogenated in acidic media to give only the Δ^3-pyrroline **2.12**,[8] suggesting that, in this case, protonation occurs exclusively at the vacant 2 position (cf. **2.11**), in contrast to the reduction of 2,5-dimethylpyrrole described above.

With anhydrous hydrogen halides, the more basic 2,3,4-trialkylpyrroles form relatively stable crystalline salts (e.g., the chloride salt of **2.11**), which can be isolated. The monomeric salts, such as **2.11**, revert instantaneously to the parent pyrroles on treatment with base, or even on dissolution in water or alcohols. In contrast, treatment of unsubstituted pyrrole with anhydrous hydrogen chloride affords a trimer, while other monoalkyl- and dialkylpyrroles form dimers, trimers, and sometimes polymers[20] (see Section 3.2.5).

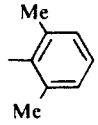
The ^{1}H NMR spectra of the trialkylpyrrole salts in deuterochloroform solution clearly show that the vacant α position is protonated. Thus, for example, the spectrum of the salt **2.11** is quite different from that of the parent pyrrole **2.10**, which shows a broad low-field singlet for the 5-proton, whereas the 5-CH_2 group of **2.11** resonates at higher field and the 4-methyl resonance appears as a triplet due to coupling with the CH_2 group. Abraham et al.[13] have also studied the ^{1}H NMR spectra of a number of other pyrroles in concentrated hydrochloric acid, including 2,4-dimethyl-, 3,4-trimethyl-, 2,3,5-trimethyl-, and 2,3,4,5-tetramethylpyrroles. The spectral data show that protonation occurs at the 2 position. In the former two cases, protonation occurs at the unsubstituted 5 position, whereas in the latter two cases, protonation occurs at a 2 position bearing a methyl group, and direct coupling is observed between the proton introduced and the methyl substituent.

Chiang and Whipple have studied the ^{1}H NMR spectra of a series of pyrroles in 16 M sulfuric acid, and their results agian show that α-protonation is predominant.[12] Unsubstituted pyrrole in sulfuric acid shows four resonances: doublets (J = 6 Hz) at 7.2 and 7.8 corresponding to the 4- and 3-protons, respectively (cf. **2.4**) and broad singlets at δ9.0 (1*H*) and δ5.0 (2*H*), corresponding to the 5-proton and 2-CH_2 group, respectively. The upfield shift of the CH_2 resonance compared with the 2-CH resonances of free pyrrole (δ6.73 in chloroform) clearly testify to the loss of the aromatic ring current on *C*-protonation. The ^{1}H NMR spectra of 1-methylpyrrole and of pyrrole, when measured in sulfuric acid, are very similar. The 1-methyl resonances is moved to lower field, compared with its position in the spectrum of the unprotonated species. Interestingly, however, the ^{1}H NMR spectra of 2,5-dimethylpyrrole **2.13a** and 1,2,5-trimethylpyrrole **2.13b** showed resonances corresponding to the simultaneous formation of the 2- and 3-protonated species **2.14** and **2.15** in a ratio of about 2:1.[14] 2,5-Dimethyl-1-phenylpyrrole **2.13c**, however, showed a 5:1 preference



2.13 **2.14** **2.15**

a. R = H
b. R = Me
c. R = Ph
d. R =



for 2- over 3-protonation, but the more sterically hindered 2′,6′-dimethylphenyl analog **2.13d** afforded approximately equal amounts of the 2- and 3-protonated forms **2.14d** and **2.15d**.[16]

The data for the 2,5-dimethyl- and 1,2,5-trimethylpyrroles accord with results from the earlier work on the reduction of these compounds in acidic media (described above) that afford Δ^3-, Δ^2-, and Δ^1- pyrrolines.

These ^{1}H NMR studies show that, in general, protonation of a 2-alkylpyrrole occurs at the 5 position, whereas 3-alkyl groups direct protonation into the neighboring 2 position, as observed in other electrophilic substitution reactions. Since proton exchange occurs at any unsubstituted position of pyrrole or of the alkyl-substituted pyrroles, however, kinetic protonation must occur at both the 2 and 3 positions, although clearly in most cases the thermodynamically stable products observed correspond to 2-protonation. In the case of the 2,5-dimethylpyrroles referred to above, the 2- and 3-protonated forms **2.14** and **2.15** must be of comparable thermodynamic stability.

The ^{1}H NMR studies of protonation of pyrroles have also been complemented and supported by UV spectral investigations.[8,12,13] Pyrrole, for example, absorbs at $\lambda_{max.}$ 205 nm ($\varepsilon_{max.}$ 6700) in aqueous solution, whereas the conjugated acid **2.4**, corresponding to 2-protonation, absorbs at 241 nm ($\varepsilon_{max.}$ 3900) in 7.6 M H_2SO_4. 1-Methylpyrrole and other simple *C*-alkylpyrroles generally behave in a similar fashion, although the $\lambda_{max.}$ is shifted to slightly longer wavelengths (see Table 3.2.1 for some representative examples). Not unexpectedly, the 2,5-dimethylpyrroles **2.13** show two maxima, when measured in sulfuric acid, corresponding to the 2- and 3-protonated species **2.14** and **2.15**; the 3-protonated species absorbs at longer wavelengths (ca. 280 nm).

The spectroscopic studies of *C*-protonation in pyrroles have also given information regarding the relative rates of proton exchange at the positions 2 and 3 of the pyrrole ring and have also made it possible to estimate pK_a values. Thus, spectrophotometric studies of the protonation of pyrrole at the 2 position, measured at 240 nm in dilute sulfuric acid, gave a pK_a value of -3.8 on the H_O scale.[12] However, subsequent studies indicated that equilibria for both 2- and 3-protonation follow the H_R acidity function, and the corrected value of the pK_a on

TABLE 3.2.1. UV SPECTRA OF SOME ALKYLPYRROLES AND THEIR CONJUGATE ACIDS[12,14-16]

Substituents	Free Base[a] λ_{max}	Conjugate Acid[b] α-Form (2.4) λ_{max}	Conjugate Acid[b] β-Form (2.5) λ_{max}
None	205	241	
1-Methyl	210	247	
2-Methyl	208	253	
3-Methyl	208	258	
1,2-Dimethyl	210	240	
2,3-Dimethyl	208	246	
3,4-Dimethyl	205	217	
2,4-Dimethyl	209	249	
2,5-Dimethyl	209	237	275
1,2,5-Trimethyl	211	243	280
1-Phenyl			
1-(2,6-Dimethylphenyl)	207 inflexion	207	
	203 inflexion	250	
2,5-Dimethyl-1-phenyl	230	239	270
2,5-Dimethyl-1-(2,6-dimethylphenyl)	207	206	
		252	

[a] In water.
[b] In sulfuric acid.

this scale is -4.4.[16] Similarly, 1-methylpyrrole has a pK_a of -2.9 on the H_O scale and -3.4 on the H_R scale. Differences between the pK_a values of *C*-alkylpyrroles measured on the two scales are somewhat smaller (0.1–0.3 units). Difficulties were encountered in some of the work, as a result of the instability of the pyrroles in acid solutions, and it is possible that interaction between the partially formed conjugate acids and the pyrrole free bases had occurred with formation of small amounts of oligomers.

A representative series of pK_a measurements is given in Table 3.2.2, and this shows that an *N*-methyl group increases the basicity of pyrrole by a factor of 10, whereas 2- and 3-alkylpyrroles are, respectively, about 4000 and 1000 times more basic than pyrrole. The effects of additional methyl groups are essentially additive.[12] For example, the calculated value of the pK_a for protonation of 2,4-dimethylpyrrole at the 5 position is 2.6, on the basis of substituent effects for the 2-methylpyrrole (+3.6 units) and 3-methylpyrrole (+2.8 units), compared with pyrrole. The experimental pK_a value is 2.55. It has been estimated from these data and the changes that occur in its UV spectrum with decreasing pH, that the pK_a value for 3-protonation of pyrrole is -5.9; thus, pyrrole is 100 times less basic at the 3 position than at the 2 position in aqueous acid.

Although 2-protonation of the pyrrole ring is clearly favored thermodynamically, kinetic protonation of the 3 position is more rapid, and ^1H NMR studies[12] of deuterium exchange of 1-methylpyrrole in 16 M D_2SO_4 showed that exchange at the 3 position was 2.3 times faster than that at the 2 position. On the

TABLE 3.2.2. pK_a VALUES FOR THE CONJUGATE ACIDS OF ALKYLPYRROLES IN AQUEOUS SULFURIC ACID[12,14,16]

	pK_a Values				
	α-Protonation		β-Protonation		Ratio
Substituent	A	B	A	B	β:α
None	− 3.80	− 4.40			
1-Methyl	− 2.90	− 3.40			
2-Methyl	− 0.21				
3-Methyl	− 1.00				
3,4-Dimethyl	0.66				
2,4-Dimethyl	2.55				
2,5-Dimethyl	− 0.71	− 0.80	− 1.07	− 1.20	0.42
1,2,5-Trimethyl	− 0.24	− 0.20	− 0.49	− 0.50	0.56
1-Phenyl		− 5.8			
1-(2,6-Dimethylphenyl)		− 6.3			
2,5-Dimethyl-1-phenyl	− 2.01	− 2.30	− 2.73	− 3.00	0.19
2,5-Dimethyl-1-(2,6-dimethylphenyl)		− 3.90			
2,3,5-Trimethyl	2.00				
	A[12,14] H_0 scale		B[16] H_R scale		

other hand, in less acidic media, the rate of exchange at the 2 position was more rapid.

Specific rate constants for proton exchange in D_2O/dioxan containing deuterioacetic acid, buffered with potassium acetate, have been measured by Bean and Wilkinson for pyrrole and several alkyl derivatives.[21] The reactions were found to be subject to general acid catalysis, and the data obtained fit to a least-squares plot to obtain rate constants for 2- and 3-substitution in pyrrole:

$$K_\alpha = (3.9 \pm 0.7) \times 10^{-2}[D^+] + (3.9 \pm 0.2) \times 10^{-6}[DOAC]$$

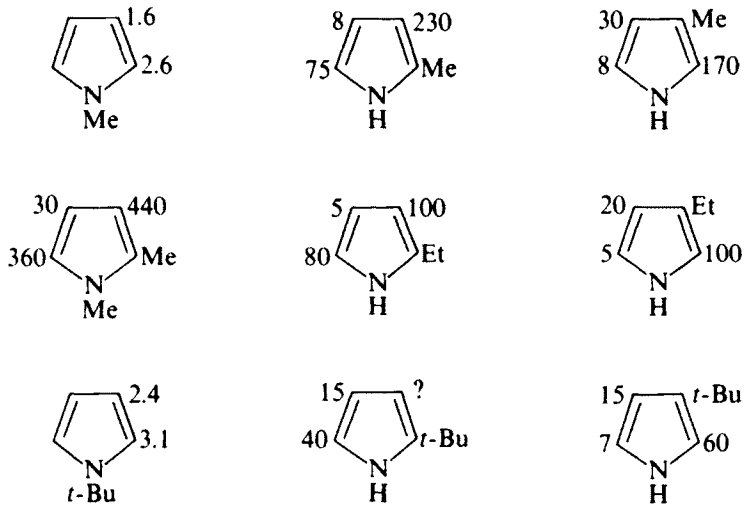
$$K_\beta = (3.9 \pm 0.8) \times 10^{-2}[D^+] + (0.9 \pm 0.4) \times 10^{-6}[DOAC]$$

In the more acidic solutions, exchange at the 2 and 3 positions occurred at similar rates. Thus, for example, at pD 3.86 and 25°C, rate constants of 6.01 and 5.57×10^{-6} s^{-1} were obtained for protonation at the 2 and 3 positions, whereas at pD 5.8, the corresponding rate constants were respectively 8.88 and 2.83×10^{-6}. In solutions of higher acidity (pD ~ 1.2), when trifluoroacetic acid was used as catalyst, the rates of exchange at the 2 and 3 positions were equally rapid. Muir and Whiting also showed that deuteriation in an acetonitrile–D_2O mixture containing 4×10^{-2} M $HClO_4$ was subject to general acid catalysis, and that exchange at the 3 position was only slightly faster than at the 2 position.[6]

The slower rates of exchange at the 3 position of pyrrole and 1-methylpyrrole in less acidic solution was attributed to two opposing effects.[21] Proton exchange at the 2 position for both compounds is favored by a lower enthalpy of

activation, but it is almost canceled by an unfavorable negative entropy in the case of pyrrole, due partly to solvation of the NH group. The inductive effect of the methyl group in 1-methylpyrrole produces a lowering of the enthalpy of activation for the 2-proton exchange, but this is offset by the greater negative entropy caused by the bulk of the *N*-methyl group. The entropies of activation for exchange at the 3 position of both pyrrole and 1-methylpyrrole are about the same (ca. $-70\ J\ mol^{-1}\ K^{-1}$).

The rate measurements for deuteriation of a series of alkyl pyrroles in deuterioacetic acid–potassium acetate buffer in D_2O–dioxan enabled Bean and Wilkinson[21] to estimate the reactivities of various positions of the pyrroles relative to the 2 and 3 positions of the unsubstituted pyrrole ring as shown in Scheme 2.1. These data are in qualitative accord with the effects of alkyl groups on reactivities in electrophilic substitution reactions of other aromatic compounds. For example, as in benzene, alkyl groups activate the "ortho" and "para" positions toward electrophiles, although, in pyrrole, the *N*-substituent has less effect than the corresponding substituent on carbon. Relative positional reactivities were found to agree[21] with predictions of Klopman's polyelectron perturbation theory[22] (derived from Pearson's hard–soft acid–base theory) using orbital energies and functions obtained by the INDO MO method.



Scheme 2.1. Relative reactivities of alkylpyrroles for proton exchange relative to exchange at the corresponding positions of pyrrole.

Infrared studies[4] of the rate of exchange of 2,3,4,5-tetradeuteriopyrrole in aqueous methanol containing sulfuric acid showed that under these conditions the rate of exchange at the 2 position was 2–4 times that at the 3-position. In a more recent study, Alexander and Butler[23] compared the rates of protodetritation of *C*-tritiated 1,2,5-trimethyl- and 1,3,4-trimethylpyrroles in phosphate

buffer. The rates varied linearly with the acid concentration and had a positive slope, indicating that the protodetritiation was being effected by hydrogen ions and, assuming that the effect of an α-methyl group on a β-position is the same as that of a β-methyl group on the neighboring α position, the $k_\alpha : k_\beta$ ratio was found to be 0.9.

Not unexpectedly, the results described above show that stronger acids are less selective than weaker acids, although the rate differences observed for 2- and 3-protonation are not, in any case, very large in the case of pyrroles and 1-methylpyrrole. The predominance of electrophilic substitution reactions at the 2 position of pyrrole must, therefore, be due to thermodynamic factors. The pK_a values for 1,2,5- and 1,3,4-trimethylpyrroles are − 0.1 and 1.4, respectively, and, therefore, there is no straightforward correlation of these values with the rates of protonation.

Whereas an *N*-methyl or *C*-methyl group has a pronounced base-strengthening effect, *N*-phenyl groups are electron-withdrawing and decrease the basicity of the pyrrole ring.[16] Thus, the pK_a for 2-protonation of 1-phenylpyrrole is − 5.8 on the H_R scale, and that for 2,5-dimethyl-1-phenylpyrrole is − 2.30. Both values are about 1.50 units lower than the corresponding *N*-unsubstituted pyrroles. In the case of 2,5-dimethyl-1-phenylpyrrole, the slight preference for 2-protonation versus 3-protonation is shown by the lower pK_a value (− 2.30 compared with − 3.0). However, the more bulky *N*-(2,6-dimethylphenyl) group, which inhibits solvation of the positively charged pyrrolyl nitrogen atom in the protonated forms, also causes a further reduction in basicity and shows pK_a values of − 3.9 for 2-substitution and − 3.6 for 3-substitution. In this case, the 2 : 1 preference for 3-protonation can be attributed, in part, to steric hindrance to 2-protonation.[16]

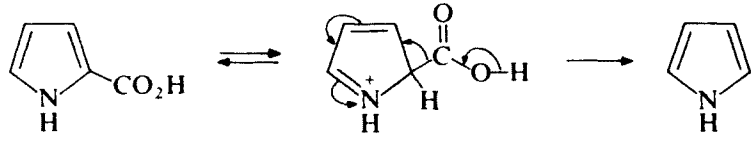
Theoretical calculations of the ground-state molecular potentials for the interaction of a positive point charge and an isolated pyrrole molecule have led to the conclusion that the 3 position of the pyrrole ring should be the preferred position for attack by an approaching charged electrophile.[24] However, most experimental studies have been carried out in solution in which environmental factors such as solvation may have a profound effect on the rate and course of reaction. On the other hand, gas-phase studies[25] of tritiation with the powerful Brønsted acid $^3He^3H^+$ show a distinct preference for 3-substitution, with ratios for tritiation at the *N*, 2, and 3 positions of 1 : 2 : 2.5. It is evident from these results that not only does the solvent and ion pairing have a marked effect on the position of substitution, but that the nature of the electrophile is also important. The preference for 3-substitution is also predicted from analysis of orbital energies, and the general factors affecting the reactivity of pyrrole (and other heteroaromatic compounds), including gas-phase basicity, have recently been reviewed by Speranza.[26] Gas-phase studies of the alkylation of 1-methylpyrrole by the *t*-butyl cation have also been carried out, and the results showed only a small preference for 3- over 2-substitution (53 : 47), whereas furan and thiophene show a large preference for 2-substitution.[25] Gas-phase proton affinities have been calculated for pyrrole, and the values obtained were 806.7 and

845.4 kJ mol^{-1} for the 2 and 3 positions, respectively, suggesting that the 2-protonated form is the more stable, but the calculated C_{TS} orbital energies for the 2 and 3 positions show that protonation at the 3 position should be favored under kinetically controlled conditions.[27]

While these theoretical calculations predict that the 3 position is the preferred site of protonation, the experimental evidence (showing a preference for 2-substitution) was interpreted by some authors in terms of a subsequent 3- to 2-position migration.[27] As these calculations show that the greater negative charge is located at the "hard" centre (i.e., the 3 position), this should be the position of attack by "hard" electrophiles, as shown by the gas-phase reactions. Majchrzak and Simchen recently studied[28] the reaction of 1-methylpyrrole with trimethylsilyl trifluoromethane sulfonate and found that the major product is the corresponding 3-trimethylsilylpyrrole, with small amounts of the 2-isomer. By carrying out a similar reaction with the 2,5-dideuterio-1-methylpyrrole and analyzing the products, they were able to rule out $\alpha \rightleftarrows \beta$ isomerization processes, thereby providing further support for the theoretical calculations.

3.2.4. Displacement of Substituents by Protonation

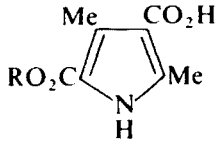
Pyrrole-2- and -3-carboxylic acids readily undergo thermal decomposition at their melting points with evolution of carbon dioxide. The presence of electron-donating substituents, such as alkyl groups, renders the acids even more susceptible to decarboxylation. Kinetic studies[29] of the decarboxylation of pyrrole-2-carboxylic acid **2.16** in buffered aqueous solution show that the rate increases rapidly below pH 1. The intermediate for decarboxylation is almost certainly the *C*-protonated species **2.17**, which then undergoes a fragmentation reaction to form pyrrole. At higher pH values, the protonation of the ring is rate-determining, but, at lower pH, the decarboxylation stage is the slow step, as shown by the ^{13}C-carbonyl isotope effect.



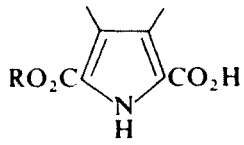
2.16 **2.17**

Electron-withdrawing groups in the ring stabilize pyrrole carboxylic acids. For example, 5-alkoxycarbonyl-2,4-dimethyl-pyrrole-3-carboxylic acids **2.18** decarboxylate only on dry distillation at temperatures in excess of 200°C, or by heating in glycerol.[30] However, heating in 2-aminoethanol lowers the decarboxylation temperature,[31] presumably because the carboxylate anion is formed.

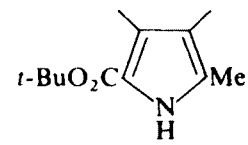
In the case of 5-alkoxycarbonylpyrrole-2-carboxylic acids **2.19** (useful intermediates in dipyrromethane and porphyrin synthesis), indirect decarboxylation



2.18



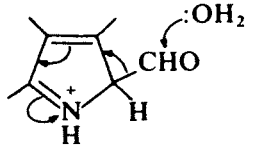
2.19



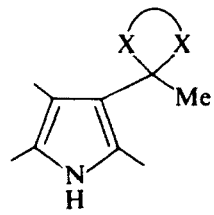
2.20

by iodinative decarboxylation followed by hydrogenolysis of the intermediate iodopyrrole[32] is generally necessary and pyrrolecarboxylic acids with two other electron-withdrawing groups in the ring will not decarboxylate even under drastic conditions. *t*-Butyloxycarbonyl groups, often used as *C*-protecting groups in pyrroles required for porphyrin synthesis (e.g., **2.20**), are readily decarboxylated by neat trifluoroacetic acid.[32] It is a moot point, however, whether cleavage occurs directly or after deesterification.

Acyl pyrroles can also be deacylated in acidic media, although they are somewhat more stable than the carboxylic acids and require heating to relatively high temperatures in phosphoric acid.[33] On the other hand, treatment of formyl pyrroles with dilute sulfuric acid affords the corresponding unsubstituted pyrroles, presumably by protonation of the ring at the formyl substitutent (cf. **2.21**). Heating with sodium methoxide (or ethoxide) also effects cleavage of acyl groups, but the products of such reactions are the corresponding methyl (or ethyl) pyrroles formed by alkylation by the alkoxide.[34,35] Protodeacylation of 3-acetylpyrroles can also be carried out via ketal or dithioketal derivatives (e.g., **2.22**), and both protodeformylation and protodeacylation have been effected via the corresponding ethylene ketals (e.g., **2.23**) using clay catalysts.[36]

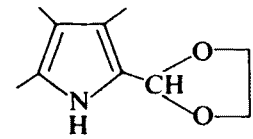


2.21



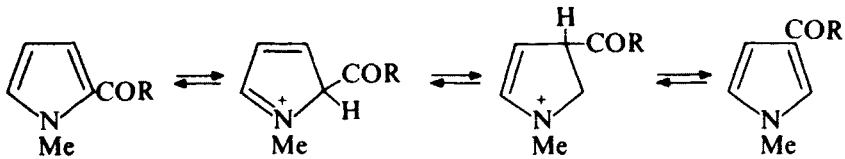
2.22

X = O, S



2.23

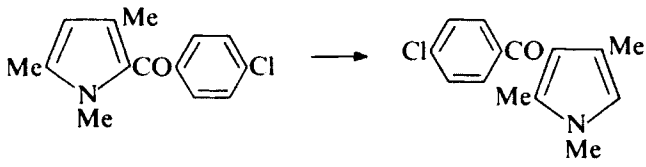
2-Acyl-1-alkylpyrroles **2.24** undergo a facile rearrangement[37,38] on heating in anhydrous acid (e.g., trifluoroacetic acid, methane sulfuric acid, trifluoromethane sulfuric acid, or polyphosphoric acid) to give the 3-acyl analogs **2.25** in



2.24 R = Me, Ar 2.25

40–80% yield as the sole monomeric products. Treatment of 2- or 3-acylpyrroles in a similar manner afforded equilibrium mixtures of the 2- and 3-acylpyrroles, as did the corresponding formylpyrroles regardless of whether the system was *N*-methylated.[38]

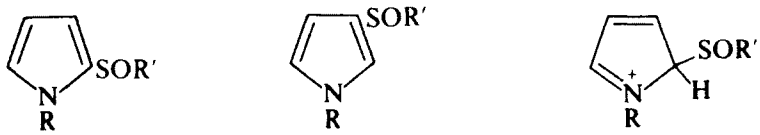
Evidence against the formation of free acylium ions was obtained by the failure of crossover experiments, and the mechanisms of these reactions are thought to involve 1,2-intramolecular migration after protonation at the ring carbon bearing the acyl group, as shown in the reaction sequence **2.24** → **2.25**. In one case, a cross-ring migration was observed (**2.26** → **2.27**) in which two such migrations would have to be involved unless, of course, this rearrangement differs from the general mechanism and a free acylium ion is formed. A similar intramolecular acyl group migration has been proposed for the acid-catalyzed rearrangement of 2-acetylindole to the 3-acetyl isomer.[39]



2.26 **2.27**

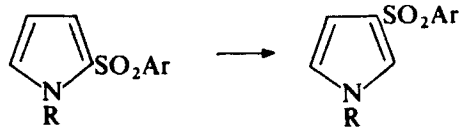
Acylation of 1-benzenesulfonylpyrrole affords a mixture of 2 and 3-acyl substituted pyrroles under the influence of aluminum chloride as a catalyst, but the 2-acylpyrrole is produced mainly with boron trifluoride.[40] It was suggested that substitution at C-3 was favored by charge control in attack by a highly polarized electrophile, whereas attack at C-2 was under orbital control, although, alternatively, the C-3 acyl product might have arisen by acid-catalyzed rearrangement.

The disparate reactions of pyrrole and 1-methylpyrrole, which give the pyrrole-2-sulfoxides **2.28**, when they are treated with sulfinyl chloride at 0°C in the presence of triethylamine, but produce the 3-sulfoxides **2.29** (with smaller amounts of the 2-isomers) when the base is omitted,[41] have been shown to be due to free hydrogen chloride (formed due to the absence of triethylamine), which catalyzed the rearrangement of the sulfoxide group. This rearrangement occurred extremely easily, but crossover experiments showed that, in contrast to the acylpyrrole rearrangements, it was at least in part an intermolecular process. Whichever mechanism prevails, the reactions must have involved protonated intermediates such as **2.30**. In a closely related process,[42] it has been shown that



2.28 **2.29** **2.30**

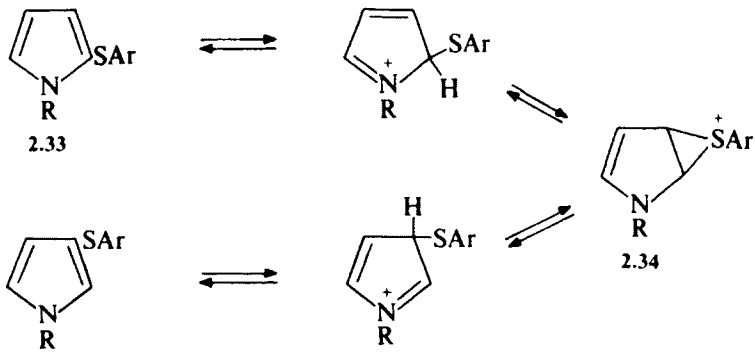
R = H, Me



2.31 2.32

1-substituted pyrrolyl-2-sulfones **2.31** rearranged to give the 3-sulfones **2.32** in refluxing trifluoroacetic acid–polyphosphoric acid (1 : 1).

Phenylsulfenylpyrroles **2.33a** also undergo rearrangement[41,43] under acidic conditions (CF_3CO_2H) to form an equilibrium mixture of 2- and 3-sulfenyl pyrroles **2.35a**. The corresponding 1-tosyl-2-sulfenylpyrroles **2.33b** rearrange under more vigorous acidic conditions[43] to form the 3-sulfenyl derivatives **2.35b**. The failure of crossover experiments showed that sulfenyl rearrangements were intramolecular and presumably occur via protonation at the carbon bearing the sulfenyl residue, followed by formation of an intermediate sulfonium species (cf. **2.34**).



2.33

2.34

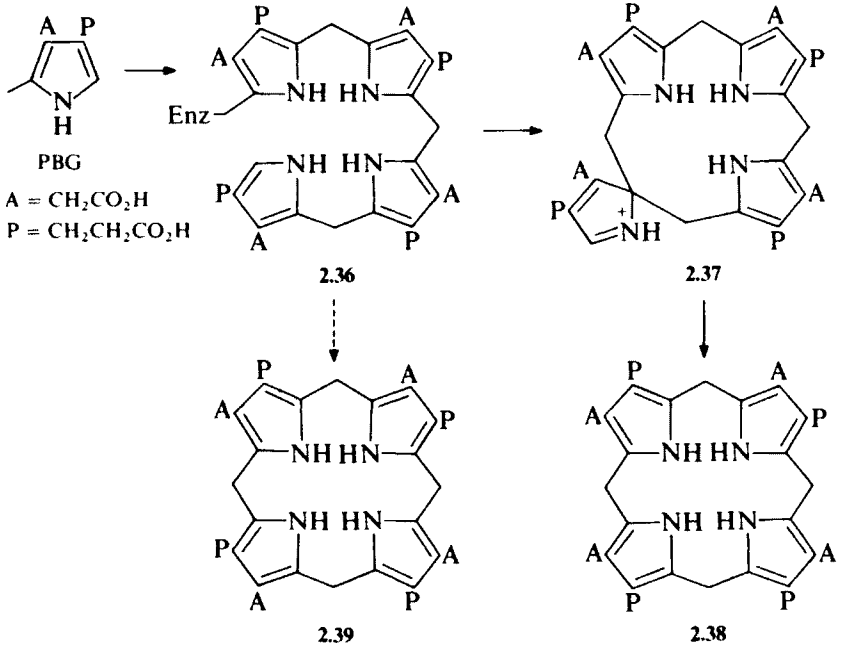
2.35

a. R = H

b. R = Tos

Acid-catalyzed isomerization has been invoked to account for the formation of 3-bromopyrroles in addition to the 2-bromopyrroles in the bromination of pyrrole and 1-substituted pyrroles by molecular bromine in carbon tetrachloride. The related brominations, using *N*-bromosuccinimide (where no hydrogen bromide is formed in the reaction) give mainly the 2-isomers. *N*-Chlorosuccinimide is less selective in effecting chlorination.[44]

Alkyl group rearrangements, or displacements, under acidic conditions are of considerable interest, not only because of the mechanistic aspects but also in relation to the mechanism of formation[41] of the macrocyclic uroporphyrinogen-III **2.38** from porphobilinogen during the biosynthesis of porphyrins, chlorophylls, and vitamin B_{12}. Numerous hypotheses have been advanced for this process, but the weight of evidence now favors the mechanism involving a spirocyclic intermediate **2.37**, as shown in Scheme 2.2, to account for the

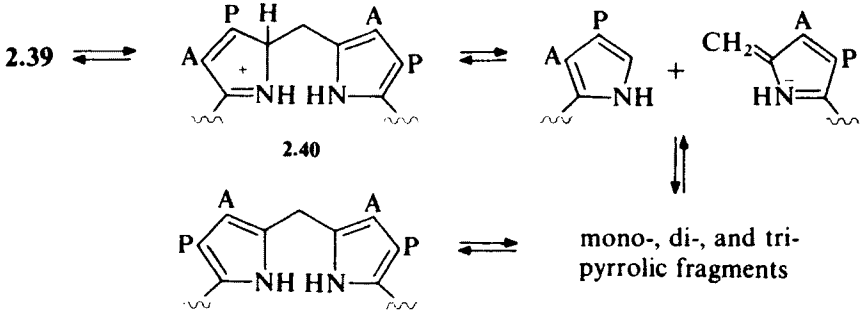


Scheme 2.2

formation of the unsymmetrical uroporphyrinogen-III **2.38**, rather than the centrosymmetrical type I isomer **2.39**, which would be formed by head-to-tail coupling of the bilane **2.36**. It has long been known that acid-catalyzed polymerization of porphobilinogen **2.31** affords mixtures of all four uroporphyrinogen isomers, and isomeric mixtures of other porphyrins are also produced by acid-catalyzed cyclization of porphobilinogen analogs.[46] One of the contributions to the earlier speculations regarding porphyrin biosynthesis was the finding that uroporphyrinogen-I **2.39** also underwent an acid-catalyzed rearrangement process to give a mixture of all four uroporphyrinogen isomers.[47] This process was thought to involve protonation of the individual pyrrole rings of the porphyrinogen at the α positions (cf. partial structure **2.40**), followed by cleavage and recombination reactions.

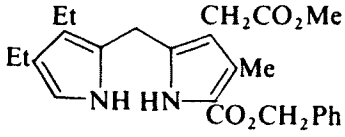
There are also many examples of the formation of mixtures of products in attempts to synthesize specific porphyrins from dipyrromethanes and related tri- and tetrapyrrolic intermediates; the mixtures are again thought to result from acid-catalyzed cleavages of the type illustrated in Scheme 2.3.

Direct evidence for such processes has recently been obtained in Cardiff by Jackson et al.[48] in crossover experiments involving the simultaneous treatment of two α-unsubstituted dipyrromethanes **2.41** and **2.42** with equimolar amounts of trifluoroacetic acid in chloroform solution. Four products, **2.41**,

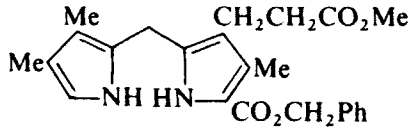


Scheme 2.3

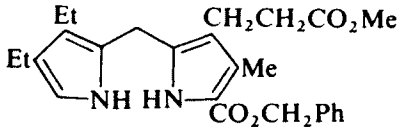
2.42, **2.43**, and **2.44**, were obtained, showing conclusively that protonation of the α-unsubstituted pyrromethanes must have occurred at the α′ positions followed by cleavage and recombination to give the observed products.



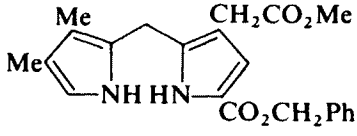
2.41



2.42



2.43

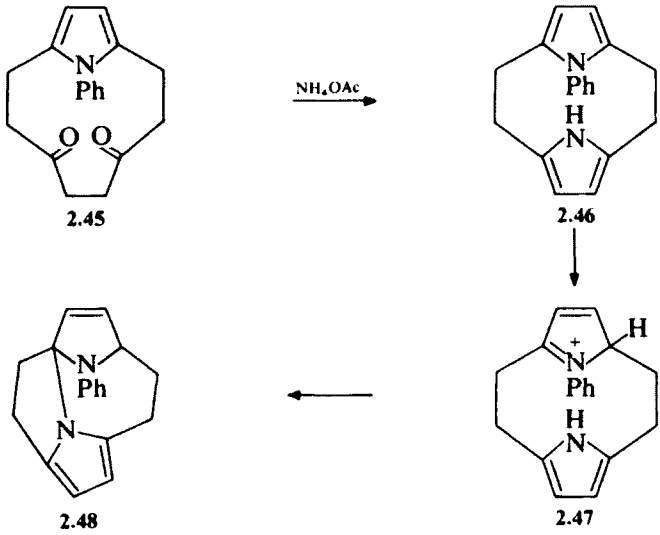


2.44

A novel product, formed in the preparation of the *N*-arylpyrrolocyclophane **2.46** from the dioxopyrrolophane **2.45** on treatment with ammonium acetate in dilute aqueous acid, is the intramolecular cyclization product **2.48**. The latter compound was also prepared from **2.46** by heating in acetic acid.[49] The conversion of **2.46** into **2.48** presumably occurs via α-protonation of the aryl-pyrrole moiety of the pyrrolophan leading to the intermediate **2.47**, which then undergoes intramolecular nucleophilic attack by the other pyrrole ring.

3.2.5. Acid-Catalyzed Polymerization of 1*H*-Pyrroles

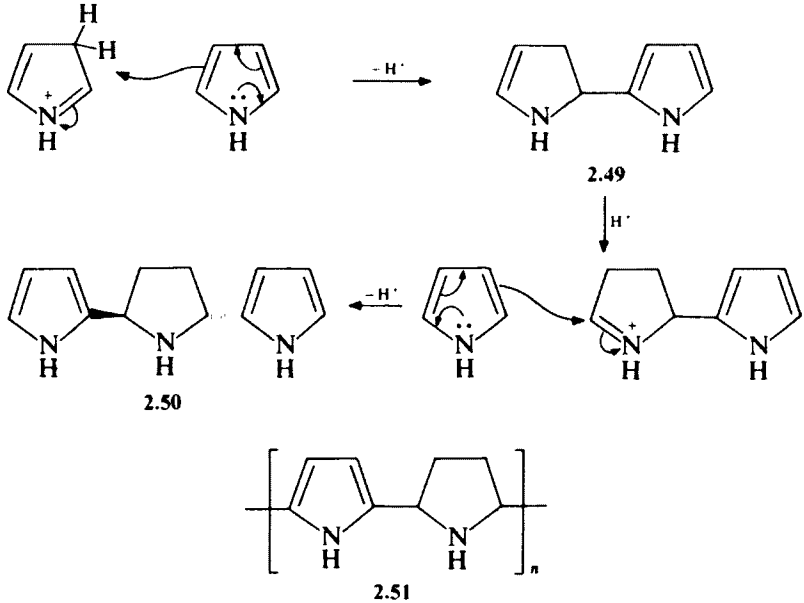
Although pyrroles are converted into monomeric salts in strongly acidic media, as shown by ^{1}H NMR and UV spectroscopy, it has been known for a 100 years that pyrrole and its alkyl derivatives undergo oligomerization under acidic conditions and ultimately form intractable polymers.[20] The precise



2.45 2.46 2.47 2.48

course of the reactions depends on the substitution pattern, and dimers, trimers, and indole derivatives have been characterized as well as monomer salts.

Pyrrole itself forms a trimer on treatment with dry hydrogen chloride in ether, or on brief contact with 6 M hydrochloric acid.[50] The structure of this trimer (**2.50**) was first proposed by Pieroni and Moggi[51] following the isolation of succinic acid after chromic acid oxidation, and this structure was confirmed by Potts and Smith by successive Hofmann degradations and reductions to form



2.51

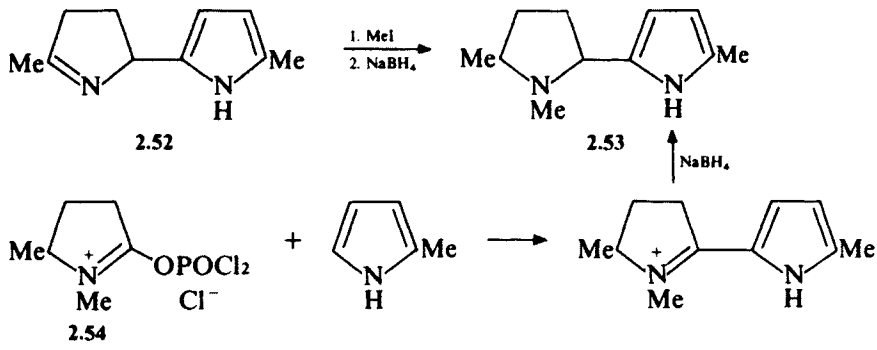
1,4-dipyrrol-2-ylbutane.[52] The trans arrangement of the two pyrrole rings was shown by chromic acid degradation of the *N*-tosyl trimer to give *N*-tosylpyrrolidine trans-2,5-dicarboxylic acid.[53]

The mechanism of formation of the trimer is presumably by way of initial nucleophilic attack of a neutral pyrrole molecule on the 3-protonated form of pyrrole. Subsequent protonation of the intermediate dipyrrole derivative **2.49** and attack by a further molecule of pyrrole then affords the trimer.[20]

The unexpected involvement of the β-pyrrolenine salt, although it is less abundant that the α-pyrrolenine salt, has been attributed to its greater electrophilic reactivity.

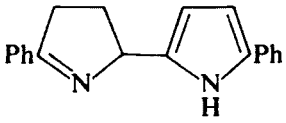
The pyrrole trimer **2.50** can be obtained only under carefully controlled conditions and, when treated with acid under anaerobic conditions,[20] undergoes further polymerization to form colorless materials, which may have the general linear structure **2.51**[20] (although considerable branching may occur). On exposure to air, the polymer turns red. It has been suggested[20] that branching may involve protonation on the more basic pyrrolidine nitrogen of **2.51**, followed by nucleophilic substitution by pyrrole at the β position of the pyrrolidine in a manner reminiscent of the behavior of indole and pyrrole Mannich base salts.

1-Methylpyrrole, like pyrrole, forms a monomeric cation in strong acid solution,[12] but this has not been isolated as a crystalline salt. In weaker acid, it polymerizes and no stable dimer or trimer has been obtained. 2-Methylpyrrole and some dialkylpyrroles form crystalline dimer salts on treatment with dry hydrogen chloride, or picric acid in ether, although polymers may also be formed.[49,54-57] 3-Methylpyrrole gives only an amorphous polymer under these conditions.[58,59] Most of the dialkylpyrroles, including those that do not give isolable dimers, all show ^{1}H NMR spectroscopic evidence for the formation of monomeric salts in strongly acidic media.[12] Most trialkyl- and tetraalkylpyrroles also form monomeric α-pyrrolenine salts in strong mineral acid solution, but, interestingly, 3-ethyl-2,4-dimethylpyrrole (kryptopyrrole) and 4-ethyl-2,3,5-trimethylpyrrole (phyllopyrrole) form dimeric picrate salts in hot ethyl acetate,[60] although the structures of these dimers are not yet known. The structure[61] of the 2-methylpyrrole dimer **2.52** was confirmed by *N*-methylation followed by borohydride reduction to give the pyrrolidinopyrrole **2.53**, which

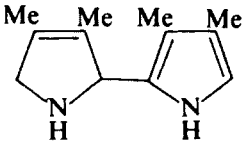


was independently synthesized by condensation of the phosphoryl chloride complex of 1,5-dimethylpyrrolidone **2.54** with pyrrole followed by reduction.[62] The mechanism of the acid-catalyzed dimerization of 2-methylpyrrole must presumably be essentially the same as the first stages of the formation of pyrrole trimer, specifically, condensation of the 3-protonated salt with the 2-methylpyrrole, followed by isomerization of the initially formed enamine (cf. **2.49**) to give the imine **2.52**.

Similar dimers have also been obtained as their crystalline salts from 2-isopropyl-, 2,3-dimethyl-, 3-ethyl-2-methyl-, and 2-ethyl-3-methylpyrrole, and these presumably have structures analogous to **2.52**. 2-Phenylpyrrole is readily converted into the dimer salt **2.55** by treatment with dry hydrogen chloride in ether solution. The dimeric structure followed by analogy with that of 2-methylpyrrole dimer[61] and was confirmed by a similar synthesis.[62]

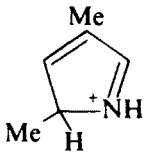


2.55

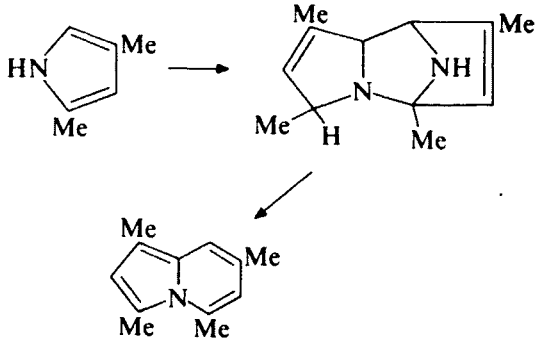


2.56

2,4-Dimethyl- and 2-ethyl-4-methylpyrroles form monomeric salts,[63,64] but other 2,5-dialkylpyrroles do not form isolable monomeric or dimeric salts, even though the monomeric salts are formed in strongly acidic solution.[14] The failure to isolate the dimeric salts in these cases may be due to steric hindrance to the formation of stable dimers, although the dimer **2.56** is formed from 3,4-dimethylpyrrole, presumably via the 2-protonated dimethylpyrrole.[65] In refluxing glacial acetic acid in presence of zinc acetate, however, 2,4-dimethylpyrrole affords the tetramethylindolizine **2.58**.[66] The mechanism of this process may involve concerted cycloaddition of a 2-protonated intermediate **2.57** to the neutral pyrrole, followed by a series of prototropic rearrangements and loss of ammonia.

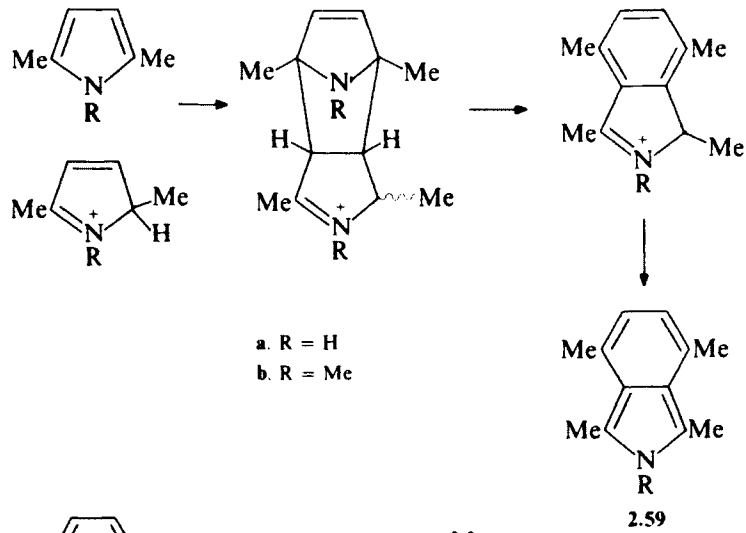


2.57

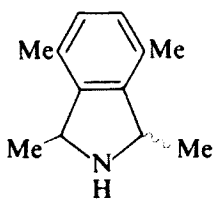


2.58

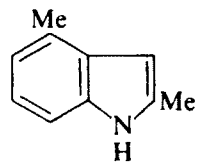
Interestingly, 2,5-dimethylpyrrole, in which both α positions are blocked, undergoes dimerization in hot dilute sulfuric acid to produce 1,3,4,7-tetramethylisoindole **2.59a**.[67] This may occur by 2-protonation, followed by cycloaddition of the free pyrrole to the 3,4-double bond of the pyrrolenine. Elimination of ammonia, followed by loss of a proton, would then afford the isoindole. Alternative mechanisms in which a nonconcerted cyclization process, or even addition of the free-base pyrrole to a 3-protonated form, are also conceivable. 1,2,5-Trimethylpyrrole also undergoes a similar acid-catalyzed condensation to yield the *N*-methylisoindole **2.59b**, which can also be synthesized by the acid-catalyzed condensation of hexane-2,5-dione with 1,2,5-trimethylpyrrole.[67,68] Reduction of 2,5-dimethylpyrrole with zinc and acetic acid gives rise to the dihydroisoindole **2.60**,[69] presumably by a similar dimerization process, followed by reduction of one of the intermediates shown in the mechanistic scheme leading to the isoindole **2.59**. Also, Δ^3-, Δ^2-, and Δ^1-pyrrolines may be formed[15,70] by reduction of 2,5-dimethylpyrrole and its *N*-methyl derivative, as described earlier (cf. **2.6**, **2.7**, and **2.8**).



2.59



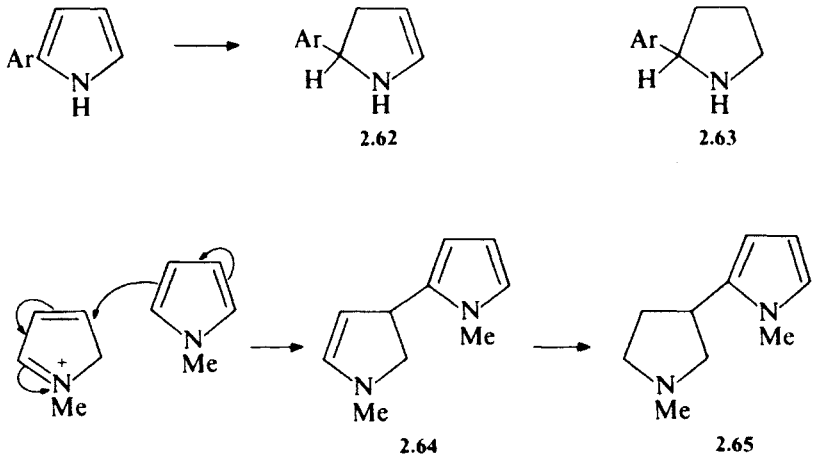
2.60



2.61

2-Methylpyrrole gives 2,4-dimethylindole **2.61** in hot aqueous sulfuric acid,[49,71] and indoles of unknown structures are formed from other monoalkyl- and dialkylpyrroles.[49,54,58,59] The mechanism of the dimerization of 2-methylpyrrole is less clear but could involve a concerted cycloaddition reaction.

2-Arylpyrroles, on reduction with zinc in acid solution, afford the Δ^2-pyrrolines **2.62**, but the latter can then undergo disproportionation to the arylpyrrolidines **2.63** and the parent arylpyrroles.[72] 1-Methylpyrrole, on the other hand, affords a dimeric product **2.65**,[72] as well as the Δ^3-pyrroline and *N*-methylpyrrolidine. The dimer presumably arises by initial attack of the neutral molecule on the 2-protonated species, followed by reduction of the intermediate enamine **2.64**.



The general picture that emerges from these results and those discussed in the earlier sections is that the more basic polyalkylpyrroles form stable crystalline monomeric salts, whereas pyrrole and monoalkyl- and dialkylpyrroles are only partially protonated on treatment under mildly acidic conditions. Hence, oligomerization occurs as a result of interaction of free-base and protonated forms. However, in strongly acidic solution, pyrrole and its alkyl derivatives form monomeric *C*-protonated salts. Electron-withdrawing groups inhibit ring protonation but are probably protonated on the electronegative centre and do not undergo polymerization. Under sufficiently vigorous conditions, removal of the electron-withdrawing group may occur, for example, protodecarboxylation or protodeacylation.

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3.3. NITRATION, SULFONATION, AND HALOGENATION

Marino Artico

Dipartimento di Studi Farmaceutici, Facoltà di Farmacia
Università degli Studi di Roma "La Sapienza"
Piazzale Aldo Moro 5, 00185 Roma, Italy

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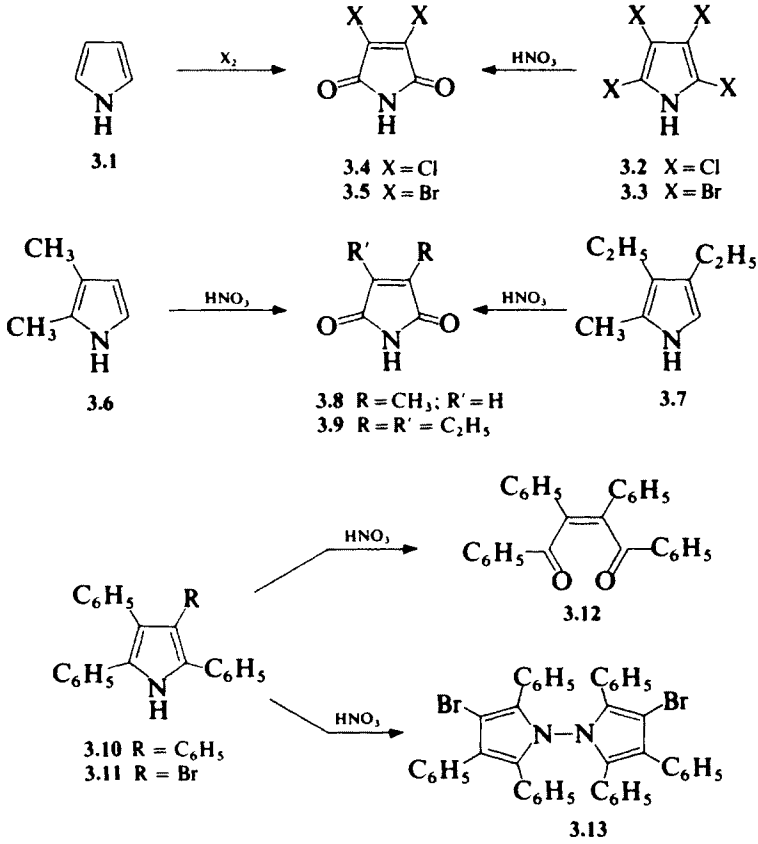
3.3.1. Introduction

As indicated in Section 3.1, the electron-rich pyrrole ring undergoes electrophilic substitution at the ring more readily than benzene and other heterocycles,[1-5] but, with strong electrophiles, such as nitric acid, sulfuric acid, and the halogens, concomitant polymerization and oxidation occur under the normal conditions required for the preparation of nitro and halogenated derivatives of benzene, benzene sulfonic acids, and thiophene. Hence, very mild conditions and selected reagents must be chosen in order to introduce into the pyrrole ring one or more nitro, sulfonic, and halogeno groups and to obtain a high regiospecific substitution.

Monosubstitution is extremely difficult in nitration and halogenation, and a mixture of several isomers is generally isolated, the isomer ratios depending on the reaction conditions and the nature of substituents already present. The medium also plays a significant role in determining the ratios of isomers.

Strongly acidic or oxidizing conditions should be avoided when electrophiles react with pyrrole, to minimize isomerization and to prevent polymerization and oxidation leading to intractable tars or oxidized pyrrolines. Thus, for example, 3,4-dihalomaleimides **3.4** and **3.5**[6-10] are obtained from the reaction of pyrrole **3.1** with chlorine or bromine under homogeneous conditions. Similarly, fuming nitric acid cannot be used in the nitration of pyrrole because of its strong oxidizing effect, which can lead to cleavage of the ring and formation of

oxidation and polymerization products. Ring opening with the formation of *cis*-dibenzoylstilbene **3.12**[11] has been observed in the action of nitric acid at high temperature on 2,3,4,5-tetraphenylpyrrole **3.10**. Loss of α-alkyl groups and halogeno groups with concomitant oxidation leads to the maleimides **3.8**, **3.9**, **3.4**, and **3.5**, respectively, when 2,3-dimethyl-, 3,4-diethyl-2-methyl-, 2,3,4,5-tetrachloro-, and 2,3,4,5-tetrabromopyrroles **3.6**, **3.7**, **3.2**, and **3.3** are allowed to react with nitric acid.[12-17] The dipyrrole **3.13** was obtained[11] under similar conditions from 3-bromo-2,4,5-triphenylpyrrole **3.11**.



3.1

3.4 X = Cl
3.5 X = Br

3.2 X = Cl
3.3 X = Br

3.6

3.8 R = CH₃; R' = H
3.9 R = R' = C₂H₅

3.7

3.12

3.10 R = C₆H₅
3.11 R = Br

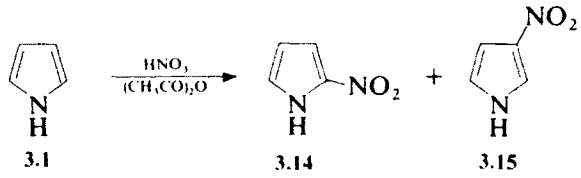
3.13

3.3.2. Nitration

Because of the facile oxidation and concomitant polymerization that pyrroles undergo in strongly acidic media, their nitration is usually performed at low temperatures, ranging from 20 to − 70°C, with nitric acid in acetic anhydride as the nitrating system.

Direct nitration of pyrrole **3.1** with a solution of 98% nitric acid in acetic anhydride at − 50°C furnishes a brown resinous material from which a solid

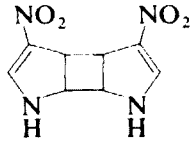
crystalline product, which melts within the range 52–58°C, can be extracted. Repeated recrystallization of this solid did not raise the melting point over 58°C. This material, initially identified as 2-nitropyrrole **3.14**,[15,16] has since been shown to be a mixture of the 2- and 3-nitro isomers **3.14** and **3.15**.[17,18]



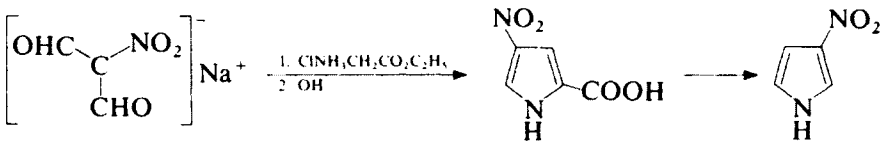
3.1 3.14 3.15

Pure 2-nitropyrrole (m.p. 63.5°C) has been isolated in paltry yield (1%) from the black mixture formed by the action of isoamyl nitrate on pyrrolyl sodium.[19] It has been erroneously claimed that this reaction affords 3-nitropyrrole **3.15**,[20–23] and the confusion in identity of the 2- and 3-nitro isomers has been resolved by Morgan and Morrey.[19] These authors reexamined the synthesis and the physicochemical properties of 2-nitro and 3-nitropyrrole in detail and concluded that the dimeric structure **3.16** postulated for 3-nitropyrrole[24] was fallacious. In fact, 3-nitropyrrole cannot be prepared by direct nitration in any reasonable yield under either acidic or alkaline conditions. The most convenient route to this compound is provided by the copper-chromite-catalyzed decarboxylation of 4-nitropyrrole-2-carboxylic acid **3.17** in quinoline.[24] An analytically pure sample of 3-nitropyrrole, obtained by this indirect procedure, has a melting point of 101°C, while column chromatography of the crude mixture obtained from direct nitration of pyrrole afforded, after recrystallization from light petroleum, pure 2-nitropyrrole (m.p. 65–66.5°C). Evidently, the lower melting points previously reported in the literature[15,16] for 2-nitropyrrole were due to the presence of small amounts of the 3-nitro isomer. The structures of the two isomers were confirmed by ^{1}H NMR spectroscopy.

The effect of solvents on the nitration of pyrrole has been investigated by Cooksey et al.[25] over a wide temperature range. When nitration was carried out



3.16



3.17 3.15

with nitric acid in solvents other than acetic anhydride, no nitropyrroles were isolated. Addition of acetic anhydride was generally found to favor the nitration in various solvents, although the yield of nitrated material was always lower than that obtained when acetic anhydride alone was used as the solvent.

The isomer ratios for the nitration of pyrrole with an equimolar amount of fuming (98%) nitric acid–acetic anhydride mixture in various solvents at $-10°C$ are presented in Table 3.3.1. When a 2:1 ratio of fuming nitric acid–acetic anhydride was employed, the formation of small quantities of 2- and 3-acetylpyrrole was observed and the addition of perchloric acid increased the total yield of 2- and 3-acetylpyrroles to 34%. Under these conditions no 1-acetylpyrrole or nitroacetylpyrroles were formed. No substantial changes in the relative yields were observed when 70% nitric acid–acetic anhydride (1:1) was used as the nitrating system.

TABLE 3.3.1. DIRECT NITRATION OF PYRROLE WITH 98% HNO_3–ACETIC ANHYDRIDE (RATIO 1:1) IN VARIOUS SOLVENTS AT $-10°C$

	Yield (%) of	
Solvent	2-Nitropyrrole	3-Nitropyrrole
Acetic anhydride	50.7	13.0
Nitromethane	33.5	9.5
Carbon tetrachloride	28.6	1.8
Acetic acid[a]	27.0	6.3
Acetonitrile	26.9	6.3
Tetrahydrofuran	2.5	0.7
Diethyl ether	0.5	0.1

[a] Temperature of reaction: 20°C.

Acetyl nitrate, which is formed by the reaction of nitric acid with acetic anhydride, has been invoked as the effective nitrating agent. However, the concentration of this species is strictly dependent on the reagent present in excess. The further addition of acetic anhydride to the 1:1 mixture of the nitric acid–acetic anhydride system increases the concentration of the acetyl nitrate, but this species is destroyed by an excess of nitric acid with formation of dinitrogen pentoxide.[25]

$$(CH_3CO)_2O + HNO_3 \rightleftarrows CH_3COONO_2 + CH_3COOH$$

$$CH_3COONO_2 + HNO_3 \rightleftarrows N_2O_5 + CH_3COOH$$

It has also been observed that the nitration of pyrrole with solutions of acetyl nitrate, prepared by distillation of a solution of dinitrogen pentoxide in acetic anhydride, gave a black tar with yields of the nitropyrroles inferior to those obtained by nitration with fuming nitric acid–acetic anhydride mixture (Table 3.3.2). Further nitration experiments with dinitrogen tetroxide, which could originate from dinitrogen pentoxide or acetyl nitrate by partial decompo-

TABLE 3.3.2. NITRATION OF PYRROLE WITH ACETYL NITRATE OR WITH THE MIXTURE 98% NITRIC ACID–ACETIC ANHYDRIDE (1 : 1)

Solvent	Total Yields of Nitropyrroles (%)	
	CH_3COONO_2	98% $HNO_3/(CH_3CO)_2O$
Acetic anhydride	25	64
Nitromethane	28	43
Acetic acid	0	34
Acetonitrile	25	33
Carbon tetrachloride	5	30
Tetrahydrofuran	0	3
Diethyl ether	5	0.6

TABLE 3.3.3. EFFECTS OF TEMPERATURE ON NITRATION OF PYRROLE WITH 98% NITRIC ACID–ACETIC ANHYDRIDE (1 : 1) SYSTEM

Reaction Temperature (°C)	Overall Yields of Nitropyrroles (%)	
	a	*b*
20	69.5	69.5
− 10	63.7	59.0
− 30	43.8	30.2
− 40	37.0	21.3
− 50	31.5	9.8
− 70	28.4	2.5

[a] Nitric acid was added to acetic anhydride at 20°C and then the mixture was cooled to reaction temperature.
[b] Nitric acid was cooled to reaction temperature before addition to acetic anhydride.

sition, clearly indicate that preliminary nitrosation is not involved in the nitration of pyrrole.

The effect of temperature on the nitration of pyrrole is reported in Table 3.3.3. Generally, the yields of nitropyrroles decrease notably when the temperature falls from 20 to − 70°C, but the decrease can be minimized if the nitrating species is preformed at 20°C before the system is subsequently cooled to the reaction temperature [the formation of acetyl nitrate is more rapid at 20°C (within 10 min) than at lower temperatures], as high concentrations of the nitrating species are obtained by this procedure.

The use of 70% nitric acid in acetic anhydride does not produce any nitropyrroles at temperatures below − 20°C because of the low concentration or the absence of acetyl nitrate in the nitrating mixture, and it is difficult to avoid the acid-catalyzed formation of black tars even at − 70°C (see Table 3.3.3).

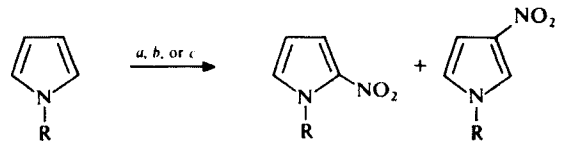
Further nitration of both 2-nitro- and 3-nitropyrrole results in the formation of 2,4-dinitropyrrole as the major product.[17] However, a concomitant production of minor amounts of the 2,5-dinitro and 3,4-dinitro isomers was also

observed during nitration of 2-nitro- and 3-nitropyrroles, respectively. Thus, the nitration of 2-nitropyrrole led to a 8:1 ratio of 2,4-dinitro- and 2,5-dinitropyrrole in an overall yield of 37.5%,[15,16] while nitration of 1-methyl-3-nitropyrrole furnished a more complex mixture of dinitro and trinitro isomers.[26]

The nitration pattern of unsubstituted pyrrole changes notably when a methyl, benzyl, or phenyl group is introduced at the 1 position. The steric effect of the 1-substituent inhibits the relative ease of 2-substitution. Consequently, nitration at the 3 position of the pyrrole ring is more favored in the case of both 1-methylpyrrole and its derivative bearing electron-withdrawing groups in the 2 position, compared with the corresponding 1-unsubstituted systems. A similar behavior is shown by 1-benzylpyrrole[27] and 1-phenylpyrrole.[28]

Nitration of various 1-substituted pyrroles with 100% nitric acid in acetic anhydride at $-20°C$ (R = alkyl) or 0°C (R = aryl) has been investigated by Doddi et al.[26] A mixture of 2-nitro- and 3-nitro-1-substituted pyrroles was obtained in acceptable yields, and the isomers were easily separated by column chromatography on silica gel (Table 3.3.4). By far the greatest steric effect is exerted by the triisopropylsilyl group,[30] followed in the order by *t*-butyl, *i*-propyl, and benzyl groups. Almost equivalent amounts of the two isomers were obtained with 1-aryl substituents, whereas no appreciable presence of the

TABLE 3.3.4. NITRATION OF PYRROLE AND ITS 1-SUBSTITUTED DERIVATIVES



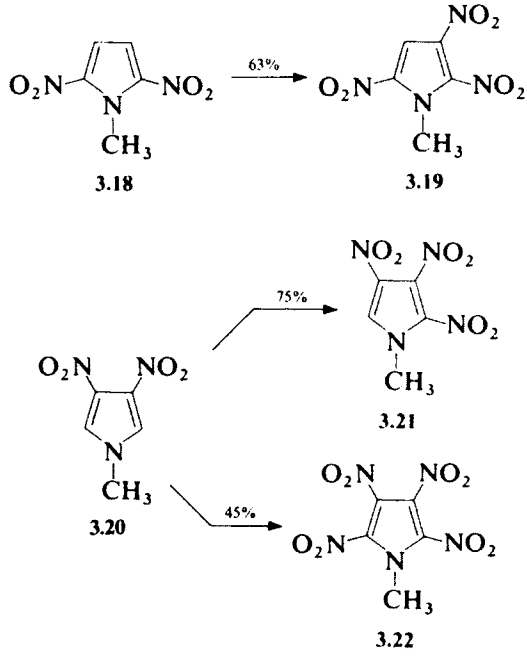
R	Nitrating System	Overall Yield (%)	Yield (%) and Ratio of α and β-isomers α	β	α/β	Reaction Temp. (°C)	Ref.
H[a]	*b*	55	55.0	Trace	—	− 50	19
CH_3	*c*	34	25.8	8.2	3.15	− 20	26
	b	26	19.0	7.0	2.71	− 10	17, 18
i-Pr	*c*	62	22.3	39.7	0.56	− 20	26
t-Bu	*c*	55	11.0	44.0	0.25	− 20	26
$CH_2C_6H_5$	*b*	62	25.0	37.0	0.68	− 10	27
$SO_2C_6H_5$	*b*	24	Trace	24.0	—	—	29
$Si(i\text{-}Pr)_3$	*d*	~ 85	< 5.0	80.0	~ 0.06	—	30
C_6H_5	*b*	66	44.0	22.0	2.00	− 10	28
2-$NO_2C_6H_4$	*c*	53	27.4	25.6	1.07	0	26
4-$NO_2C_6H_4$	*c*	34	20.0	14.0	1.43	0	26

[a] Chromatographic purification of the 2- and 3-nitro isomers mixture did not allow to separe the 3-nitro isomer in detectable yield.
[b] 98% nitric acid–acetic anhydride.
[c] 100% nitric acid–acetic anhydride.
[d] $Cu(NO_3)_2$/acetic anhydride.

3-isomer was observed with pyrrole. The combined electronic and steric effect of a 1-benzenesulfonyl substituent results in the exclusive formation of the 3-nitro derivative.[29]

No nitration of the pyrrole ring was observed when 1-phenylpyrrole was reacted with nitric acid in concentrated sulfuric acid. The conjugate acid of pyrrole, which is formed under these conditions, is much less reactive toward electrophiles than is the phenyl ring, and 1-(4-nitrophenyl)pyrrole was obtained as the only product from the reaction in a 25% yield.[28]

The synthesis of the 1-methyltrinitropyrroles **3.19** and **3.21** has been effected by nitration of 2,5-dinitro- **3.18** and 3,4-dinitro-1-methylpyrrole **3.20**, respectively, with 100% nitric acid in 96% sulfuric acid at 0°C.[26] Under more vigorous conditions (fuming sulfuric acid and heating at 65°C for 15 min), 1-methyl-2,3,4,5-tetranitropyrrole **3.22** was obtained in 45% yield from 3,4-dinitropyrrole **3.20** (compound **3.22** is the first tetranitrosubstituted heteroaromatic derivative described in the literature).



3.18 **3.19** **3.20** **3.21** **3.22**

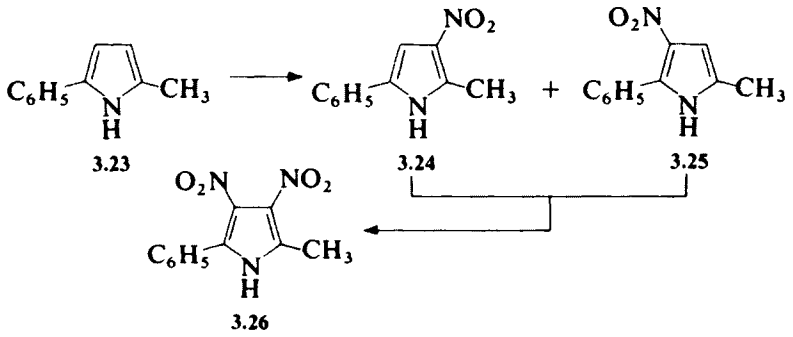
A mixture of dinitro and trinitro compounds are formed when 3-nitro-1-substituted pyrroles are nitrated with 100% nitric acid in concentrated sulfuric acid at 0°C (Table 3.3.5).

Nitration of 2-alkylpyrroles has been claimed to afford a mixture of 5-, 3-, and 4-nitropyrroles, although the presence of the 4-isomer was not always observed.[3] Thus, nitration of 2-methylpyrrole with fuming nitric acid and acetic anhydride at -50°C furnished a 4.3:1 ratio of 5- and 3-nitro-2-methylpyrrole,[31] while from 2-methyl-5-phenylpyrrole **3.23**, by sequential nitration,

TABLE 3.3.5. NITRATION OF 1-SUBSTITUTED 3-NITROPYRROLES

	Relative Yields (%)			
	Dinitropyrroles		Trinitropyrroles	
1-Substituent	2,4-Isomer	3,4-Isomer	2,3,4-Isomer	2,3,5-Isomer
CH_3	74	13	9	4
i-Pr	66	23	11	1
t-Bu	43	41	16	—
2-$NO_2C_6H_4$	72	28	—	—
4-$NO_2C_6H_4$	75	15	10	—

both the 3- and 4-nitro isomers, **3.24** and **3.25**, and then the 3,4-dinitro derivative **3.26** were obtained.[32] Despite the very low yield (2.3%), the best route, to the mononitro derivatives **3.24** and **3.25** uses 98% nitric acid–acetic anhydride (1 : 1) in nitromethane at − 20°C.

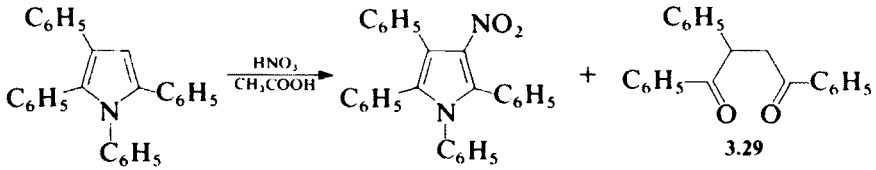


The presence of an additional electron-donating methyl substituent in the 2 position of the pyrrole ring enhances the nitration rate of 1-methylpyrrole. Hence, 1,2-dimethylpyrrole can be nitrated at a lower temperature than 1-methylpyrrole to give higher yields of a mixture of 5-, 3-, and 4-nitro-1,2-dimethylpyrrole[33] in the ratio 5 : 3 : 2. However, a tendency for the substrate to undergo undesirable side reactions with an increase in the formation of polynitro derivatives and of tars was noticed.

Difficulties have been encountered in the preparation of 1,2,5-trimethyl-3-nitropyrrole.[34] Friedel–Crafts alkylation of the known 1,2-dimethyl-3-nitropyrrole using iodomethane in the presence of aluminum chloride has been found to be unsuccessful. On the other hand, although direct nitration of 1,2,5-trimethylpyrrole with nitric acid and acetic anhydride leads to 1,2,5-trimethyl-3-nitropyrrole, the pure compound can be obtained in only very low yield (2.5%) and only after prolonged and tedious chromatographic purification. However, careful regulation of the reaction time and temperature and the use of potassium nitrate and sulfuric acid, as the nitrating system, results in the formation of 1,2,5-trimethyl-3-nitropyrrole in 73% yield. The unexpectedly high yield is due to the

fact that the water content of 98% nitric acid is avoided and the potassium nitrate–sulfuric acid nitration system is less destructive to sensitive pyrrole compounds.

3-Nitro derivatives are formed more easily with polyphenyl-substituted pyrroles.[35–37] Thus, for example, nitration of 1,2,3,5-tetraphenylpyrrole **3.27** with 98% nitric acid in acetic acid yields the expected 4-nitro derivative **3.28**, with a small amount of a ring-opened product, which has been assumed to be 1,2-dibenzoyl-1-phenylethane **3.29**.[11]



3.27 3.28 3.29

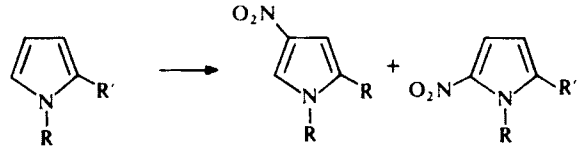
As indicated earlier, the presence of an electron-withdrawing group in the 2 position of the pyrrole ring generally produces an increased reactivity of the 4 position toward electrophilic attack, with a corresponding deactivation of the 5 position. The concomitant steric effect exerted by the 1-substituent also increases the relative amount of the 4-nitro derivative.

Extensive and detailed studies of the nitration of pyrroles having an electron-withdrawing group at the 2 position have been undertaken by several authors.[15–18,24,38–46] The directive effects of 2-cyano group on the nitration of pyrrole and 1-methylpyrrole with acetyl nitrate (the nitrating species present in the fuming nitric acid–acetic anhydride mixture) at 0–10°C have been shown[38] to lead to the formation of the 4-nitro- and 5-nitro-2-cyanopyrroles. The structures of these nitriles were confirmed by comparison with the same derivatives prepared by dehydration of 4- and 5-nitro-2-pyrrolecarboxaldehyde aldoximes.[16,49] The α-directing effect of the pyrrolyl nitrogen atom is counterbalanced by the deactivating effect of the cyano group, so that the ratio of the 4- and 5-nitro isomers is approximately 1:1.5, in an overall yield of 78.6%. However, the corresponding nitration of 2-cyano-1-methylpyrrole leads to a higher proportion of the 2-cyano-4-nitro-1-methylpyrrole, compared with the 5-isomer (2.3:1). The observation is compatible with the expected steric effect of the 1-methyl group.

It has been pointed out by Anderson[38] that the cyano group has a considerable lower meta-directing effect, compared with acetyl and nitro groups, and somewhat smaller than the effect showed by methoxycarbonyl group. This observation differs from the benzene series, where the meta-directing ability of cyano groups in nitration lies between that of the nitro and acetyl groups but is similar to that recorded for the thiophene series.

In the case of ethyl 1-methylpyrrole-2-carboxylate, nitration afforded only the 4-nitro derivative, with no trace of the 5-nitro isomer.

TABLE 3.3.6. NITRATION OF PYRROLES BEARING AN ELECTRON-WITHDRAWING GROUP AT THE 2 POSITION WITH NITRIC ACID–ACETIC ANHYDRIDE



Substrate		Overall Yield	Yield (%) 4-Nitro isomer	5-Nitro isomer	$\beta:\alpha$ Ratio	HNO_3 Conc. (%)	Temp. (°C)	Ref.
R	R′	(%)						
H	NO_2	36	32.1	3.9	8.2	98	− 25	16
		61	48.8	12.0	4.0	70	− 15	1, 15
		—	—	—	2.0	98	− 40	1, 46, 52
CH_3	NO_2	32	24.6	7.4	3.3	98	− 45	17
		46	32.9	13.1	2.5	98	− 40	1, 46, 53
H	CHO	34.6	17.3	17.3	1.0	98	− 40	16, 41[a], 44
		32	16.0	16.0	1.0	98	− 40	18
		32.56[b]	—	—	—	70	− 15	39
		—	—	—	1.4	98	− 40	1, 46
		67.9	33.3	34.6	0.96	98	− 45	40
CH_3	CHO	30	22.7	7.3	3.1	98	− 45	17, 41[a]
		26	18.6	7.4	2.5	98	− 40	1, 46
		—	—	—	4.0	98	− 40	1, 46
H	$COCH_3$	23	14.8	8.2	1.8	98	− 30	18
		—	—	—	1.3	98	− 40	1, 46
		24.1	15.6	8.5	1.8	98	− 30	16
		40	26.0	14.0	1.86	70	− 10	2, 15
		45.45[b]	—	—	—	70	− 15	39
CH_3	$COCH_3$	—	23.4	—	—	98	—	17, 18
		47	40.3	6.7	6.0	98	0	24
		—	—	—	2.1	98	− 40	1, 46
H	$COCl_3$	77	77.0	Traces	—	90	− 50	43
H	CN	73	28.0	45.0	0.6	98	0	38, 16
		—	—	—	0.7	98	− 40	1, 46
CH_3	CN	66	46.5	19.5	2.4	98	0	38, 17
		—	—	—	1.9	98	− 40	1, 46, 49
H	COOH	37	18.5	18.5	1.0	70	− 15	16, 15, 24
		—	—	—	1.2	98	− 40	46, 50, 51
		39	—	—	—	70	− 15	39
CH_3	COOH	73.4[c]	17.3[d]	4.7[d]	3.7	98	− 10	17, 42
		—	—	—	2.1	98	− 40	37
H	$COOCH_3$[e]	47.8[b]	—	—	—	70	− 15	39, 43
		46	20.4	25.6	0.8	70	− 10	1, 15, 46
CH_3	$COOC_2H_5$	—	25[f]	—	—	98	− 5	38, 24, 50

[a] Improved yields of each isomer were obtained by a minor modification of the procedure of Fournari and Tirouflet.

[b] No data on yields of the single 4- and 5-nitro isomers were reported.

[c] Calculated on crude mixture of nitroacids.

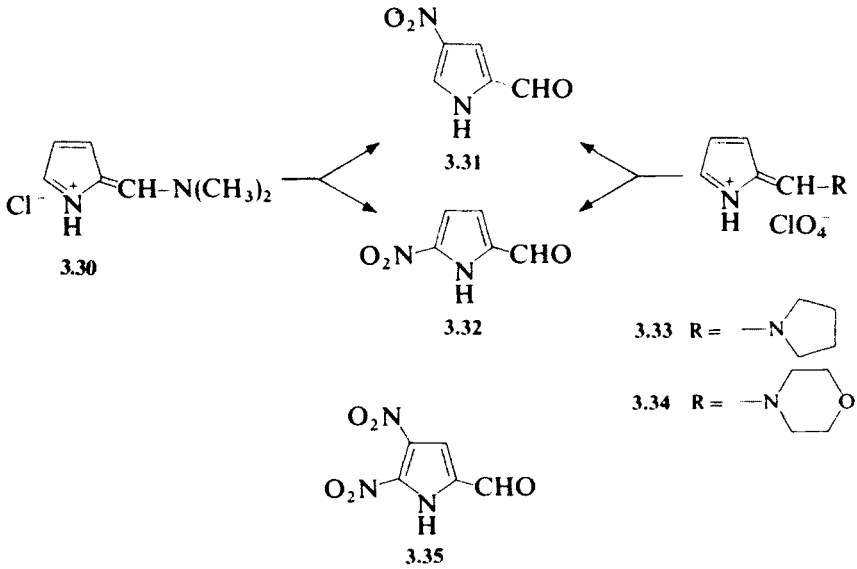
[d] Calculated after reaction with diazomethane and chromatographic separation of isomeric nitroesters.

[e] Nitration of methyl pyrrole-3-carboxylate gave only methyl 2-nitropyrrole-4-carboxylate in 55% yield.

[f] No 5-isomer detected.

Tirouflet and Fournari[16,17] have studied the nitration of pyrrole and of 1-methylpyrrole having, at the 2 position, the following electron-withdrawing groups: formyl, acetyl, ethoxycarbonyl, carboxyl, and nitro. Table 3.3.6 records the ratios of the 4- and 5-nitro isomers, which were determined by polarographic analysis, together with data obtained by other authors.

An increased regiospecific substitution at the 4 position was observed in the nitration of the 2-azafulvenium salt **3.30**.[45] The relative amounts of the 4-nitro- and the 5-nitropyrrole-2-carboxaldehydes **3.31** and **3.32**, obtained after hydrolysis of the crude mixture of reaction was 2.3:1, whereas a 1:1 ratio of the two isomers was obtained by direct nitration of 2-formylpyrrole with equimolar amount of fuming nitric acid in acetic anhydride.[16,18,40,41] In a similar reaction, the azafulvenium salt **3.33** (or **3.34**), obtained from 2-formylpyrrole and pyrrolidine (or morpholine), led to the 4-nitro- and 5-nitro-2-formylpyrroles **3.31** and **3.32** or to the azafulvenium salt of the 4,5-dinitro-aldehyde **3.35**, depending on the reaction conditions.[44]



The synthesis of nitropyrrole aldehydes has been studied[40] by Fournari et al., who identified and described all of the theoretically possible mononitropyrrole-aldehydes (Table 3.3.7) and some of the corresponding nitropyrrolecarboxylic acids.

Formyl, acetyl, and carboxyl groups may be lost during nitration of pyrroles with fuming nitric acid in acetic anhydride. Either nitration at the free ring positions or ipso-substitution of the carbonyl groups can occur with formation of mixtures. In particular, nitration of ethyl 5-formylpyrrole-2-carboxylate **3.36** has been reported to yield a mixture of **3.37**, **3.38**, and **3.39** in approximately equal amounts, whereas a similar reaction on the 4-formyl isomer **3.40** led to the predominant formation of the 5-nitro derivative **3.41**, with lesser amounts (10%) of the nitropyrroles **3.42** and **3.43**.

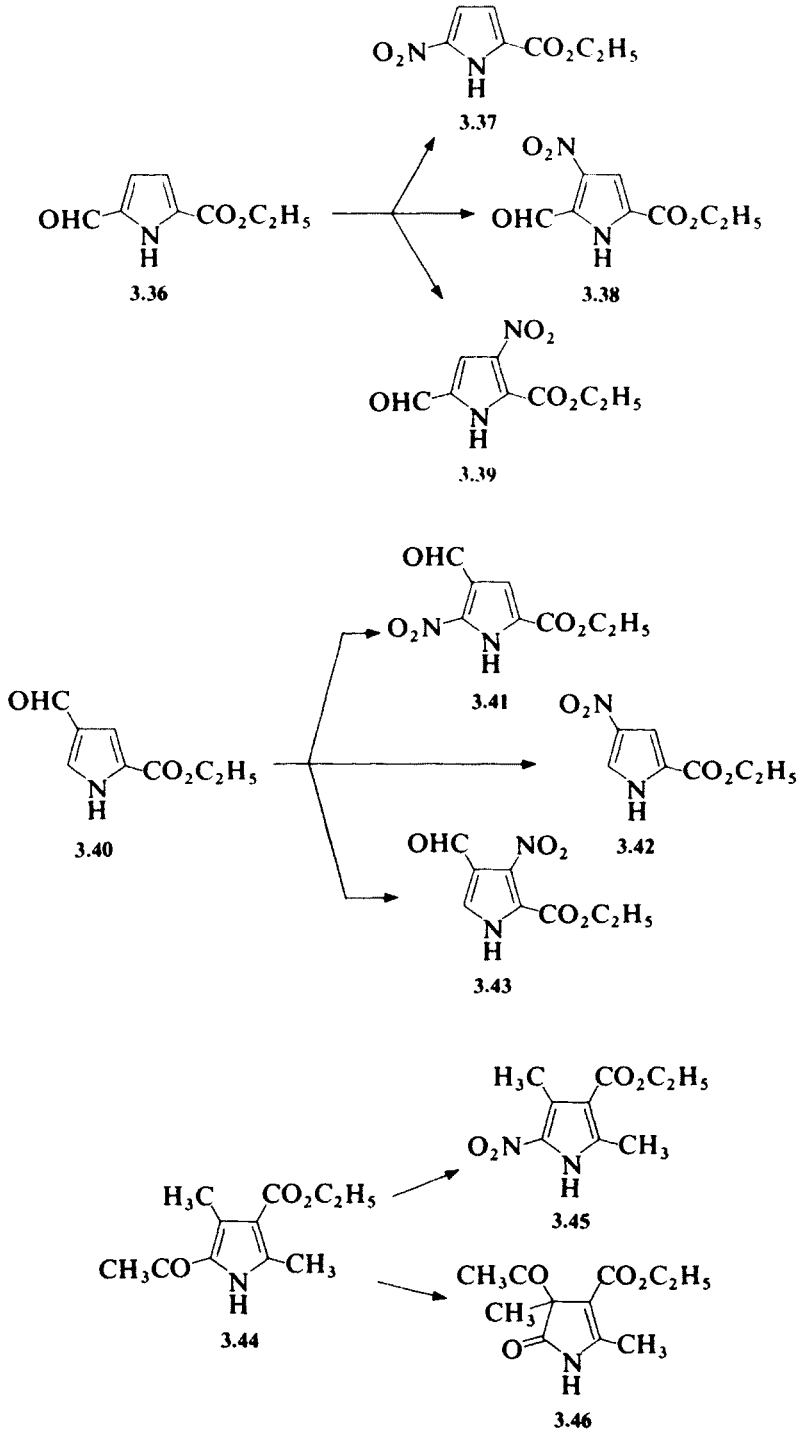
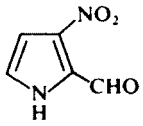
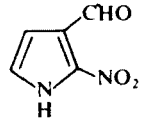
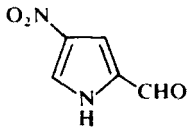
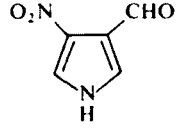
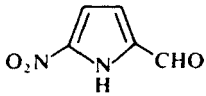
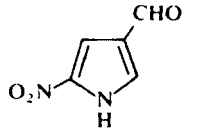
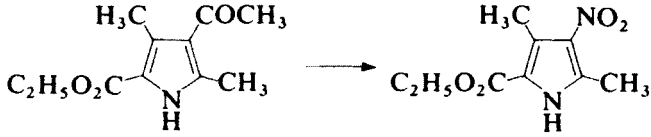

O2N
CO2C2H5
N
H
3.37
OHC
CO2C2H5
3.36
O2N
3.38
NO2
3.39
OHC
3.41
3.40
3.42
3.43
H3C
CH3CO
CH3
O
3.44
3.45
3.46

TABLE 3.3.7. MONONITROPYRROLEALDEHYDES

Formula	Melting Point (°C)	Ref.	Formula	Melting Point (°C)	Ref.
	153[a]	40		170[a,b]	40
	142[a,b]	40, 46		189[a,b]	40
	185[a,b]	40, 46		159[a]	40

[a] By direct nitration.
[b] By indirect synthesis.

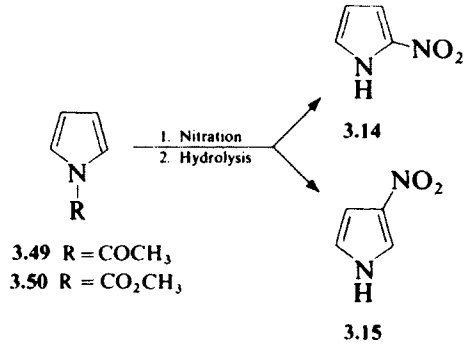
With fully substituted pyrroles, the replacement reaction takes place readily for both α- and β-acetyl groups, whereas the alkoxycarbonyl groups are unaffected by fuming nitric acid. Thus, methyl 2,4-dimethyl-5-acetylpyrrole-3-carboxylate **3.44** and methyl 2,4-dimethyl-3-acetylpyrrole-5-carboxylate **3.47** give, respectively, the 5-nitro and 3-nitro derivatives **3.45** and **3.48**.[47,48] Transformation of **3.44** into pyrrolidinone **3.46** was also observed.[48]



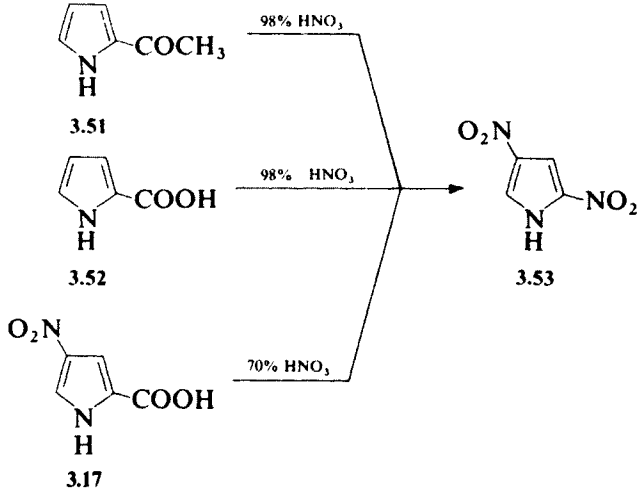
3.47 **3.48**

Nitration of 1-acetylpyrrole **3.49** with 70% nitric acid–acetic anhydride, followed by facile removal of the acetyl group in alkaline medium, furnishes a 1 : 1 mixture of the 2-nitro- and 3-nitropyrroles **3.14** and **3.15**, thus providing an useful route to the isomeric nitropyrroles for preparative purposes. The same results were obtained with methyl pyrrole-1-carboxylate **3.50** as a substrate.[39]

The nitration of acetylpyrroles is greatly affected by both the position of acetyl groups and the concentration of nitric acid in acetic anhydride. Depending on the concentration, the nitric acid can act either as a nitrating or an

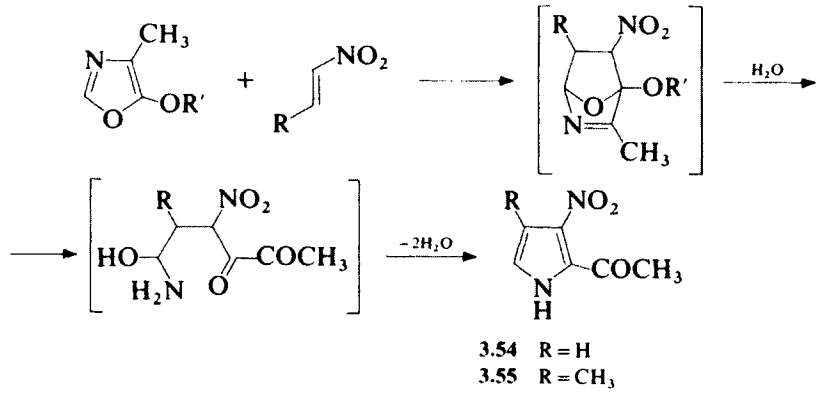


oxidizing agent, and the position of the acetyl group is crucial to whether it is lost. Both displacement reactions and nitration occur when 2-acetylpyrrole **3.51** is treated with fuming acid, leading to the formation of 2,4-dinitropyrrole **3.53**, as the main product. The dinitro derivative **3.53** is also formed from reaction of 2-carboxypyrrole **3.52** and from 4-nitro-2-carboxypyrrole **3.17** with 98 and 70% nitric acid, respectively.[52,54,55] In contrast, when the reaction of 2-acetylpyrrole **3.51** with fuming nitric acid was conducted in the presence of acetic anhydride at − 30°C, a mixture of 24% of 2-acetyl-4-nitropyrrole and 16% of 2-acetyl-5-nitropyrrole was recovered.[15]



A viable route to the 3-nitro-2-acetylpyrroles **3.54** and **3.55**, which are not available by direct nitration of the related acetylpyrroles, is offered by the reaction between a 5-alkoxy-4-methyloxazole and 2-substituted nitroethenes in benzene at − 4°C, followed by the hydrolysis of the intermediate Diels–Alder adduct in acidic medium[56,57] (Scheme 3.1).

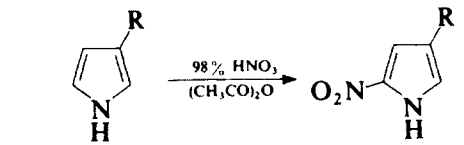
Only nitration takes place at the 5 position with formation of derivatives **3.59–3.61** through the action of fuming nitric acid on 3-acetyl- **3.56**, 3-carboxy- **3.57**, and 3-methoxycarbonylpyrrole **3.58**; however, when the 2- and 3-acetyl



3.54 R = H
3.55 R = CH_3

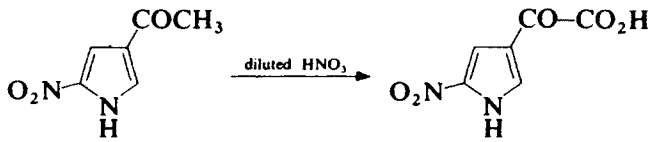
Scheme 3.1

substituted nitropyrroles are heated with diluted nitric acid, oxidized products are formed instead of the dinitropyrroles.[39] Thus, 2-nitro-4-acetylpyrrole **3.62** furnishes 2-nitropyrrol-4-ylglyoxalic acid **3.63** and, under similar conditions, 4-nitro- and 5-nitro-2-acetylpyrroles **3.64**, yield the related 3,4-di(4- or 5-nitropyrrol-2-yl)furoxans **3.65**.

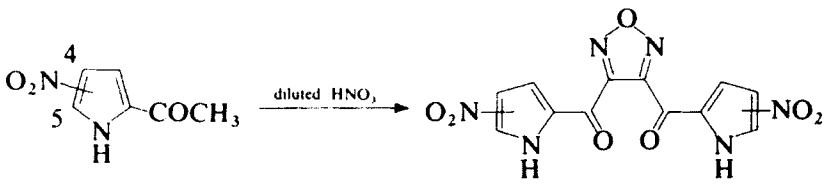


3.56 R = $COCH_3$
3.57 R = COOH
3.58 R = CO_2CH_3

3.59 R = $COCH_3$
3.60 R = COOH
3.61 R = CO_2CH_3



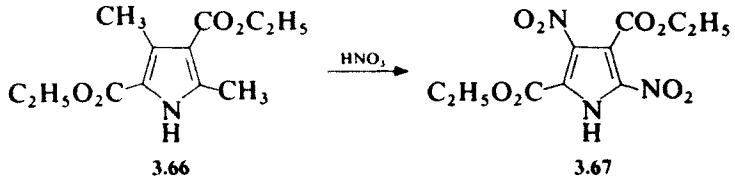
3.62 **3.63**



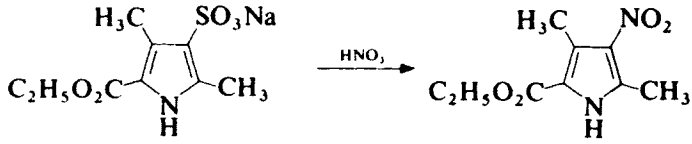
3.64 **3.65**

Methyl groups may be replaced by nitro group during the nitration with fuming nitric acid through a two-step pathway involving oxidation of methyl group and subsequent displacement of the formed carboxyl group by the

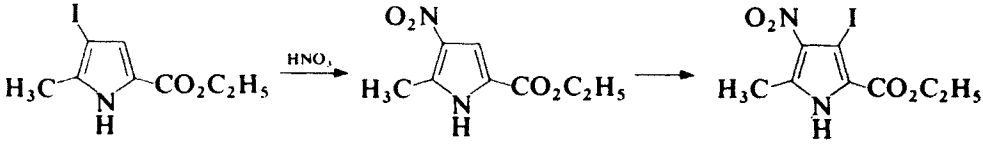
nitronium ion.[54] Sulfonic acid groups[58] and iodine[59] are also displaced during nitration of the pyrrole ring, for example, **3.66** → **3.67**; **3.68** → **3.69**.



3.66 **3.67**



3.68 **3.69**

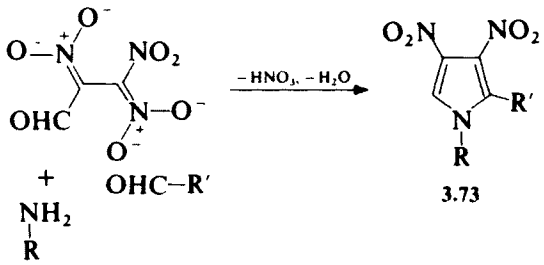


3.70 **3.71** **3.72**

In the nitration of **3.70**, the nitrated intermediate **3.71** formed by the displacement reaction of iodo group is thought to be immediately reiodinated to form the iodonitro derivative **3.72**.

The use of amyl nitrite in nitration of pyrroles is documented by the preparation of 3-nitro-2,4,5-triphenylpyrrole from 2,4,5-triphenylpyrrole.[60]

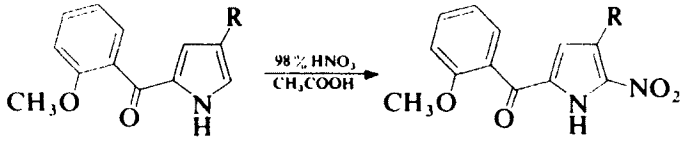
3,4-Dinitropyrroles are not available by the direct nitration of pyrroles, but they have been synthesized from the dipotassium salt of 2,3,3-trinitropropionaldehyde by the reaction with a primary amine and an aliphatic aldehyde in the presence of ammonia. Yields are generally low (10–20%), but a 40% yield has been reported for **3.73** (R = H and R′ = CH_3).[61–63]



3.73

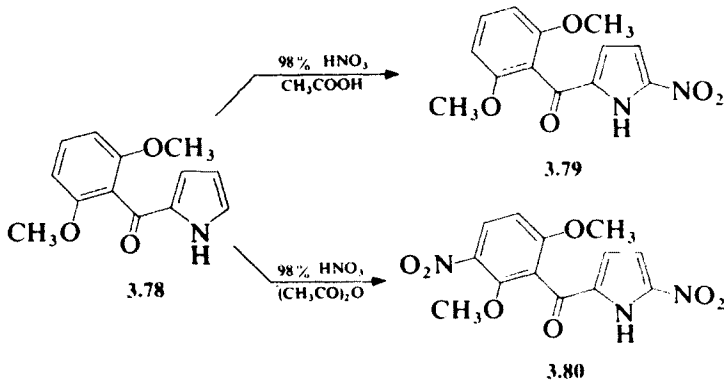
During studies on nitro analogs of pyoluteorins, nitration of 2-(2-methoxybenzoyl)pyrrole **3.74** and 2-(2,6-dimethoxybenzoyl)pyrrole **3.78** were investigated under different conditions.[64] When **3.74** was heated at 70–80°C with

fuming nitric acid in acetic acid, 2-(2-methoxybenzoyl)-5-nitropyrrole **3.76** was obtained in 75% yield, and a similar nitration of **3.78** furnished 2-(2,6-dimethoxybenzoyl)-5-nitropyrrole **3.79**. When acetic anhydride was used as the solvent, in addition to **3.79**, an unstable by-product was also formed from **3.78**, which was identified as 2-(2,6-dimethoxy-3-nitrobenzoyl)-5-nitropyrrole **3.80**. 4-Chloro-2-(2-methoxybenzoyl)-5-nitropyrrole **3.77** has also been prepared by this procedure starting from 4-chloro-2-(2-methoxybenzoyl)pyrrole **3.75**.



3.74 R = H
3.75 R = Cl

3.76 R = H
3.77 R = Cl



3.78

3.79

3.80

Studies on chemotherapeutic nitroheterocycles led Colwell et al.[41] to synthesize various nitropyrrole-2-carboxyaldehydes. They obtained 4-nitro- and 5-nitropyrrole-2-carboxaldehydes **3.31** and **3.32** by a convenient modification of the classic procedure of Fournari and Tirouflet.[16] Addition of the nitration reagent under carefully controlled temperature conditions improved the yields of each isomer, and, under similar conditions, direct nitration of 2-formyl-1-phenylpyrrole gave only the 4-nitro isomer in moderate yield (20%) and none of the 5-nitro isomer. Nitration of 2-methyl-1-phenylpyrrole, from which the required 5-nitro aldehyde could conceivably be prepared, furnished an inseparable mixture of at least three isomeric nitropyrroles. Hence, all attempts to prepare 2-formyl-5-nitro-1-phenylpyrrole either by direct or by indirect syntheses have been devoid of success, although various other 1-alkyl derivatives of 2-formyl-5-nitropyrrole[41] have been obtained by standard *N*-alkylation procedures.

3.3.3. Sulfonation

The action of concentrated sulfuric acid and oleum on pyrrole and its *N*- and *C*-alkyl derivatives produces only oxidized and polymerized products as a result of the strong conditions created by these sulfonating agents. For this reason, only few examples of sulfonation of pyrroles are found in the chemical literature. However, some pyrrolesulfonic acids can be prepared by the use of the pyridine–sulfur trioxide complex as the sulfonating agent at 100°C.

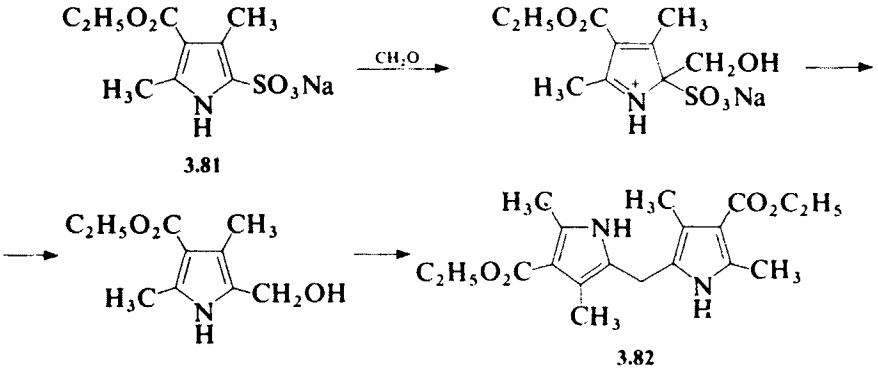
Generally, 2-sulfonation occurs in a large extent, while sulfonation at the 3 position is very difficult even when the α positions are both occupied. Sulfonation of pyrrole and alkylpyrroles has been carried out with the pyridine–sulfur trioxide complex in a sealed tube at 100°C, with the products being isolated as their barium salts.[3] Other sulfonic acids have been synthesized from 2-chloropyrrole and 1-phenylpyrrole using the pyridine–sulfur trioxide complex[65,66] at 60°C to produce, respectively, 2-chloropyrrole-5-sulfonic acid (40%) and 1-phenylpyrrole-2,4′-disulfonic acid, resulting from sulfonation on both the pyrrole and benzene rings.

Sulfonation of 2,5-dialkylpyrroles has been performed under milder conditions in benzene, whereas the presence of an electron-withdrawing substituent makes the sulfonation of the pyrrole ring more difficult and very strong reaction conditions are required, such as concentrated sulfuric acid, oleum, or chlorosulfonic acid. Thus, 2,4-dimethyl-3-ethoxycarbonylpyrrole-5-sulfonic acid has been synthesized in 80% yield from the reaction of ethyl 2,4-dimethylpyrrole-3-carboxylate with 5% oleum. A similar reaction conducted on ethyl 2,4-dimethylpyrrole-5-carboxylate furnished the 3-sulfonic acid derivative.[58] Ciamician and Silber[67] reacted 2-acetylpyrrole with sulfur trioxide and obtained the corresponding 4-sulfonic acid as the potassium salt.

2-Pyrrolylsulfones can be easily prepared by the reaction of pyrrolyl potassium with the chlorides of arylsulfonic acids, while 2-pyrrolylsulfoxides, together with traces of the 3-isomers, form when pyrrole and its 1-methylderivative are allowed to react with the chlorides of aryl- and alkylsulfinic acids. In the latter reaction the acid-catalyzed reversibility of sulfination reaction was invoked to account for the formation of 3-isomer[68] (see Section 3.2.4). 1-Pyrrolylphenylsulfone, prepared from pyrrole and benzenesulfonyl chloride, is a particularly valuable starting material in the synthesis of 3-substituted pyrroles, because of both the regiospecific attack of electrophiles at the 3 position of the pyrrole ring and the facile removal of the protecting-directing benzene sulfonyl moiety[69] (see Section 3.4.3.3). However, although the presence of the arenesulfonyl group at the 1 position has been found to affect greatly the reactivity of the electrophiles toward the preferred 3 position of pyrrole, the usefulness of the method has been proved only in the acylating processes.[2] The 1-arenesulfonyl moiety is easily removed by alkaline hydrolysis under mild conditions to afford 3-substituted pyrroles. 2-Formyl-1-(2-nitrobenzenesulfonyl)pyrrole, prepared by the reaction of 2-nitrobenzenesulfonyl chloride on

the potassium salt of 2-formylpyrrole, has been used as the key intermediate in the synthesis of potential antitumor tricyclic pyrrolobenzothiadiazepines.[70]

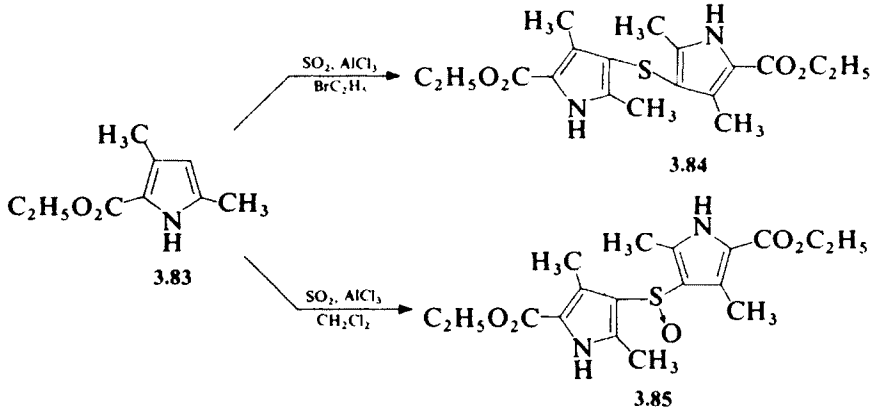
Sulfonic acids suffer displacement reaction when treated with bromine or nitric acid[58] and form dipyrromethanes when reacted with formaldehyde in an acidic medium,[71] for example, **3.81** → **3.82**.



3.81

3.82

Treibs et al. isolated the bis(3-pyrrolyl)sulfide **3.84** from the reaction of ethyl 2,4-dimethylpyrrole-5-carboxylate **3.83** in bromoethane with sulfur dioxide in the presence of aluminum chloride. The same reaction furnished the bis(3-pyrrolyl)sulfoxide **3.85** when dichloromethane instead of bromoethane was used as a solvent.[72]



3.84

3.83

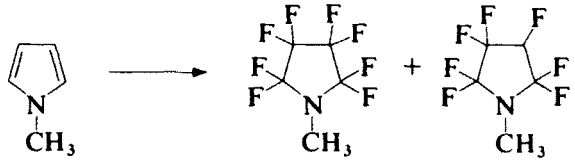
3.85

Treatment of 2-substituted pyrroles with chlorosulfonyl isocyanate affords the 4-cyano derivatives via the initial formation of the corresponding chlorosulfonyl amides as the only products when 2-formyl, 2-cyano, and 2-trichloroacetyl pyrroles were used as substrate. A 2:1 mixture of 4- and 5-cyano compounds was obtained when chlorosulfonyl isocyanate reacted with 2-acetyl- and 2-methoxycarbonylpyrroles.[73]

3.3.4. Halogenation

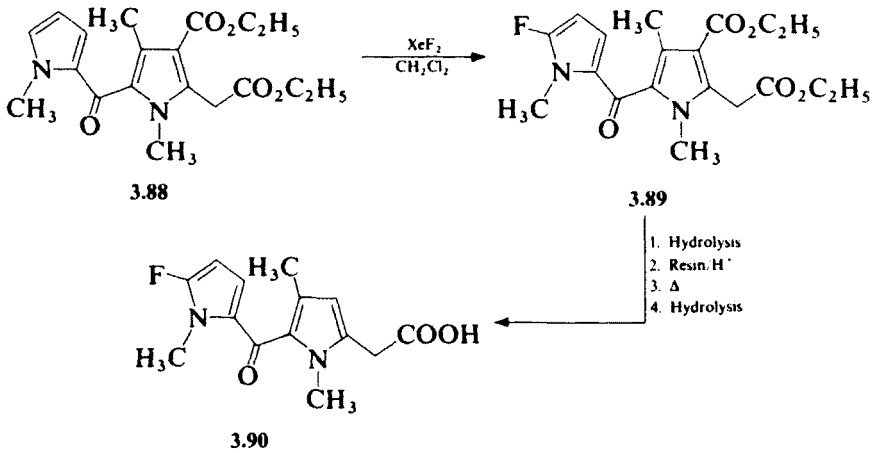
3.3.4.1. Fluorination

The reaction of pyrrole or its derivatives with elemental fluorine or hydrofluoric acid has not been described in the literature. However, it has been recorded that a mixture of polyfluoropyrrolidines were obtained, when 1-methylpyrrole was reacted with potassium tetrafluorocobaltate(III) and cobalt(III) fluoride during an attempt to introduce fluorine into the pyrrole ring. The major products were octafluoro-1-methylpyrrolidine **3.86** and 3*H*-heptafluoro-1-methylpyrrolidine **3.87**, together with traces of hexafluoro- and polyfluoro-1-fluoromethylpyrrolidines.[74]



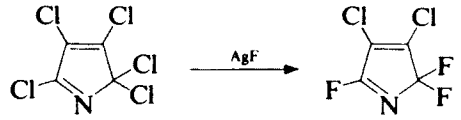
3.86 **3.87**

Recently, a fluorinated pyrrole derivative **3.89**, related to the analgesic–antiinflammatory drug zomepirac, has been synthesized by the direct fluorination of **3.88** using xenon difluoride. The reaction was carried out in dichloromethane at $-10°C$ under nitrogen, giving the derivative **3.89** with evolution of xenon. This ester was the first fluoropyrrole derivative to be described in the literature, and it can be converted into **3.90** by a several steps involving hydrolysis, selective reesterification, thermal decarboxylation, and further hydrolysis.[75]



3.88 **3.89** **3.90**

A mixed polyhalo-2*H*-pyrrole containing fluorine **3.92** has also been described as a result of the action of an excess of silver(I) fluoride at 135°C on pentachloro-2*H*-pyrrole **3.91**.[76]

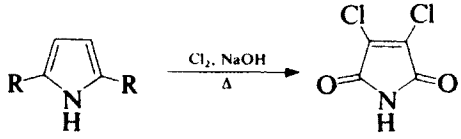


3.91 **3.92**

3.3.4.2. Chlorination

Since 1884, the action of chlorinating agents on pyrrole and its derivatives has been studied extensively. The more common systems employed in the chlorination are elemental chlorine in acetic acid, alkaline hypochlorites, sulfuryl chloride in ethyl ether or 1,2-dichloroethane, *t*-butyl hypochlorite, and *N*-chlorosuccinimide in carbon tetrachloride, chloroform, or *N*,*N*-dimethylformamide. Among these, sulfuryl chloride in ether is the most generally used system.[1,3]

The use of elemental chlorine in the chlorination of pyrrole furnishes different products depending on the conditions of reaction. In warm alkaline solution, or by the use of hot sodium hypochlorite, 3,4-dichloromaleimide **3.4** is formed, as a result of the ability of chlorine to oxidize the pyrrole ring and its α-alkyl derivatives.[6–10]



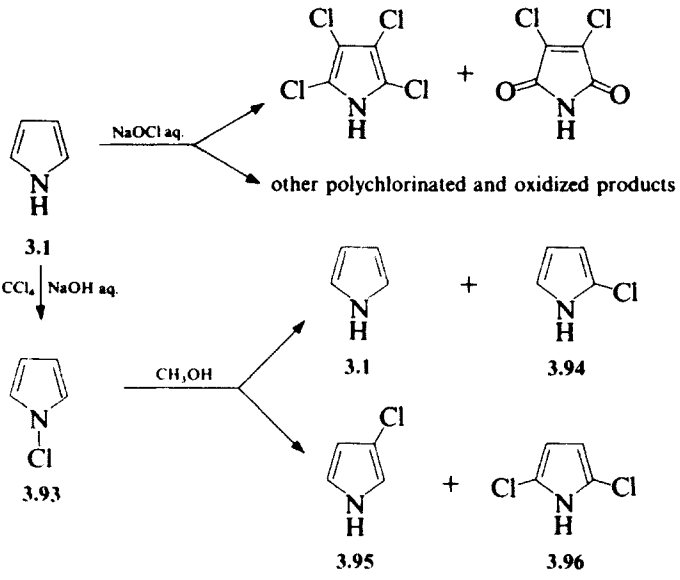
R = H, alkyl **3.4**

Chlorination of pyrrole **3.1** with chlorine in cold alkaline solution, or treatment at room temperature with sodium hypochlorite under homogeneous conditions, results in an exothermic reaction leading to the formation of 2,3,4,5-tetrachloropyrrole **3.2** and other chlorinated products, together with 3,4-dichloromaleic acid and its anhydride and ammonia. In homogeneous media, it was found to be impossible to select conditions that produced monochloropyrroles alone and avoided the formation of oxidized products.[9,10,79]

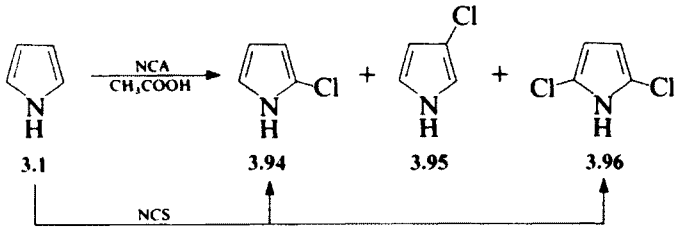
More recently, the preparation of 1-chloropyrrole **3.93** has been claimed by De Rosa[77] when pyrrole was treated with aqueous sodium hypochlorite under heterogeneous conditions. The product was obtained in 65–72% yield on treatment of a stirred solution of pyrrole in carbon tetrachloride with aqueous sodium hypochlorite (pH 13) at 0°C. The 1-chloro compound promptly rearranges when the carbon tetrachloride solution is treated with methanol. The

reaction may occur by two distinct mechanisms, a thermal rearrangement and an acid-catalyzed intermolecular reaction, and leads to the formation of 2-chloro-, 3-chloro-, and 2,5-dichloropyrroles **3.94**, **3.95**, and **3.96** in 31, 13, and 16% yield, respectively, together with 30% of unsubstituted pyrrole.

The lacrymatory solutions of 1-chloropyrrole **3.93** can be stored for up to 2 weeks at 0°C over anhydrous potassium carbonate with little alteration.

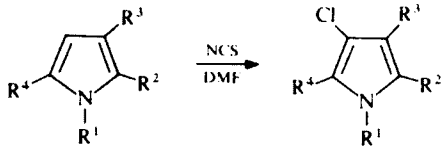


The acid-catalyzed intermolecular rearrangement of 1-chloropyrrole in methanol to give 2-chloro- and 3-chloropyrrole indicated that the conjugate acid of 1-chloropyrrole was the main source of Cl^+ and suggested that *N*-chloroacetanilide (NCA) could be used to accomplish an acid-catalyzed chlorination of pyrrole. Thus, the 2 and 3 positions of pyrrole were chlorinated directly by NCA and acetic acid forming 2-chloro- (32%), 3-chloro- (6%), and 2,5-dichloro- (2%) pyrroles,[78] together with 60% of unreacted pyrrole and unidentified insoluble material. No 3-chloropyrrole was formed in a similar chlorination of pyrrole with *N*-chlorosuccinimide (NCS).[79,80]



The difficulties encountered in the preparation of monohalopyrroles have been obviated to some extent by the use of *N*-halosuccinimides in DMF as a solvent. These reagents are highly reactive and permit the isolation of halogenopyrroles **3.97** in excellent yields under very mild conditions[81] (Table 3.3.8). The action of NCS as a chlorinating agent has been also studied by Gilow and Burton[79] (Table 3.3.9).

TABLE 3.3.8. CHLOROARYLPYRROLES



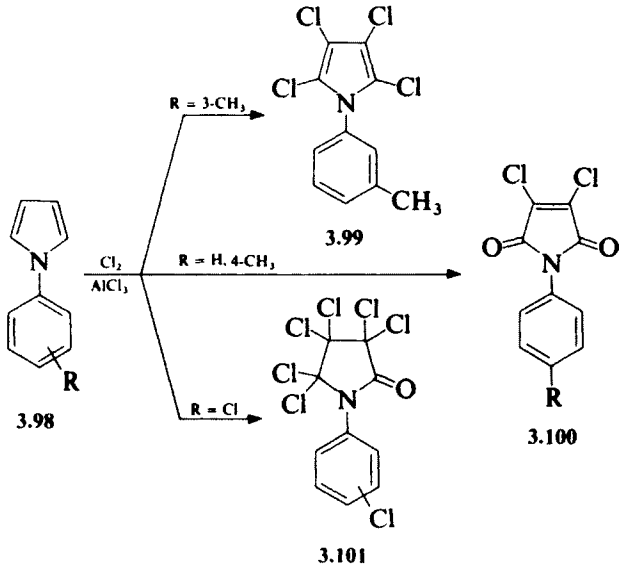
Compound	R^1	R^2	R^3	R^4	Yield (%)	Reaction Conditions	
						Time (h)	Temp. (°C)
3.97a	H	C_6H_5	H	CH_3	70	0.5	−18
3.97b	H	C_6H_5	H	C_6H_5	88	24	25
3.97c	H	C_6H_5	C_6H_5	C_6H_5	90	24	25
3.97d	H	CH_3	$CO_2C_2H_5$	C_6H_5	75	1	100
3.97e	H	C_6H_5	$CO_2C_2H_5$	C_6H_5	88	1	100
3.97f	C_6H_5	C_6H_5	$CO_2C_2H_5$	C_6H_5	91	1	100
3.97g	H	CH_3	$COCH_3$	$2\text{-}NO_2C_6H_4$	78	3	100
3.97h	C_6H_5	CH_3	$COCH_3$	$2\text{-}NO_2C_6H_4$	65	3	100

TABLE 3.3.9. CHLORINATION OF PYRROLE AND SOME 1-SUBSTITUTED PYRROLES WITH NCS IN THF OR DMF

Compound	NCS (mol)	Chloropyrroles (%)				Solvent
		2-Chloro	2,5-Dichloro	2,3,5-Trichloro	2,3,4,5-Tetrachloro	
Pyrrole[a]	1	86	9	—	—	THF
	2	25	75	—	—	
1-Methylpyrrole	1	89	11	—	—	THF
	2	1	100	—	—	
	3	44	56	—	—	
	4	—	7	33	60	
1-Phenylpyrrole	1	69	5	—	—	DMF
	2	1	100	—	—	
	3	—	83	17	—	
	4	—	—	1	100	
1-Benzylpyrrole	1	86	6	—	—	THF
	2	12	88	—	—	
	3	—	48	52	—	
	4	—	—	79	21	

[a] The use of 3 and 4 mol of NCS led to great amount of oxidized products and only small traces of the expected tri- and tetrachloropyrroles.

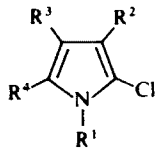
The chlorine-aluminum chloride system has been used to chlorinate 1-arylpyrroles, but the reactions are not simple. Thus, with 1-(3-tolyl)pyrrole **3.98** (R = 3-CH_3), the corresponding 2,3,4,5-tetrachloro derivative **3.99** is formed, as expected, whereas a similar reaction with 1-phenyl-, 1-(4-tolyl)-, and 1-(3- or 4-chlorophenyl)pyrrole leads, respectively, to the 1-phenyl- and 1-(4-tolyl)-3,4-dichloromaleimides **3.100** and 1-(3- or 4-chlorophenyl)-3,3,4,4,5,5-hexachloropyrrolidin-2-ones **3.101**.[82]



The chemistry of 2-halopyrroles has been reinvestigated recently by Cordell to establish their identity and range of stabilities.[83] Previously, chlorination of pyrrolylmagnesium bromide at $-50°C$ had been reported to give the 2-chloropyrrole **3.94** as a very unstable yellow oil.[1,84,85] An analogous unstable material was obtained by Mazzara and Borgo,[86,87] using sulfuryl chloride in ether as the chlorinating agent. Although other preparations of 2-chloropyrrole have been reported,[88,89] Cordell concluded that the method described by Mazzara and Borgo, after little modification, is the most effective. 2,5-Dichloropyrrole **3.96** is usually formed as a minor component in these reactions.

Studies on stability of halogenopyrroles led Cordell to the following general conclusions: (1) 2-bromopyrroles are less stable than the corresponding 2-chloropyrroles and (2) monohalogenopyrroles and 3,4-dihalogenopyrroles are more stable than the 2,5-dihalogeno derivatives. With these factors under consideration, various derivatives of 2-chloropyrrole (Table 3.3.10) were synthesized by direct chlorination or indirect procedures and their range of stability investigated. The alkyl derivatives—with the exception of *t*-butyl derivative—of 2-chloropyrrole were found to be highly unstable. However, the introduction of formyl and ethoxycarbonyl groups into 2-chloropyrrole molecule yielded stable

TABLE 3.3.10. DERIVATIVES OF 2-CHLOROPYRROLE



R^1	R^2	R^3	R^4	Method
CH_3	H	H	H	*a*, *b*
CH_3	H	H	CH_3	*b*
$CH_2C_6H_5$	H	H	H	*b*
H	H	H	CHO	*b*
CH_3	H	H	CHO	*b*
H	H	H	CH_3	*b*
CH_3	H	H	CH_2OH	*b*
H	CH_3	$CO_2C_2H_5$	CH_3	*a*, *b*
H	CH_3	CH_3	CH_3	*b*
CH_3	CH_3	CH_3	CH_3	*b*
H	H	H	*t*-Bu	*a*
CH_3	H	H	Cl	*a*

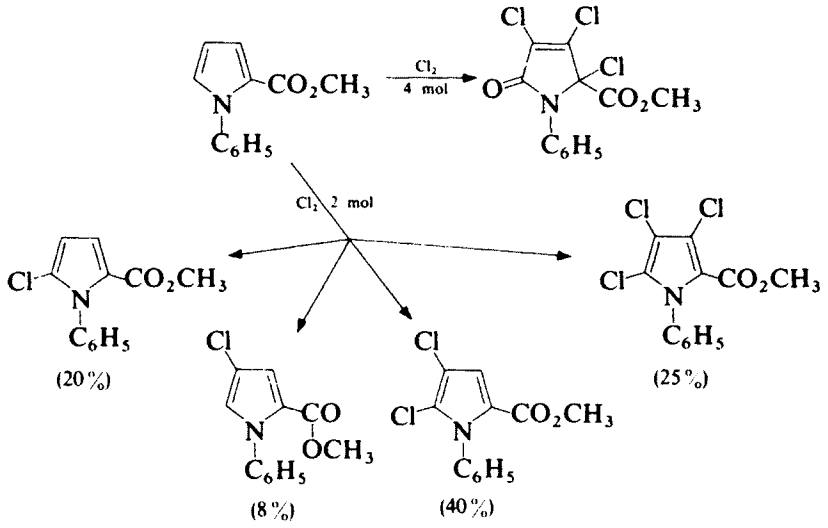
[a] Direct chlorination with SO_2Cl_2–ether.

[b] By chemical conversion of suitable chlorinated or brominated products.

products. Similar properties were observed for alkyl and carbonyl derivatives of 3,4-dichloropyrroles.[90]

Very recently, introduction of chlorine atoms at the 2 position of 3-pyrrolyl sulfoxides has been accomplished by a regiospecific Pummerer-like reaction. 3-(4-Toluenesulfinyl)pyrrole reacts instantaneously with thionyl chloride at 0°C to give a 4:1 ratio of 2-chloro- and 2,5-dichloro-3-(4-toluenesulfonyl)pyrrole, when the reaction is carried out in the presence of sodium hydrogen carbonate and excess 3-chloroperoxybenzoic acid.[91] The use of oxalyl chloride at − 78°C, as a chlorine donor, virtually suppresses the formation of the dichloro derivatives, giving higher yields of the monochlorosulfones. When minor amounts of oxidizing agent (1.1 equivalents) are employed, the reaction permits the isolation of stable 2-chloro-3-(4-toluenesulfinyl)pyrroles.

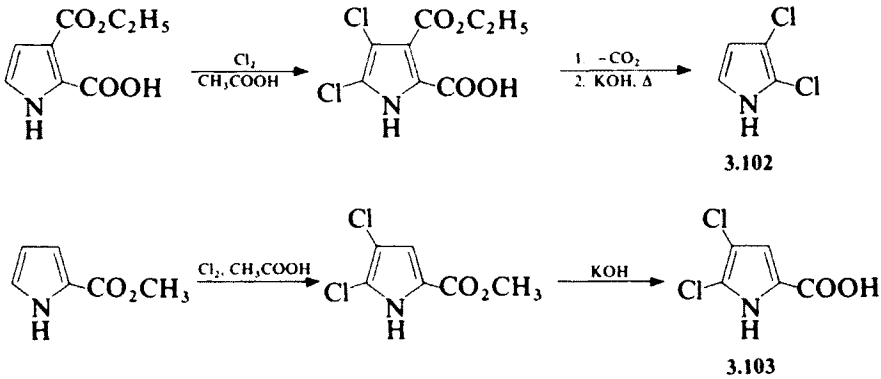
Chlorination of pyrroles containing electron-withdrawing substituents has frequently been carried out with elemental chlorine in acetic acid, although all free positions on pyrrole ring are attacked by this reagent with the formation of mixtures of mono- and dichloro derivatives (Scheme 3.2).[92] This procedure is usually preferred for its simplicity in various synthetic applications, including the indirect preparation of 2,3-dichloropyrrole **3.102** and 4,5-dichloropyrrole-2-carboxylic acid **3.103** (Scheme 3.3)[93] or the direct chlorination of 2-aroylpyrrole analogs of pyoluteorin **3.105** (Scheme 3.4).[94-98] In the latter case, it was observed that the action of elemental chlorine in acetic acid on 2-(2,6-dimethoxybenzoyl)pyrrole **3.104** led to the incorporation of chlorine into the pyrrole ring



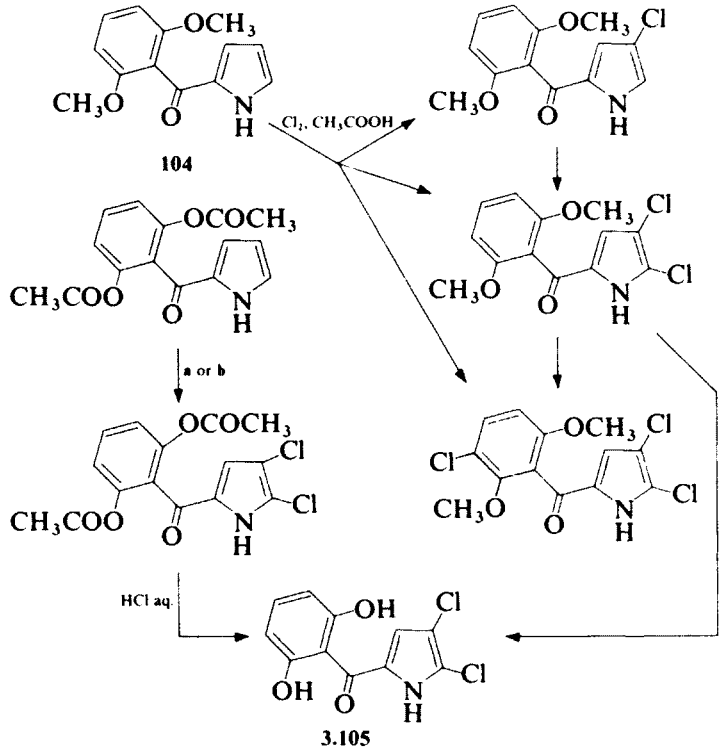
Scheme 3.2

as well as the phenyl ring.[94] Therefore, more regioselective agents, such as *t*-butyl hypochlorite[98,99] and *N*-chlorosuccinimide,[100] were selected for the synthesis of pyoluteorin analogs. Chlorination of 2-(2-methoxybenzoyl)pyrrole **3.106** with *t*-butyl hypochlorite (1 or 2 moles) gave the 4,5-dichloro derivative **3.107**, with small amounts of the 4-monochloro compound **3.108**. Further chlorination of **3.108** afforded alternatively the 4,5- or the 3',4-dichloro derivatives **3.107** and **3.109**.

Other aroylpyrroles **3.110**, **3.111**, **3.112**, and **3.113** have been obtained by direct halogenation of pyrrole ring with *t*-butyl hypochlorite or with elemental chlorine.[94] Both reagents lead to chlorination of the pyrrole and phenyl rings. Thus, 2-(2,6-dimethoxybenzoyl)pyrrole reacts with *t*-butyl hypochlorite (2

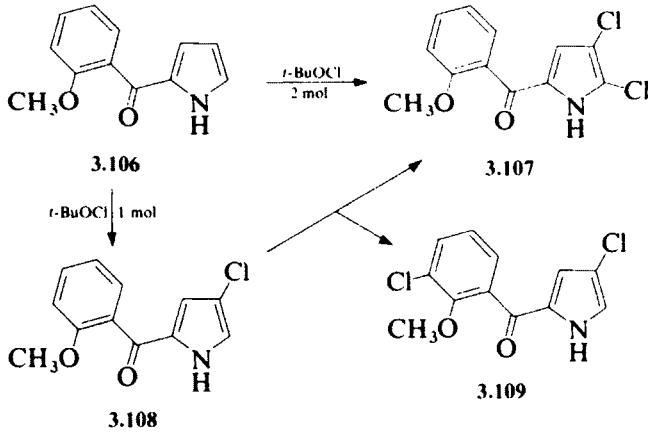


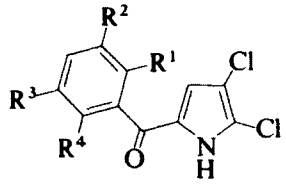
Scheme 3.3



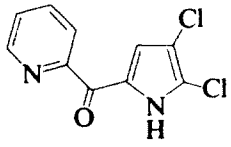
a. 2.2 mol of chlorine in acetic acid (60% yield)
b. 2.2 mol of NCS in refluxing chloroform (74% yield)

Scheme 3.4





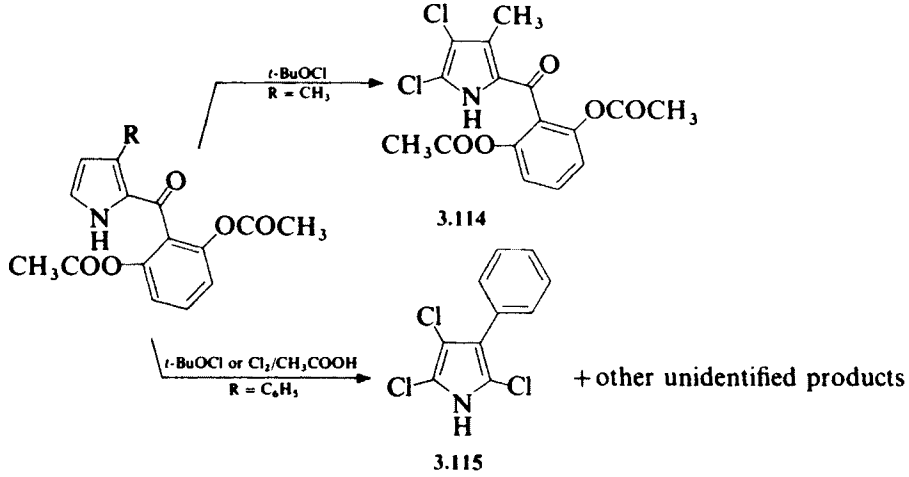
3.110 $R^1 = OH$; $R^2 = R^3 = Cl$; $R^4 = OCH_3$
3.111 $R^1 = R^4 = Cl$; $R^2 = R^3 = H$
3.112 $R^1 = OCH_3$; $R^2 = R^4 = H$; $R^3 = Cl$



3.113

equivalents), forming three chloro derivatives: 2-(3-chloro-2,6-dimethoxybenzoyl)-4,5-dichloropyrrole and its 4-monochloro analog and 4-chloro-(2,6-dimethoxybenzoyl)pyrrole. When the same reaction is carried out at $-70°C$ using 1 equivalent of the hypochlorite, 2-(3-chloro-2,6-dimethoxybenzoyl)pyrrole is also formed.

The introduction of no more than two chlorine atoms into the pyrrole ring of 2-(2,6-diacetoxybenzoyl)pyrrole to form pyoluteroin *O,O*-diacetate (74% yield), devoid of any other chlorinated by-products, has been performed by Davies and Hodge[96] using slightly more than 2 equivalents of *N*-chlorosuccinimide in refluxing chloroform. Hydrolysis of the *O,O*-diacetate gave pure pyoluteorin **3.105** in 95% yield (Scheme 3.4).[96–98] The chlorination of related systems, using *t*-butyl hypochlorite in dichloromethane at 5°C, instead of elemental chlorine in acetic acid, has been employed in the conversion of 2-(2,6-diacetoxybenzoyl)-3-methylpyrrole into 2,3-dichloro-5-(2,6-diacetoxybenzoyl)-4-methylpyrrole (4-methylpyoluteorin *O,O*-diacetate) **3.114**. In this case, the use of either chlorine in acetic acid, or *N*-chlorosuccinimide in carbon tetrachloride at reflux, led to much lower yields.

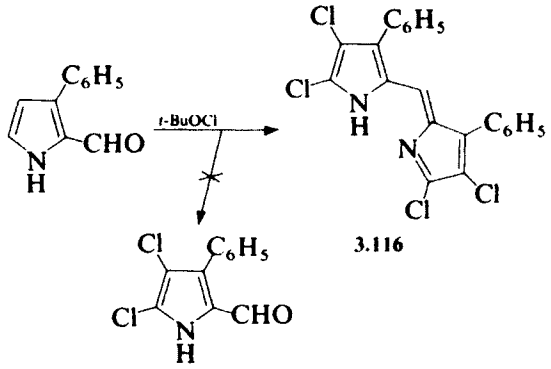


3.114

3.115

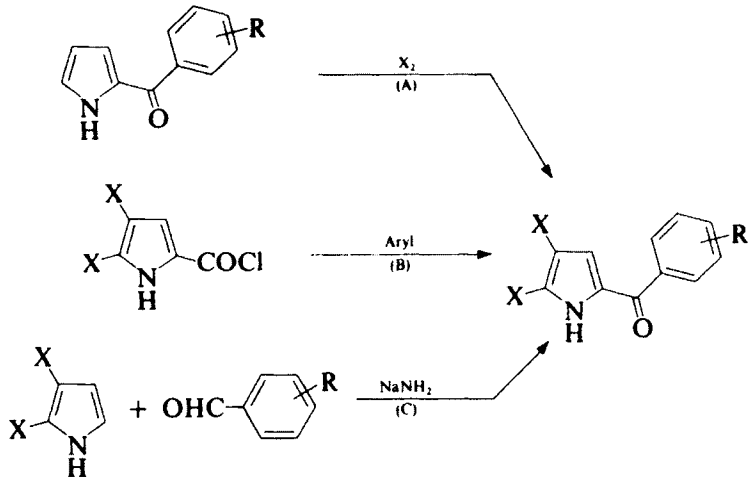
Facile cleavage of the diacetoxybenzoyl moiety to yield (2,4,5-trichlorophenyl)pyrrole **3.115** during chlorination of 3-phenyl-2-(2,6-diacetoxybenzoyl)pyrrole has been observed[99] under various reaction conditions

(*t*-BuOCl, Cl_2–acetic acid, and NCS–carbon tetrachloride). Cue and Chamberlain attributed this instability of pyoluteorin analogs bearing aryl substituents at C_4 in the pyrrole ring to a combination of factors, including the steric effect of the C_4 substituent, as well as the electronic effect of the chlorine atoms at the C_2 and C_3 positions. The chlorination of 2-formyl-3-phenylpyrrole with *t*-butyl hypochlorite in dichloromethane yields the dipyrromethene **3.116** (18% yield) instead of the expected dichloroaldehyde. This is presumably a result of normal acid-catalyzed reaction of formylpyrroles.



The direct halogenation reaction (method A in Scheme 3.5) and the alternative routes (methods B and C) for the preparation of 2-aroyl-4,5-dichloropyrroles have been thoroughly investigated by Bailey et al.[101,102]

Chlorination with sulfuryl chloride in ether is a method of choice for the preparation of many chloro-substituted pyrroles. However, this method suffers

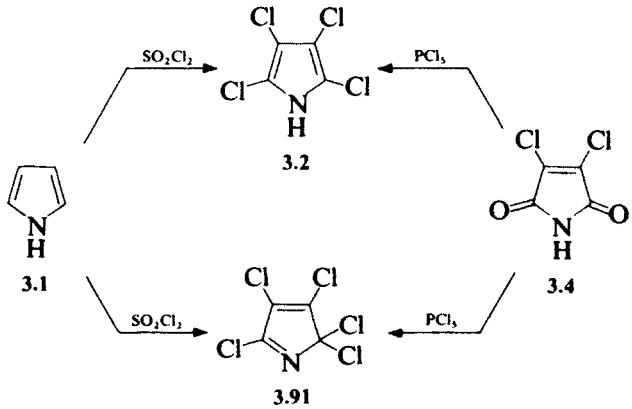


X = Cl, Br
R = Cl, Br, F, CH_3, CF_3

Scheme 3.5

the disadvantages of poor regioselectivity and high reactivity of reagent. Consequently, the careful selection and control of the reaction temperature, with the appropriate concentration of reagent, together with the use of regiospecific directing and removable substituents are crucial for optimization of this procedure.

Although the control of the molar ratio of the pyrrole substrate and sulfuryl chloride permits the sequential entry of one or more atoms of chlorine, the reagent usually attacks all vacant positions on the pyrrole ring. Thus, when the reaction is carried out in the presence of an excess of sulfuryl chloride, the fully halogenated product or mixtures of monochloro and polychloro derivatives are formed. For example, pyrrole yields, under carefully controlled conditions, 2-chloro-, 2,5-dichloro-, and 2,3,5-trichloropyrrole, and, with an excess of the chlorination reagent, 2,3,4,5-tetrachloropyrrole **3.2** or 2,2,3,4,5-pentachloro-2*H*-pyrrole **3.91** are formed, depending on the reaction conditions. Both **3.2** and **3.91** have been also obtained from dichloromaleimide **3.4**, on treatment with phosphorus pentachloride.[6]

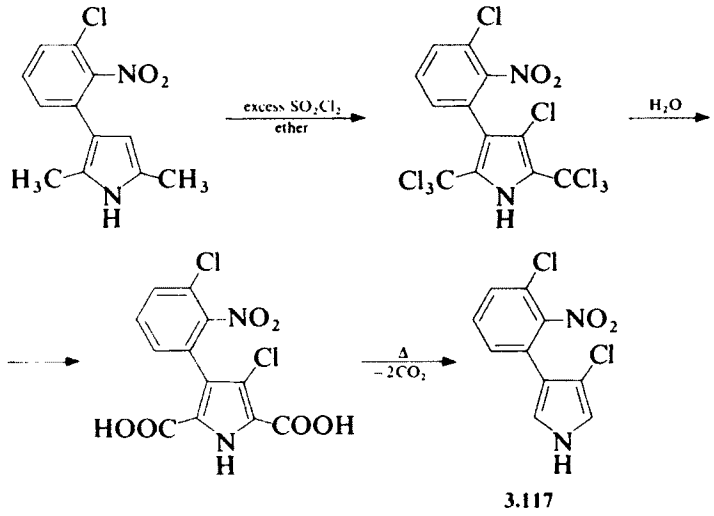


3.1 **3.2** **3.4** **3.91**

Chlorination with sulfuryl chloride proceeds by radical processes or electrophilic substitution. Therefore, alkyl side chains may be halogenated simultaneously with the pyrrole ring. This sequence offers the opportunity to eliminate the α-methyl side chain from pyrrole through a three-step sequence involving trichlorination, hydrolysis, and thermal decarboxylation; the synthesis of antifungal antibiotic pyrrolnitrin **3.117**[103] provides a good example of such a procedure (Scheme 3.6).

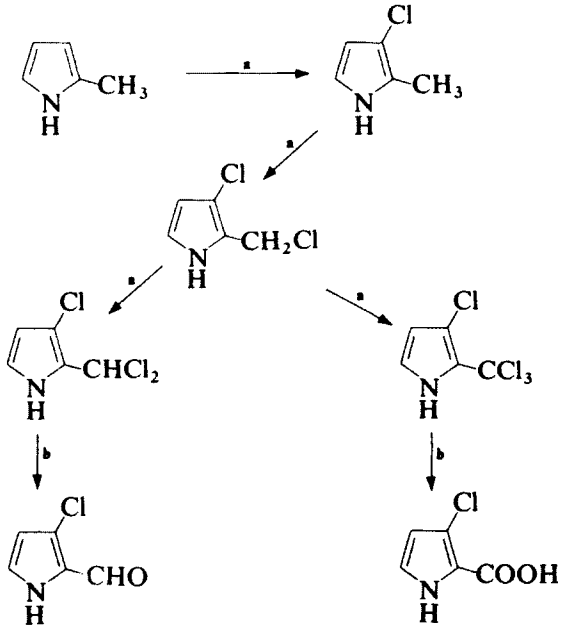
Transformation of α-methyl groups into aldehyde and carboxylic acid functions has been carried out by controlled chlorination of 2-methylpyrrole with sulfuryl chloride in ether, followed by hydrolysis of the dichloromethyl and trichloromethyl intermediates[6] (Scheme 3.7). Similarly, 2,5-dimethylpyrrole **3.118** has been converted into 3,4-dichloro-2,5-diformylpyrrole **3.119** and 2,5-dicarboxy-3,4-dichloropyrrole **3.120**.[104–106]

Methylpyrroles, also possessing carboxyl functions, react easily with sulfuryl chloride to give the fully halogenated products,[1,105] for example, **3.121** → **3.122**



3.117

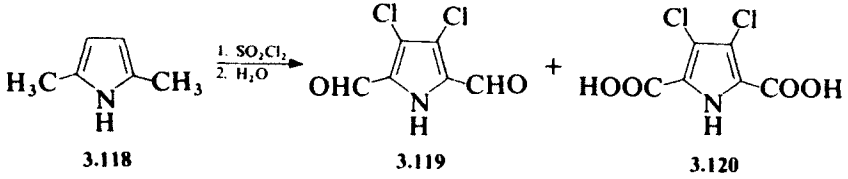
Scheme 3.6



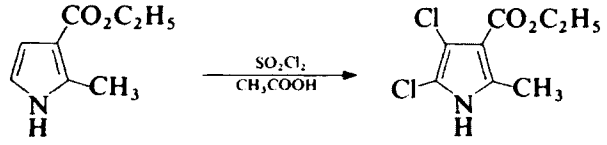
a. Chlorination with controlled amount of SO_2Cl_2

b. Hydrolysis

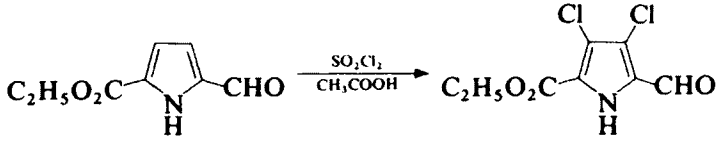
Scheme 3.7



3.118 3.119 3.120

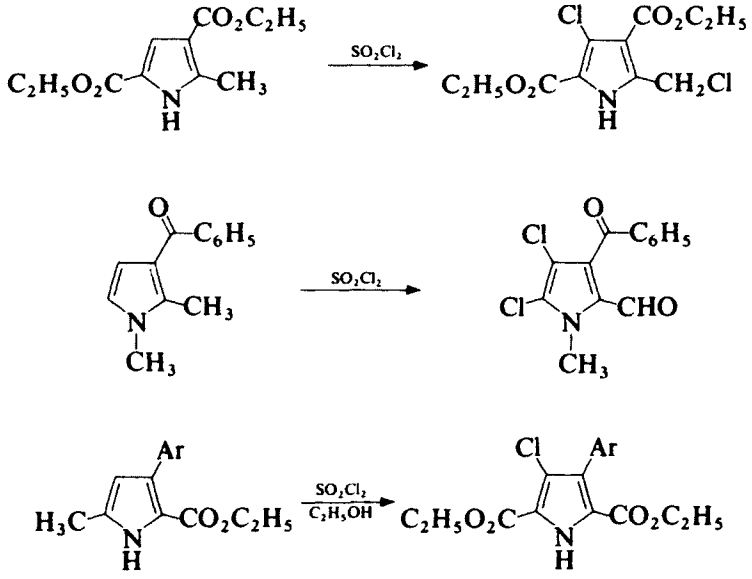


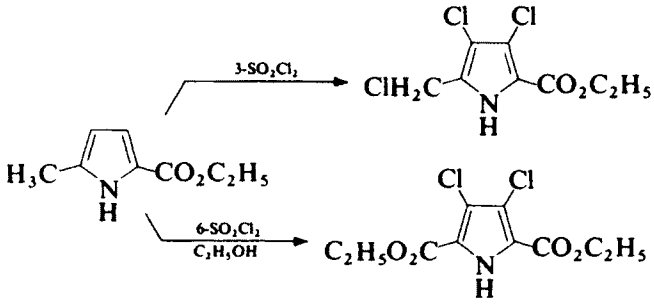
3.121 3.122



3.123 3.124

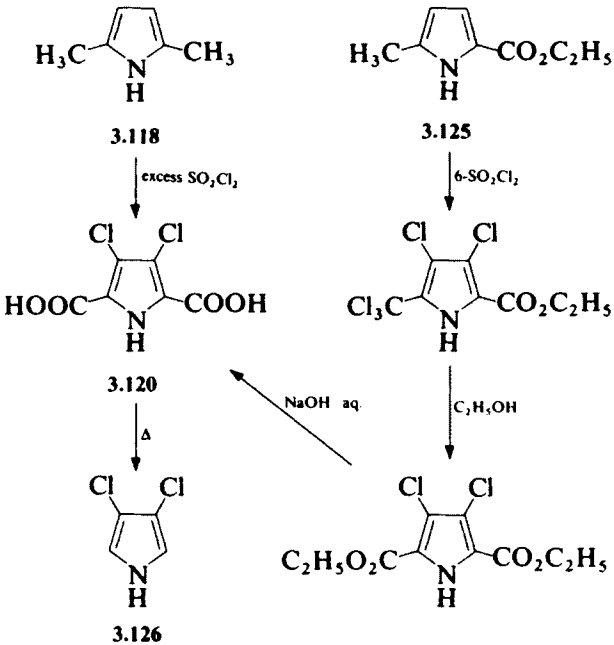
and **3.123** → **3.124**. With an excess of the reagent formation of monochloromethylpyrroles or conversion of methyl group into aldehyde or carboxylic acid groups is always accompanied by chlorination of pyrrole ring (Scheme 3.8).[90,107–109]



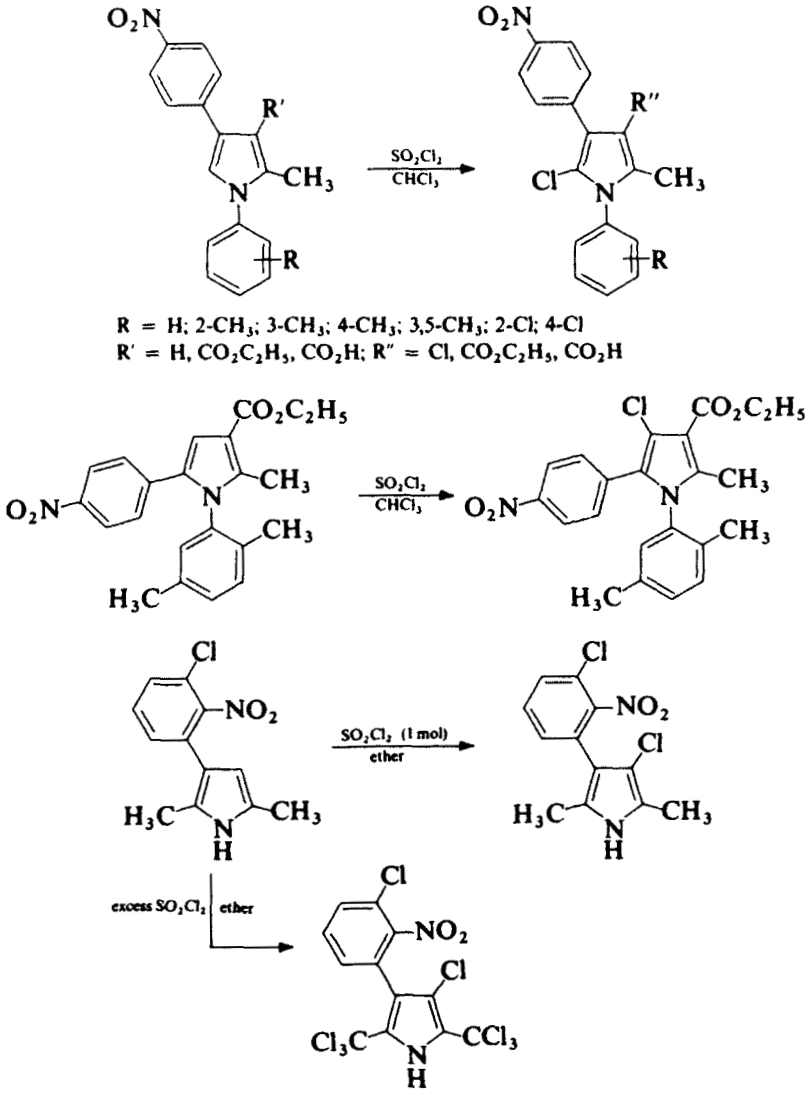


Scheme 3.8

Frequently, the use of sulfuryl chloride as a chlorinating agent has made possible the preparation of certain dichloropyrroles, which are not available by direct chlorination. The conversion of either 2,5-dimethylpyrrole **3.118** or 2-ethoxycarbonyl-5-methylpyrrole **3.125** into 3,4-dichloropyrrole **3.126**, via the 3,4-dichloropyrrole-2,5-dicarboxylic acid **3.120**, illustrates the convenient use of sulfuryl chloride in the indirect synthesis of chloropyrroles.[90,104,105]



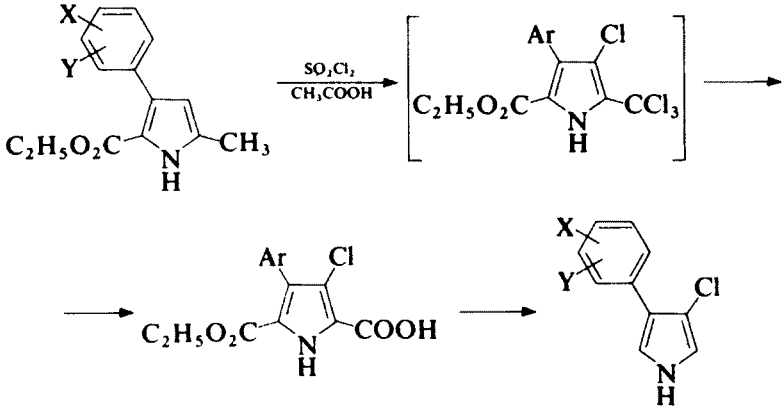
Both direct and indirect chlorination have been used extensively in the synthesis of antimicrobial chloro analogs of the antifungal antibiotic pyrrolnitrin. Sulfuryl chloride in boiling chloroform converts 1-aryl-2-methyl-4-*p*-nitrophenylpyrroles and their 3-ethoxycarbonyl derivatives into their 3,5-dichloro- and 5-chloro derivatives.[89] Other examples of such transformation are illustrated in Scheme 3.9.[103,110–114]



Scheme 3.9

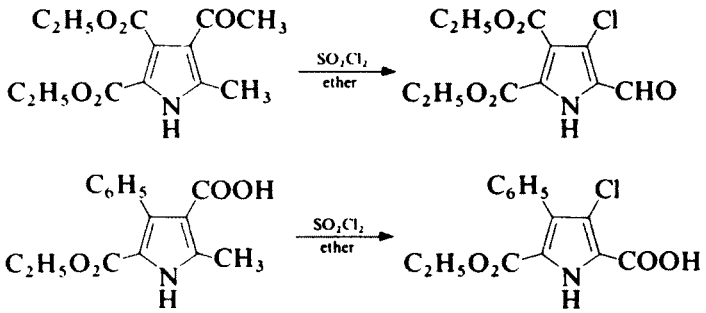
In a one-pot transformation, 4-aryl-5-ethoxycarbonyl-2-methyl pyrroles are converted into 4-aryl-3-chloro-5-ethoxycarbonylpyrrole-2-carboxylic acids by sulfuryl chloride in acetic acid at $-10°C$, via the trichloromethyl derivative, which is solvolyzed under the reaction conditions. By this route, various 4-aryl-3-chloropyrroles have been synthesized for structure–activity relationship studies of pyrrolnitrin analogs (Scheme 3.10).[115]

Ipso-substitution of acyl or carboxyl groups have been observed during the halogenation of certain pyrroles with sulfuryl chloride (Scheme 3.11).[112–117]



X = NO_2, Cl, Br, OCH_3, CF_3; Y = H, Cl, NO_2, OCH_3

Scheme 3.10



Scheme 3.11

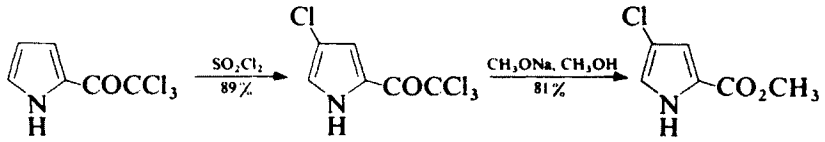
In order to compare the reactivity of sulfuryl chloride with that of *t*-butyl hypochlorite in their reaction with formylpyrroles, Farnier and Fournari[118] studied their action on 2-formylpyrrole amongst others. Both reagents produced a mixture of 4-chloro-, 5-chloro, and 4,5-dichloro-2-formylpyrrole, with only slight differences in their overall yield and in the molar ratio of the separate products (Table 3.3.11). From these data, Farnier and Fournari concluded that Sonnet's method[44] was the most suitable for the preparation of 4-chloro- and 4,5-dichloro-2-formylpyrrole. It is noteworthy that they obtained different

TABLE 3.3.11. CHLORINATION OF 2-FORMYLPYRROLE

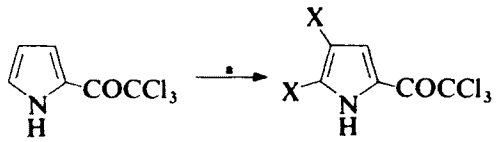
Chlorinating Agent	Molar Ratio (%) of Mixture Derivatives			Total Yield (%)
	4-Chloro	5-Chloro	4,5-Dichloro	
SO_2Cl_2	30	65	5	80
t-BuOCl	43	52	5	75

physicochemical characteristics for 5-chloro-2-formylpyrrole from those reported by Hodge and Rickards.[119]

The electron-withdrawing effect of a 2-trichloroacetyl group deactivates the 5 position to such an extent that, with an equimolar amount of the chlorination reagent, substitution occurs only at the 4 position, with virtually no reaction at the 5 position. Thus, depending on the reaction conditions, 4-halo-2-trichloroacetylpyrroles or 4,5-dihalo-2-trichloroacetylpyrroles are generally obtained from **3.127**. Using sulfuryl chloride at 0°C, Bélanger[43] converted 2-trichloroacetylpyrrole into **3.128** in a 98% yield. Subsequent methanolysis of the product gave methyl 4-chloropyrrole-2-carboxylate **3.129**. The reaction is generally applicable to a wide variety of electrophiles, including bromine, nitric acid, and iodine–$AgOCOCF_3$, providing a convenient route to 4-substituted pyrrole-2-carboxylates via the 2-trichloroacetyl intermediates (Table 3.3.12). With elemental chlorine, or bromine, in glacial acetic acid at room temperature,



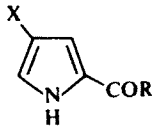
3.127 **3.128** **3.129**



3.127 **3.130**

a. Cl_2, Br_2, or $NaCl_2I$; X = Cl, Br, I

TABLE 3.3.12. 4-SUBSTITUTED 2-TRICHLOROACETYL- AND 2-METHOXYCARBONYLPYRROLES

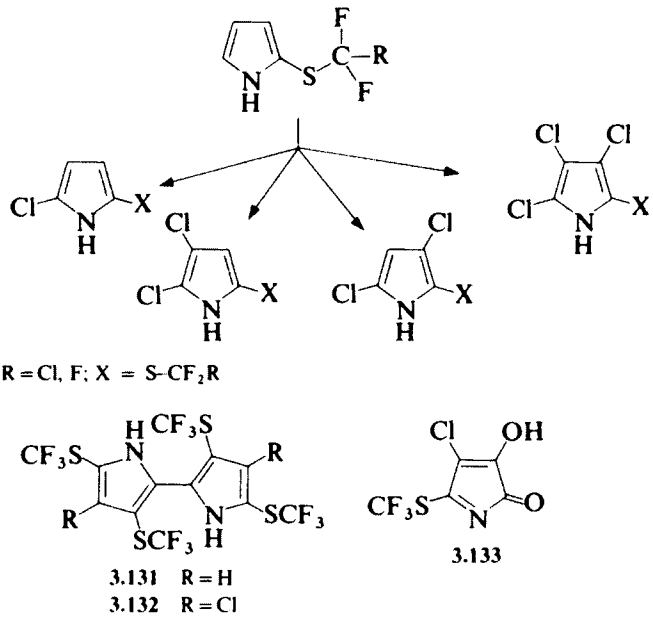


	Conditions of Reaction				R	
X	Solvent	Temp. (°C)	Time (min)	Reacting System	CCl_3 Yield (%)	OCH_3 Yield (%)
Cl	$CHCl_3$	0	10	SO_2Cl_2	89	81
Br	$CHCl_3$	0	10	Br_2	75	86
I	$CHCl_3$	22	60	$I_2/AgOCOCF_3$	73	85
NO_2	—	− 50	60	90% HNO_3	77	89

or by the action of aqueous $NaCl_2I$ at approximately 100°C, **3.127** is converted in high yields into the 4,5-dihalogenopyrroles **3.130**.[101,102]

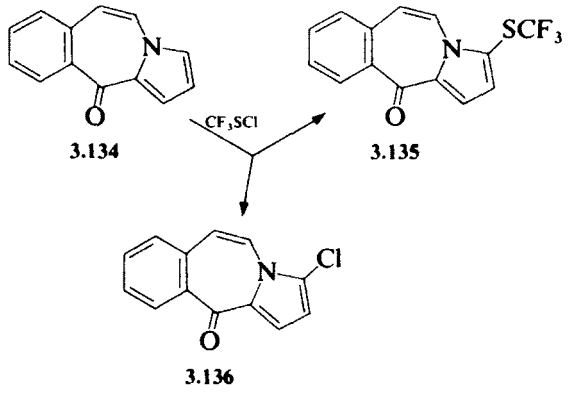
The dichloro derivatives **3.130** have been used as highly versatile intermediates to various halogenopyrrolecarboxylic acid amides for antimicrobial screening as pyoluteorin analogs. The use of dichloroacetyl or trifluoroacetyl group in these synthetic sequences instead of the trichloroacetyl group does not offer any advantages. *N*-Alkylation of 4,5-dihalo-2-dichloroacetylpyrroles with potassium carbonate and methyl iodide afforded the related 4,5-dichloro-1-methyl derivatives.[102]

Sulfuryl chloride–silicon dioxide and sulfuryl chloride–sulfur dioxide–aluminum chloride[120] have been used to chlorinate mono- and bis(trifluoromethylthio)pyrroles and the related chlorodifluoromethylthiopyrroles. Complex mixtures of monochloro and polychloro derivatives were generally obtained (Scheme 3.12), together with various by-products, including **3.131**, **3.132**, and **3.133**, which were isolated in low yields. The trihalomethylthiopyrroles were also halogenated with bromine, or with I_2–KI, to give mixed halogenated pyrroles.



Scheme 3.12

The trifluoromethylthiopyrroles are generally prepared by the action of trifluoromethylsulfenyl chloride on pyrrole, but, in some cases, chlorinated products were also formed together with the expected trifluoromethylthio derivatives.[120,121] Thus, for example, the chloro compound **3.136** accompanied the formation of the trifluoromethylthio tricyclic derivative **3.135**, when **3.134**



was allowed to react with trifluoromethanesulfenyl chloride in a 1:1 mixture of pyridine and $CHCl_3$ at 50°C.[121]

With the aim of establishing the orientation of partial chlorination in pyrroles, a comparative investigation with common chlorinating agents has been conducted by Hodge and Rickards[119] using methyl pyrrole-2-carboxylate and related pyrroles as substrates. The results of their work are presented in Table 3.3.13.

TABLE 3.3.13. CHLORINATION OF METHYL PYRROLE-2-CARBOXYLATE

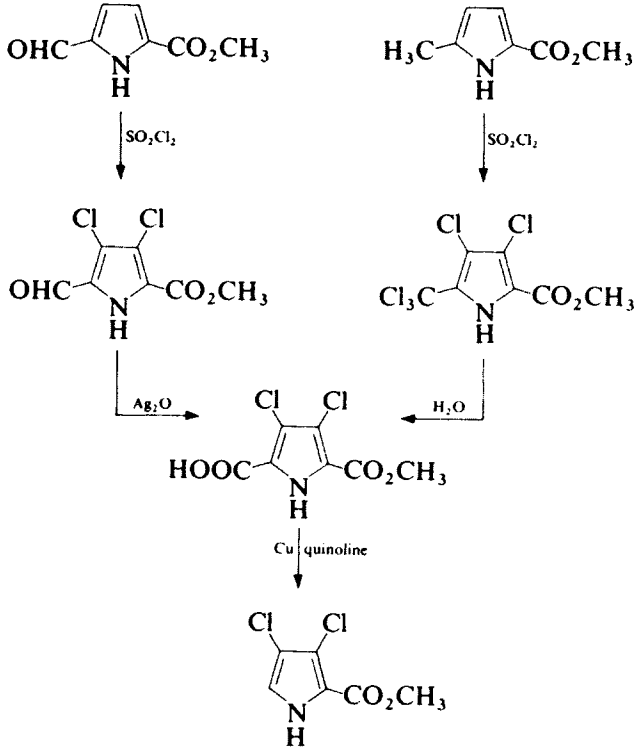
Chlorinating Agent	Number of Moles	Products of Reaction (Yield %)[a]					
		Monochloro		Dichloro		Trichloro	Total Material (%)
		4-Isomer	5-Isomer	4,5-Isomer	3,5-Isomer	3,4,5-Isomer	
Chlorine	1.0–1.1	23	20	20	0	1	99
	2.0–2.2	8	5	71	0	2	86
Sulfuryl chloride	1.0–1.1	40	44	4	4	2	94
	2.0–2.2	0	0	50	37	4	91
	3.5	0	0	0	0	42	42
t-Butyl hypochlorite	1.0–1.1	0	80	0	20	0	100
	2.0–2.2	0	0	0	82	17	99

[a] Neither 3-chloro- nor 3,4-dichloropyrrole-2-carboxylate was present in the mixtures.

Chlorine in acetic acid was found to be a more reactive but less selective reagent, always giving mixtures, that were sometimes difficult to resolve. Reaction of methyl pyrrole-2-carboxylate with 1 equivalent of elemental chlorine furnished a mixture of the 4- and 5-chloro esters and the 4,5-dichloro ester. When the amount of halogen was increased to 2 equivalents, the 4,5-dichloro ester was the main product.

In contrast, the reaction of methyl pyrrole-2-carboxylate with sulfuryl chloride led to different results depending on the number of equivalents of reagent employed. With 1 equivalent of reagent, a mixture of the 4- and 5-chloro esters,

together with lesser amounts of higher chlorosubstituted derivatives, was produced. However, when 2 equivalents of sulfuryl chloride were allowed to react with methyl pyrrole-2-carboxylate, an apparently homogeneous product formed, which was initially described in the literature as methyl 3,4-dichloropyrrole-2-carboxylate.[86,119] Careful analysis of this product revealed the presence of equal parts of the 4,5- and 3,5-dichloro esters forming a 1:1 solid compound with a well-defined melting point, probably as the result of a particular packing of the two esters in the crystal. To confirm this observation, methyl 3,4-dichloropyrrole-2-carboxylate **3.137** was prepared by indirect synthesis by two different unequivocal routes (Scheme 3.13). The fully substituted 3,4,5-trichloro ester is the only product (42%), when an excess of sulfuryl chloride (3.5 equivalents) was used. Hodge and Rickards also studied the chlorination of 2-formylpyrrole with sulfuryl chloride and found that, with a 2.2 molar ratio of reagent, the reaction occurs only at the 5 position in a very low yield (9%).



3.137

Scheme 3.13

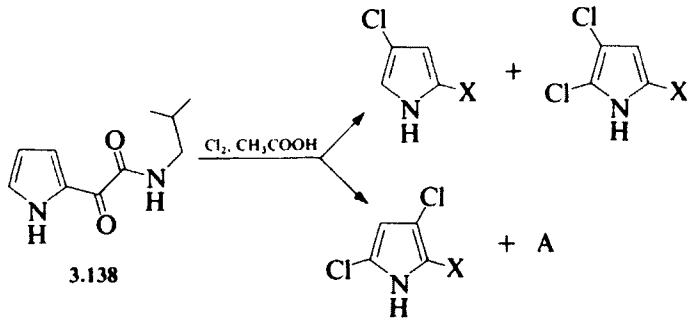
The high yields and the greater selectivity of reaction with methyl pyrrole-2-carboxylate makes *t*-butyl hypochlorite the reagent of choice for the preparation of the 5-chloro and 3,5-dichloro derivatives. With 1 equivalent of reagent in

carbon tetrachloride the primary attack occurred selectively at the 5 position with formation of the 5-monochloro ester (80%). A secondary selective attack at the 3 position accounted for the presence of 20% methyl 3,5-dichloropyrrole-2-carboxylate. When 2 equivalents of reagent were employed, the 3,5-dichloro and 3,4,5-trichloro esters were formed in a 5:1 ratio in a 99% overall yields. Separation of these mixtures was easily achieved by column chromatography.

A similar high regioselectivity was found in the reaction of the hypochlorite with methyl 1-methylpyrrole-2-carboxylate to form the corresponding 5-chloro ester in 91% yield.

In the synthesis of pyoluteorin, pure 4,5-dichloropyrrole-2-carboxylate is frequently needed in large quantities. Bailey and Rees[98] used chlorine in acetic acid and *t*-butyl hypochlorite in carbon tetrachloride for chlorination of methyl pyrrole-2-carboxylate. However, as indicated above, column chromatography or fractional recrystallization fails to separate the 4,5- and 3,5-dichloro isomers formed from the above reactions and, in order to avoid tedious separations, they hydrolyzed the mixture and used the corresponding acids in subsequent reaction steps. In contrast, Durham et al.[94] chlorinated methyl pyrrole-2-carboxylate with chlorine (2.5 equivalents) in acetic acid and obtained the 4,5-dichloro ester as the main product with some traces of the 3,4,5-trichloro ester. Contamination remained after hydrolysis but was unimportant for the required purposes. In a similar way, chlorination of pyrrole-2-carboxylic acid furnished 4,5-dichloropyrrole-2-carboxylic acid in 24% yield.

Birchall and Rees[93] tried to surmount the difficulties encountered in the direct chlorination of methyl pyrrole-2-carboxylate by preparing the 4,5-dichloro derivative by an indirect route. They used, as starting material, pyrroles bearing bulky substituents at the 2 position, which were easily transformed after chlorination into the required carbomethoxy function; the rationale was that the hindered 3 position would be less readily attacked by the electrophilic agent and the formation of the 3,5-dichloro isomer would be avoided. With this in mind, the chlorination of pyrrol-2-ylglyoxylic acid, and its isobutylamide and isobutyl pyrrol-2-ylglyoxylate with chlorine in acetic acid was studied. Thus, the action of chlorine (2.1 mol) on the isobutylamide **3.138** led to an approximately 3:8:1



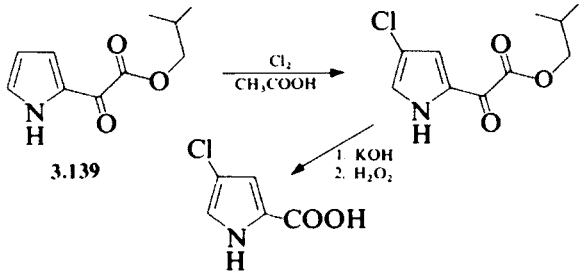
3.138

X = $COCONHCH_2CH(CH_3)_2$

A = trichloroderivatives and other products (12%)

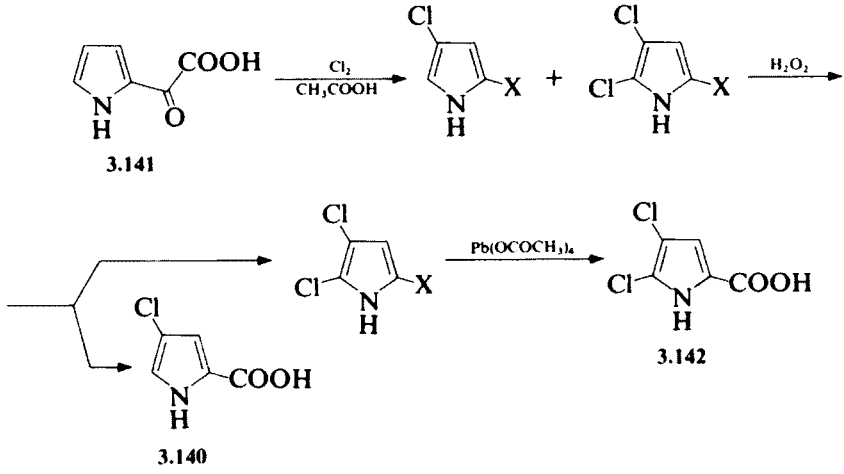
mixture of 4-chloro, 4,5-dichloro, and 3,5-dichloro derivatives in a 56% overall yield, which were very easily separated by column chromatography on silica gel. Alkaline hydrolysis of the amides gave the 4-chloro- and the 4,5-dichloropyrrol-2-ylglyoxylic acid in high yields.

Chlorination of the isobutyl ester of pyrrol-2-ylglyoxalic acid **3.139** by the same procedure led to the 4-chloro ester (50%), together with a 30% of a 1 : 3 mixture of 3,5- and 4,5-dichloro isomers. Base-catalyzed hydrolysis of the monochloro derivative, followed by oxidation with hydrogen peroxide, afforded 4-chloropyrrole-2-carboxylic acid **3.140**.



3.139 **3.140**

A cocrystalline mixture of 4-chloro and 4,5-dichloro derivatives formed on chlorination of pyrrol-2-ylglyoxylic acid **3.141** with chlorine in acetic acid. Sequential oxidation with hydrogen peroxide and then with lead tetraacetate furnished 4,5-dichloropyrrole-2-carboxylic acid **3.142**; the chloro acid **3.140** was formed after the initial oxidation with hydrogen peroxide.

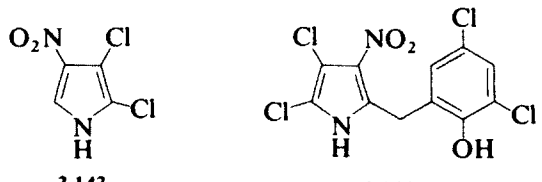


3.141 **3.142** **3.140**

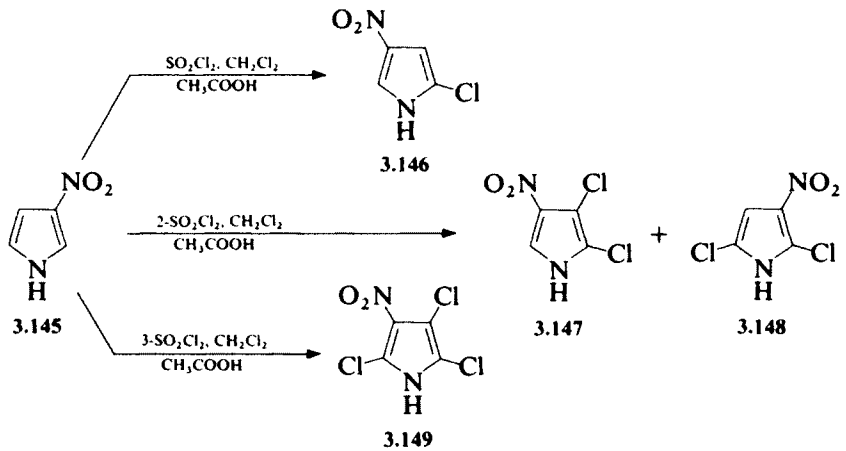
X = COCOOH

Examples of chlorinated nitropyrroles have been reported in the literature with the discovery of antibiotics pyrrolomycin A (2,3-dichloro-4-nitropyrrole) **3.143** and pyrrolomycin B **3.144**. The preparation of **3.143** is theoretically

achievable either by nitration of 2,3-dichloropyrrole or by chlorination of 3-nitropyrrole. The former reaction was discarded because of the high instability of 2,3-dichloropyrrole and the preferential nitration at the α position of the pyrrole ring. Hence, the method of choice was the chlorination of 3-nitropyrrole **3.145** with sulfuryl chloride at 80°C in acetic acid. When the reaction was carried out at low temperature (ca. 15°C), only 2-chloro-4-nitropyrrole **3.146** was formed, but use of a molar excess of sulfuryl chloride gave a mixture of 2,3-dichloro-4-nitropyrrole **3.147** (13%) and 2,5-dichloro-3-nitropyrrole **3.148** (47%). The reaction of 3-nitropyrrole with 3 mol of sulfuryl chloride afforded 2,3,5-trichloro-4-nitropyrrole **3.149** in 57% yield.



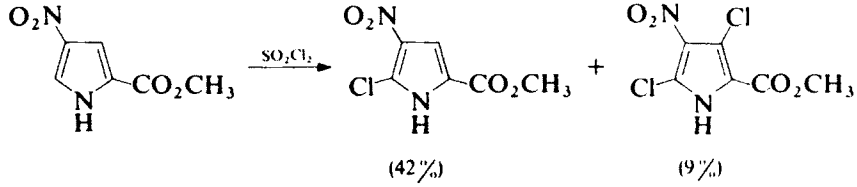
3.143 **3.144**



3.145 **3.146** **3.147** **3.148** **3.149**

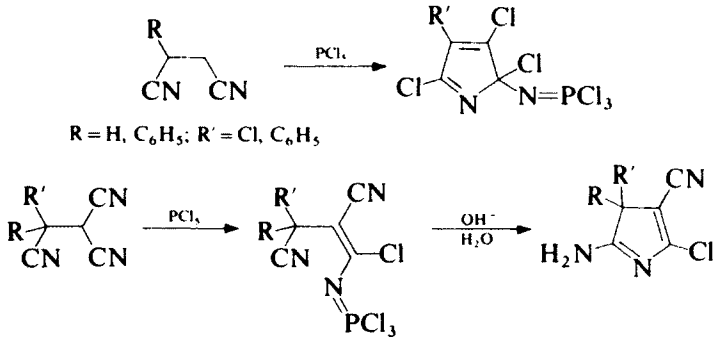
Starting from methyl 4-nitropyrrole-2-carboxylate (Scheme 3.14), the use of sulfuryl chloride in acetic acid at 80°C led to the formation of a mixture of monochloro and dichloro derivatives, which were easily separable by fractional crystallization. Removal of methoxycarbonyl group from these esters furnished 2-chloro-3-nitropyrrole and 2,4-dichloro-3-nitropyrrole respectively, which are not available by direct chlorination of 3-nitropyrrole. Using all these procedures, a range of chloronitropyrroles have been synthesized by Koyama et al.[122]

The chlorination of 2*H*-pyrroles[123] has been not described; however, as indicated earlier, pentachloro-2*H*-pyrrole can be prepared by either the direct reaction of sulfuryl chloride on 1*H*-pyrrole or the action of phosphorus



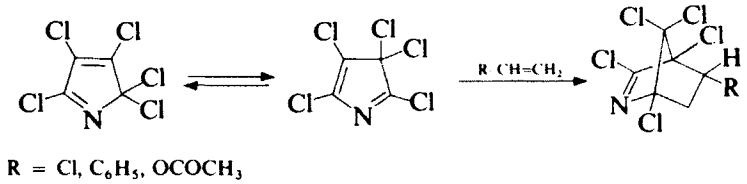
Scheme 3.14

pentachloride on 3,4-dichloromaleimide. Other chloro-2*H*-pyrroles have been prepared by the action of an excess of phosphorus pentachloride on succinonitrile and its 2-phenyl derivatives. In their reaction with phosphorus pentachloride, more highly substituted nitriles are transformed to phosphorus intermediates, which form chlorinated amino-3*H*-pyrroles in high yields under basic conditions (Scheme 3.15).



Scheme 3.15

In the course of the preparation of azabornene, which has insecticidal activity, pentachloro-3*H*-pyrrole occurs as an intermediate in the Diels–Alder addition of pentachloro-2*H*-pyrrole with monosubstituted ethenes.

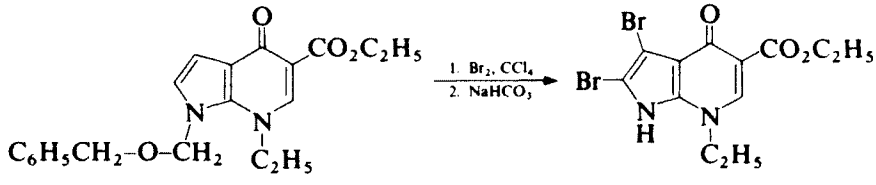


3.3.4.3. Bromination

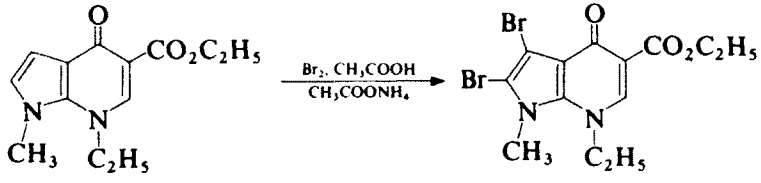
Bromination of pyrrole derivatives has been accomplished generally with molecular bromine in carbon tetrachloride or acetic acid, although a large number of other brominating systems have been also employed.

As observed for chlorination, the exhaustive bromination of pyrrole leads to the stable 2,3,4,5-tetrabromopyrrole, but bromination under warm alkaline conditions leads to oxidation of the pyrrole ring with the formation of dibromomaleimide as the main product. No reports on the formation of partially brominated derivatives by electrophilic bromination of pyrrole with bromine are to be found in the literature.[1] On the contrary, the bromination of 1-substituted pyrroles by the use of one molar equivalent of bromine in carbon tetrachloride results in the formation of a complex mixture. The presence of various polybrominated products is accounted for by the high reactivity of pyrrole ring toward bromine. Thus, bromination of 1-benzylpyrrole at 0°C, under conditions in which the hydrogen bromide produced by the reaction is continuously removed, afforded 1-benzyl-3-bromopyrrole as the main component (55%),[27] with none of the 2-bromo derivative. However, various other brominated products, in addition to the 3-bromo isomer, were detected, including 1-benzyl-2,5-dibromopyrrole, 1-benzyl-2,3,4,5-tetrabromopyrrole, and a trace of 1-benzyl-2,3,5-tribromopyrrole, together with a considerable amount of unidentified material and some unreacted starting product.

Like chlorination, the reaction with elemental bromine is influenced by the solvent. Ethyl 2,3-dibromo-7-ethyl-4,7-dihydro-4-oxo-1*H*-pyrrolo[2,3-*b*]pyridine-5-carboxylate **3.151** (an intermediate related to the antibacterial 4-pyridone-3-carboxylic acid) has been prepared in good yield (87%) by the treatment of **3.150** with bromine in carbon tetrachloride, whereas the use of acetic acid as the solvent resulted in formation of a complex mixture containing **3.151** in low yield, together with four minor unidentified by-products. In contrast, reaction of **3.152** with bromine–glacial acetic acid system furnished **3.153** in appreciable yield (39%).[124]



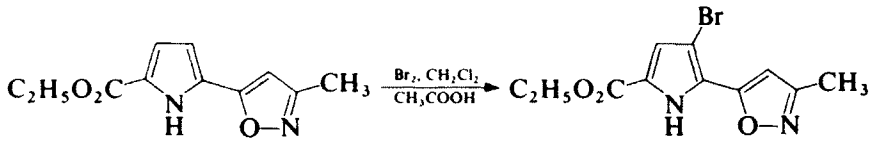
3.150 **3.151**



3.152 **3.153**

As observed in the preceding examples, bromination of all the free positions of the pyrrole ring is common with elemental bromine, although it has been found possible to obtain monobromo derivatives. For example, bromination of ethyl

5-(3-methylisoxazol-5-yl)pyrrole-2-carboxylate **3.154** with bromine in dichloromethane–acetic acid takes place selectively at the C_4 position of the pyrrole ring, leading to the formation of ethyl 4-bromo-5-(3-methylisoxazol-5-yl)pyrrole-2-carboxylate **3.155**, a key compound in the syntheses directed to the phosphodiesterase inhibitors PDE-I and PDE-II.[125]



3.154 **3.155**

2-Bromopyrrole has been prepared by the reaction of pyrrolylmagnesium bromide with bromine at $-20°C$ according to Hess and Wissing.[88] Reinvestigation of this reaction by Cordell[83] confirmed the high instability of the oily 2-bromopyrrole and revealed the presence of contaminating quantities of 2,5-dibromopyrrole, a low-melting solid. Attempts to prepare 2-bromopyrrole by decarboxylation of 5-bromopyrrole-2-carboxylic acid were unsuccessful.[83, 131]

The regiospecific formation of 2-bromopyrroles has been successfully accomplished using *N*-bromosuccinimide (NBS) in dimethylformamide.[79] With this reagent, bromination of pyrrole and its 1-derivatives has been reported to afford the monobromo compound, or selectively all the possible polybromo-derivatives depending on the number of moles of reagent employed. Using 1 equivalent of NBS, the reaction is regiospecific for the 2 position with a little disubstitution. However, oxidation of the pyrrole ring may also occur, and it was frequently found to be difficult to separate the bromopyrroles from the solvent. Increasing the number of moles of the reagent from two to four enhanced the yields of the di-, tri-, and tetrabromo derivatives with little evidence of isomeric material. When tetrahydrofuran instead of dimethylformamide was used as the solvent, the reaction was regiospecific for the 2 position and selective for mono-, di-, tri-, and tetrabromo substitution, with little or no concomitant oxidation. There is also the advantage that the solvent was easily removed from the bromopyrroles. As shown in Table 3.3.14, the bromination with 1 equivalent of NBS was more selective with pyrrole, 1-methylpyrrole, and 1-benzylpyrrole than with 1-phenylpyrrole. In the latter case, the use of dimethylformamide as the solvent was preferred because of a more selective formation of 2-bromo-1-phenylpyrrole with minor amounts of the 3-bromo isomer and the 2,5-dibromo derivative.

Partially brominated pyrroles are generally unstable, but they can be stabilized by the addition of tributylamine. In contrast, fully brominated 1-substituted pyrroles are stable. The acid-induced rearrangement of 2-bromopyrroles to the thermodynamically more stable 3-bromopyrroles has been also reported[79] (see Section 3.2).

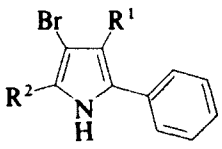
TABLE 3.3.14. BROMINATION OF 1-SUBSTITUTED PYRROLES

Compound	Solvent	Brominating Agent	Moles of Reagent	Bromopyrroles (%) 2-	3-	2,5-	2,3,5-	2,3,4,5-
Pyrrole	THF	NBS	1	91	1	—	—	—
			2	1	—	98	2	—
			3		—	33	66	—
1-Methylpyrrole	THF	NBS	1	99	1	1	—	—
			2	1	—	99	1	—
			3	10	—	90	—	—
			4	—	—	—	1	100
	CCl_4	Br_2	1	19	8	24[a]	23	12
1-Benzylpyrrole	THF	NBS	1	99	1	1	—	—
			2	1	—	99	1	—
			3	8	—	92	—	—
			4	—	—	—	1	100
	CCl_4	Br_2	1	10	28	1[b]	20	2
1-Phenylpyrrole	THF	NBS	1	49	1	14	—	—
			2	1	—	100	1	—
			3	1	—	96	3	—
			4	—	—	—	1	100
	DMF	NBS	1	81	1	6	—	—
	CCl_4	Br_2	1	10	36	21[c]	7	—

[a] Some 2,4- and 3,4-dibrominated products (4%) were also detected.
[b] A mixture of 2,4- and 3,4-dibromoderivatives formed as the major (37%) dibrominated component.
[c] The presence of some amount of 2,4- and 3,4-dibromoisomers was observed.

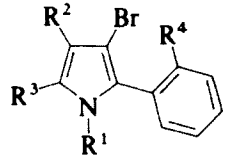
Although the presence of pyridine is crucial for the exclusive formation of the 2-bromo- and 2,5-dibromo derivatives, the reaction of 1-methylpyrrole with bromine in carbon tetrachloride is not as selective as the NBS–THF brominating system.

Controlled bromination in dimethylformamide under mild conditions with *N*-bromosuccinimide of various pyrrole derivatives to give monobromopyrroles **3.156** and **3.157** in high yield has been examined by Aiello et al.[80,81]



3.156

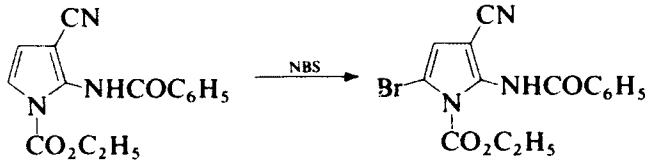
R^1	R^2
H	CH_3
H	C_6H_5
C_6H_5	C_6H_5

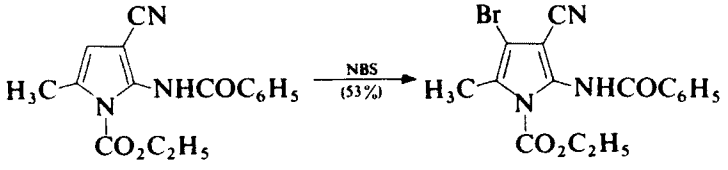


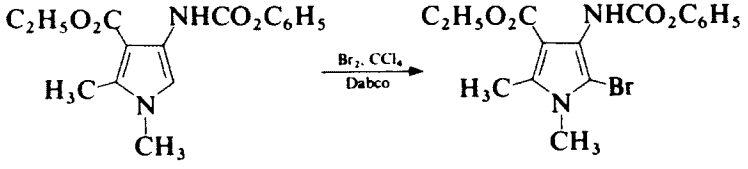
3.157

R^1	R^2	R^3	R^4
H	$CO_2C_2H_5$	CH_3	H
H	$CO_2C_2H_5$	C_6H_5	H
C_6H_5	$CO_2C_2H_5$	C_6H_5	H
H	$COCH_3$	CH_3	NO_2
CH_3	$COCH_3$	CH_3	NO_2
C_6H_5	$COCH_3$	CH_3	NO_2

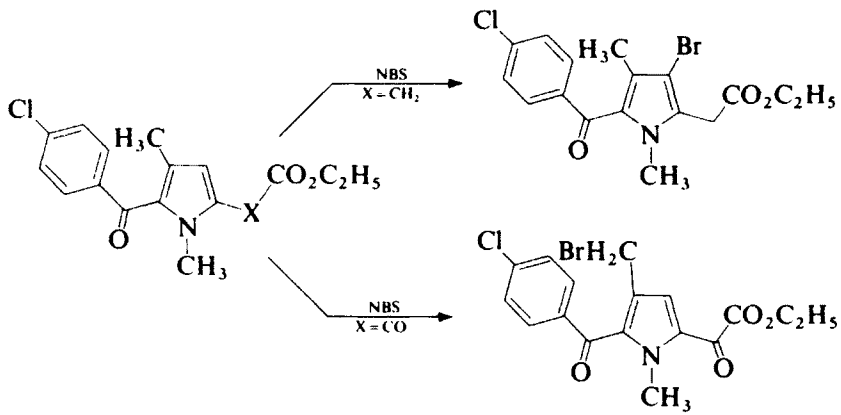
Monobromination of pyrroles has also been achieved by Sonoda et al.,[126] using the stoichiometrically amount of NBS in carbon tetrachloride, without concomitant reaction of any α-methyl group that was present, for example, **3.158** → **3.159** and **3.160** → **3.161**.







Similarly, bromination of **3.162** with bromine in carbon tetrachloride in the presence of diazabicyclo[2.2.2]octane (Dabco), as an acid acceptor, led to **3.163**. Again, the 5-bromomethyl derivative was not found.[127] However, the deactivating effect of substituents on reaction on the pyrrole ring can direct the



Scheme 3.16

bromination toward the alkyl side chains, leaving free positions of pyrrole ring unreacted. A typical example is to be found in the bromination of certain aroylpyrroles[128] (Scheme 3.16).

As indicated earlier (see Section 3.1), electron-withdrawing groups at the 2 position and bulky 1-substituent profoundly affect the orientation of electrophilic bromination of the pyrrole ring. Table 3.3.15 illustrates the influence of the 1-substituent, and, as with the chlorination reactions, the use of readily removable substituents of this type provides a viable route to 3-bromopyrroles.

The reaction of bromine on pyrroles having an electron-withdrawing group in the 2 position has been found to produce mixtures of isomeric 4- and 5-bromo derivatives, or the 4,5-dibromopyrroles when an excess of reagent was employed. Methyl pyrrole-3-carboxylate and 3-acetylpyrrole form the 5-bromo derivatives almost exclusively. Any other products are obtained in too small a yield to be isolated or identified. With such substrates, monobromination was preferably carried out with dioxane dibromide, and tribromination was achieved with bromine in carbon tetrachloride or in dimethylformamide. The formation of the dibromo derivatives could be suppressed completely by the addition of anhydrous sodium acetate to the dioxane dibromide.[130]

TABLE 3.3.15. BROMINATION OF PYRROLES WITH BULKY SUBSTITUENT AT 1 POSITION

Substrate	Brominating System	Bromoderivative Formed or α:β Ratio (Yield %)	Ref.
N-Triisopropylsilylpyrrole	NBS–THF	5.6 (74)[a]	30
N-Trimethylsilylpyrrole	NBS–THF	α-Isomer	30
N-Tritylpyrrole	$C_5H_5N \cdot HBr \cdot Br_2$ (C_5H_5N)	β-Isomer (75)[b]	129

[a] Removal of the *N*-silyl group with tetra-*n*-butyl ammonium fluoride from 3-bromo-1-triisopropylsilylpyrrole afforded 3-bromopyrrole in 65% yield.

[b] The use of bromine in dichloromethane afforded mainly the 3,4-dibromo-1-tritylpyrrole together with minor amounts of the 3-bromo analog.

In more detailed study of bromination of methyl pyrrole-2-carboxylate and 2-formylpyrrole, carried out by Anderson and Lee,[131] the 4-bromo, 5-bromo, and 4,5-dibromo derivatives were isolated. The highest yields of the 4-isomer were obtained when bromination was performed with elemental bromine in carbon tetrachloride in the presence of a trace of iodine, but the ratio of the 4- and 5-isomers was found to be temperature- and time-dependent. At room temperature, the bromination at the 4 position predominated and the 4:5 substitution ratio was usually in the range 6:1 to 10:1. At the boiling point of carbon tetrachloride, the amounts of 4- and 5-bromo derivatives were about equal. Additionally, the 4,5-dibromo derivatives were always produced, except at room temperature, with the predominant formation of these products at the higher temperatures after prolonged reaction. Only in one experiment was a

TABLE 3.3.16. BROMINATION OF METHYL PYRROLE-2-CARBOXYLATE WITH MOLECULAR BROMINE (PLUS TRACE OF IODINE) IN CARBON TETRACHLORIDE

Mole Ratio Ester : Bromine	Temp. (°C)	Time (h)	Overall Yield (%)	Bromo Derivatives (%)		
				4-Bromo	5-Bromo	4,5-Dibromo
1 : 1	0	1.5	74.9	68.4	6.5	
1 : 1	28	0.5	84.9	74.1	7.6	3.2
1 : 1	28	1.5	97.6	82.8	12.5	2.3
1 : 1	28	2.0	100	15.6	2.3	82.1
1 : 2	28	2.0	100	2.0	—	98.0
1 : 1	70	1.5	84.3	46.5	31.4	6.4
1 : 1.25	70	1.5	100	46.3	35.0	18.7

TABLE 3.3.17. BROMINATION OF METHYL PYRROLE-2-CARBOXYLATE WITH SYSTEMS OTHER THAN BROMINE–CARBON TETRACHLORIDE

Reagent System	Derivatives (%)		
	4-Bromo	5-Bromo	4,5-Dibromo
Br_2–Fe	47.5	16.7	5.4
Br_2–$AlCl_3$	29.1	29.7	5.7
Br_2–CH_3COOH	12.3	3.3	20.7
Br_2–dioxane	38.0	16.4	13.6
Br_2–$AgClO_4$–$HClO_4$	14.9	5.2	15.2
NBS–peroxide	15.3	14.2	11.2
HOBr–H_3O^+	4.7	0.4	1.1
NaOBr–NaOH	20.5	1.7	—
CuBr–DMF	3.3	3.0	
Pyridinium bromide perbromide	49.1	1.8	4.8

small amount of methyl 3,4,5-tribromo-2-pyrrolecarboxylate isolated. The results of these studies with methyl 2-pyrrolecarboxylate are presented in Tables 3.3.16 and 3.3.17.

2-Formyl and 2-cyano groups have also been found to be more meta directing for bromination of the pyrrole ring than is the 2-alkoxycarbonyl group, but the subsequent removal of all these groups resulted in a marked decrease of overall yield. 4-Bromopyrroles have been most successfully synthesized via the 1-(pyrrol-2-ylmethylene)pyrrolidinium salts,[44] and this route is far more effective for the synthesis of 4-bromo-2-formylpyrrole than is the direct bromination of the aldehyde (Table 3.3.18).[131] Almost quantitative regeneration of the aldehyde from the pyrrolidinium salt is easily performed by treatment with aqueous sodium bicarbonate.[44]

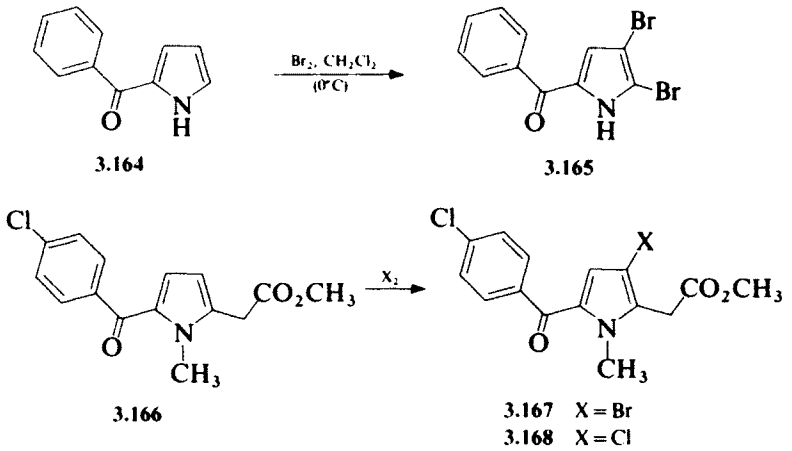
During studies on nonsteroidal antiinflammatory agents related to tolmetin, the dibromoderivative **3.165** was prepared by the action of elemental bromine on 2-benzoylpyrrole **3.164**.[132] The analogous reaction with methyl [1-methyl-5-(4-chlorobenzoyl)]pyrrol-2-ylacetate **3.166** afforded the 3-bromo derivative

TABLE 3.3.18. BROMINATION OF 2-FORMYLPYRROLE AND 1-(PYRROL-2-YLMETHYLENE)PYRROLIDINIUM PERCHLORATE (MOLE RATIO 1:1)

Time (h)	Temp. (°C)	Overall Yield (%)	Derivatives (%) 4-Bromo	5-Bromo	4,5-Dibromo	Ref.
			2-Formylpyrrole			
1.5	0	62.8	60.7	2.1	—	131
1.5	28	74.7	62.3	11.1	1.4	131
1.5	70	66.0	26.0	24.0	16.0	131
2.0	28	100[a]	5.2	0.4	94.4	131
			1-(Pyrrol-2-ylmethylene)pyrrolidinium perchlorate			
16	0–5	100	99.5	0.5	—	44
0.5	26–28	100	96.5	3.5	—	44

[a] Mole ratio aldehyde–bromine 1:2.

3.167 as the only product in good yield.[75,133] The 3-chloro analog **3.168** has also been prepared.

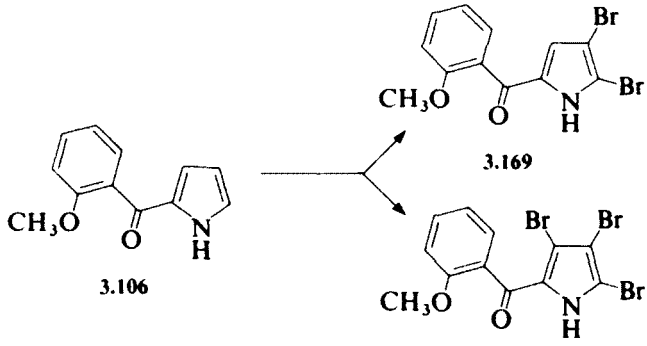


3.164 **3.165**

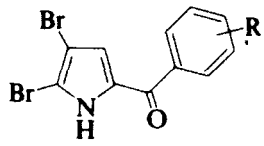
3.166

3.167 X = Br
3.168 X = Cl

In a search for potential antibacterial pyrroles, systematic studies have been conducted on the bromination of aroylpyrroles. In general, brominated pyoluteorin-like compounds were prepared using elemental bromine in the appropriate solvent. Thus, for example, the reaction of 2-(2-methoxybenzoyl)pyrrole **3.106** with bromine in chloroform at room temperature[94] gave a mixture of 4,5-dibromo **3.169** and 3,4,5-tribromo **3.170** derivatives, and Bailey et al.[101] have prepared a range of 2-aroyl-4,5-dibromo derivatives **3.171** by the action of bromine in acetic acid. However, the presence of other solvents, such as carbon tetrachloride, sometimes produced better yields. An alternative route to the 2-aroyl-4,5-dihalopyrrole derivatives has been accomplished with bromine in



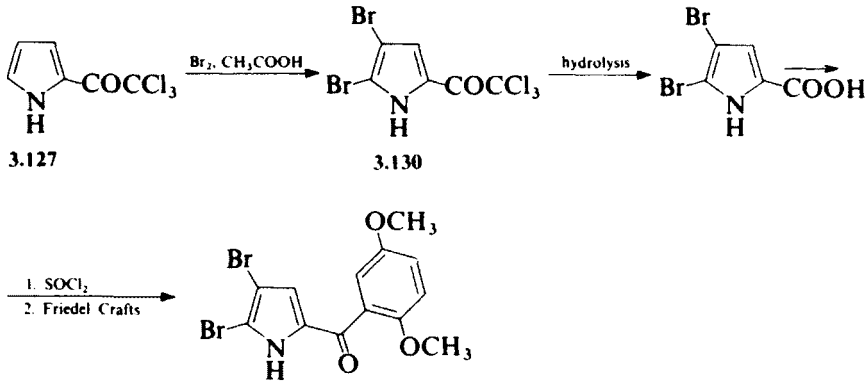
3.106 3.169 3.170



3.171

R = 2-Cl, 3-Cl, 3-Br, 3-OCH_3, 4-Cl, 4-F, 4-OCH_3, 2,5-diOCH_3, 2,5-diOH, 2,4,6-triCH_3

acetic acid, starting from 2-trichloroacetylpyrrole **3.127**, which can be transformed into the corresponding 4,5-dibromopyrrole-2-carboxylic acid chloride and then subjected to Friedel–Crafts acylation with 2,4-dimethoxybenzene or other suitable arenes[102] (Scheme 3.17). The dichloromethyl and trifluoromethyl analogs of **3.130** have been obtained in a similar manner.

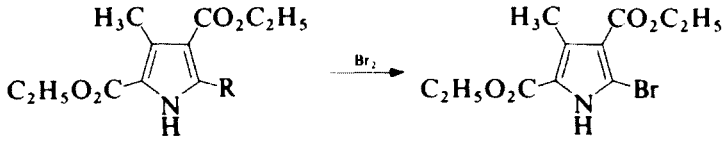


3.127 3.130

Scheme 3.17

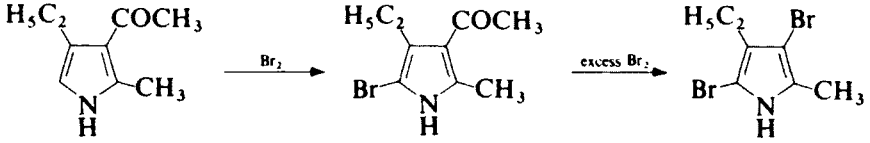
The ipso-substitution of carboxyl, formyl, and acetyl groups has also been noted during bromination of the pyrrole system. Thus, diethyl 2-carboxy-4-methylpyrrole-3,5-dicarboxylate **3.172** and its 2-formyl analog **3.173** led to the

same bromo derivative **3.174** when reacted with bromine.[134] Similarly, action of bromine on 3-acetyl-4-ethyl-2-methylpyrrole **3.175** has been shown to lead initially to the 5-monobromo derivative **3.176** and, by subsequent replacement of the acetyl group, to yield 3,5-dibromo-4-ethyl-2-methylpyrrole **3.177**.[13,135]



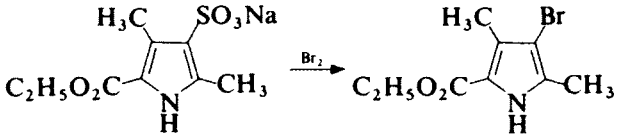
3.172 R = COOH
3.173 R = CHO

3.174

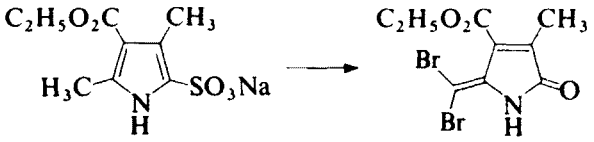


3.175 **3.176** **3.177**

β-Sulfonyl groups are also replaced by elemental bromine, as illustrated by the transformation of **3.178** into **3.179**, whereas, under similar conditions, α-sulfonyl groups undergo anomalous reactions with formation of oxidized bromo derivatives,[58,71] for example, **3.180** → **3.181**.



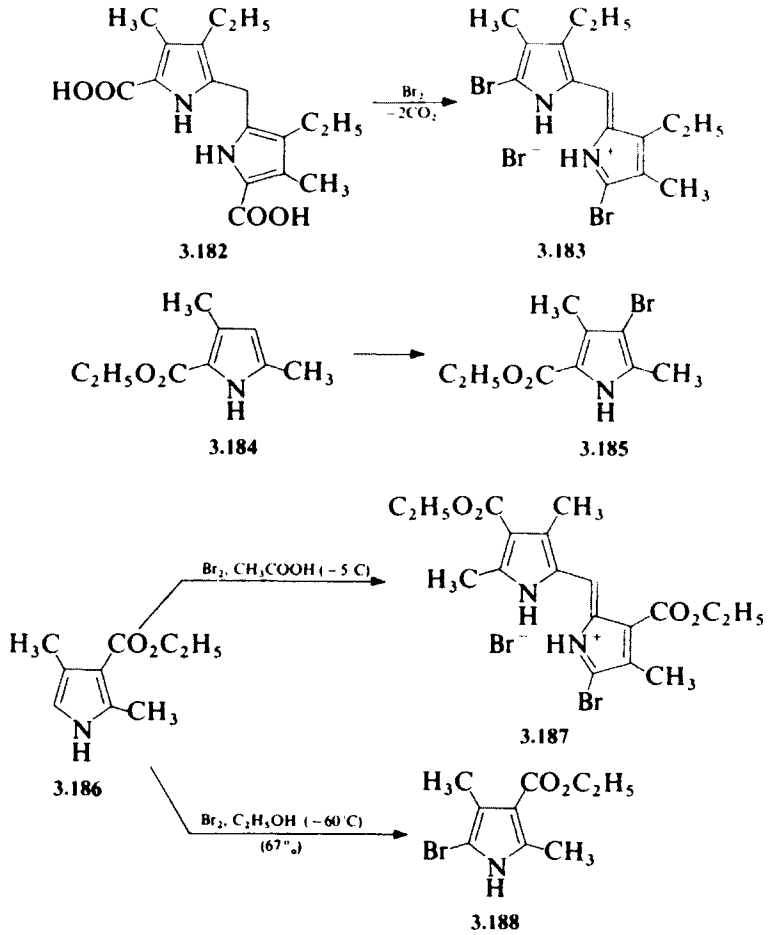
3.178 **3.179**



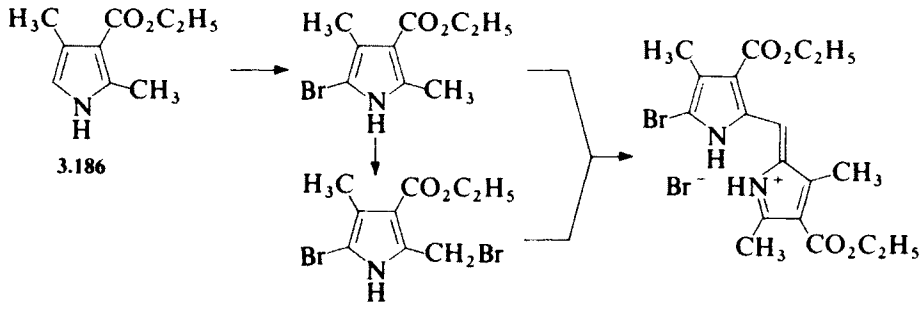
3.180 **3.181**

In the synthesis of porphyrins, the bromine-induced decarboxylation of pyrroles has been usefully employed in the preparation of the dibromodipyrromethene **3.183** from the dicarboxydipyrromethane **3.182**.[136]

Normal bromination of the pyrrole ring occurs when ethyl 3,5-dimethylpyrrole-2-carboxylate is treated with bromine, **3.184** → **3.185**,[137] but an abnormal reaction takes place with the isomeric 3-carboxylic ester **3.186** to give the bromodipyrromethene **3.187**.[138] This reaction sequence presumably results from the initially formed 5-bromo-2-bromomethyl derivative reacting with



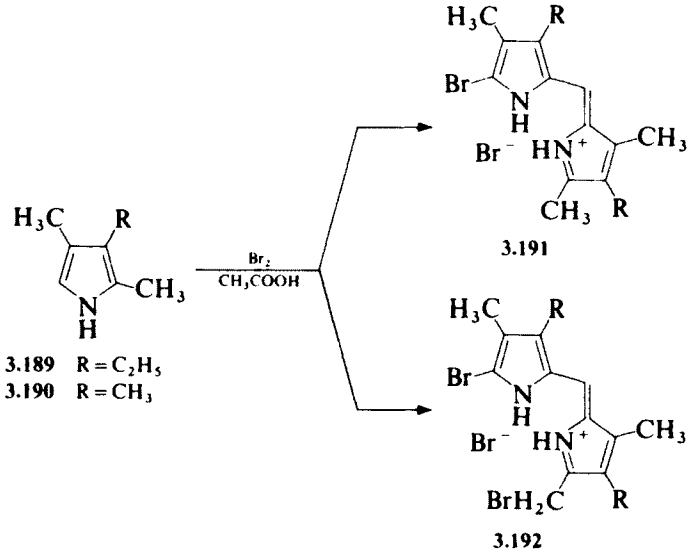
3.186 to produce a dipyrromethane, which is then oxidized by the bromine to yield the dipyrromethene[135,136,139] (Scheme 3.18). A similar sequence has been observed with the corresponding 3-acetylpyrrole. However, the normal 5-bromo



Scheme 3.18

derivative **3.188** was formed when bromination was carried out at lower temperatures.[13,135]

The four-step mechanism postulated by Fischer et al.[139] to explain the formation of 5-bromo-5′-methyldipyrromethene hydrobromide derivatives from the reaction of 3,4-disubstituted 2-methylpyrroles with bromine has been reinvestigated,[135,140] and Ellis et al. have reported that the bromination of kryptopyrrole (3-ethyl-2,4-dimethylpyrrole) **3.189** and 2,3,4-trimethylpyrrole **3.190** with 2.5 mol of bromine in acetic acid leads to the formation of a mixture of the dipyrromethenes **3.191** and the dipyrromethene perbromides (α-bromomethylderivatives) **3.192**.[140]

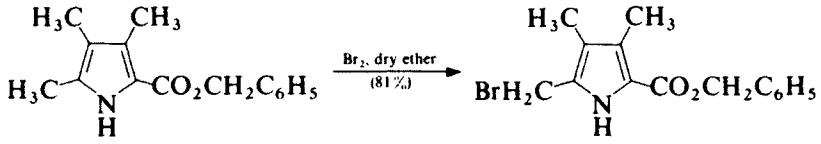


3.189 R = C_2H_5
3.190 R = CH_3

3.191

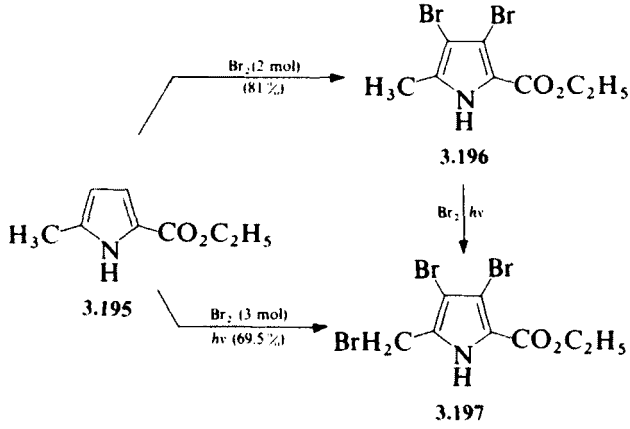
3.192

It is well established that, with fully *C*-substituted pyrroles having methyl groups at the α positions, the action of 1 equivalent of bromine results in the formation of the related α-bromomethyl derivatives, such as **3.193** → **3.194**, and several bromomethylpyrroles have been prepared by this procedure as useful intermediates in the synthesis of the related dipyrromethanes, dipyrromethenes, and porphyrins.[140] Bromination of ethyl 5-methylpyrrole-2-carboxylate **3.195** with 2 equivalents of elemental bromine in carbon tetrachloride at 3–4°C resulted in the formation of the expected 3,4-dibromo derivative **3.196**.[90] Irradiation of the latter compound with bromine furnished the 5-bromomethyl



3.193

3.194

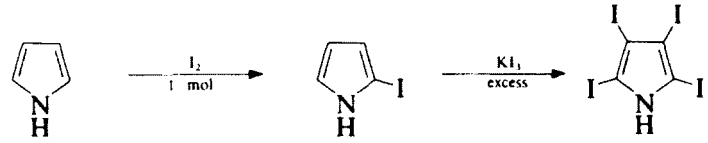


derivative **3.197**, which is also produced photochemically from **3.195** by the action of 3 equivalents of bromine in carbon tetrachloride. Other reports on 3,4-dihalopyrroles are known.[119,141–143]

3.3.4.4. Iodination

In general, iodination of pyrroles is accomplished by the direct action of iodine in aqueous potassium iodide, which is, effectively, the triiodide ion (I_3^-) in equilibrium with low concentrations of free iodine in the presence of iodide ion. Alternatively, iodination may be carried out with iodine in alkaline solution (I_2/KOH) or by the addition of hydrogen peroxide to a solution containing potassium iodide and the pyrrole substrate. Other iodinating systems to have been used include I_2/HIO_3, I_2/HgO, $I_2/AgOCOCF_3$, and *N*-iodosuccinimide (NIS).[1]

When pyrrole is treated with an equimolar amount of iodine in solution, an iodine–pyrrole charge-transfer complex forms, which rapidly degenerates to give 2-iodopyrrole **3.198**.[144] With an excess of iodine, the light-sensitive 2,3,4,5-tetraiodopyrrole **3.199**,[6,143,145–150] originally called *iodol*, is the main product of the reaction and iodination proceeds almost to completion when potassium iodide is present in a buffered solution.



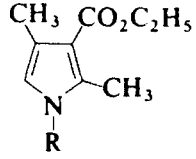
3-Iodopyrrole has not been described, although its formation is conceivable in a synthetic sequence leading, in moderate yield, to 2-formyl-3-iodopyrrole when

pyrrole is treated with iodine in the presence of *n*-butyllithium and tetramethylethylenediamine in dry ether at − 70°C, followed by Vilsmeier–Haack formylation of the crude mixture. The same compound is obtained in only trace amounts by iodination of 2-formylpyrrole.[118,151] The isomeric 3-formyl-4-iodopyrrole has been prepared by the reaction of 3,4-diiodopyrrole with *n*-butyllithium and dimethylformamide.[152]

With the exception of **3.198** and **3.199**, prepared by direct iodination of pyrrole, other iodopyrroles have been obtained by either deiodination of 2,3,4,5-tetraiodopyrrole or removal of functional groups that have aided regioselective iodination of the ring. Thus, 3,4-diiodopyrrole has been prepared in 38% yield by reduction of 2,3,4,5-tetraiodopyrrole with zinc and glacial acetic acid,[152] and sequential reaction of 2,3,4,5-tetraiodopyrrole with *n*-butyllithium, followed by hydrolysis of intermediates, led to a mixture of 2,3,4-triiodo- and 2,3,5-triiodopyrrole, together with isomeric diiodopyrroles.

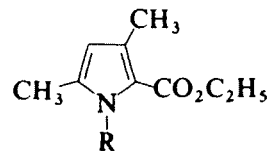
Iodination of polymethyl pyrroles with iodine in aqueous potassium iodide has been investigated in detail.[153] Generally, iodination occurs at all free positions of the pyrrole ring, giving polyiodopyrroles, although, under well-controlled conditions, monoiodo derivatives can be isolated. Both 2,4- and 2,5-dimethylpyrroles yield the 3,5- and 3,4-diiodo derivatives and, under the same conditions, 1,2,5-trimethylpyrrole is converted into the 3,4-diiodo derivative. However, when the controlled iodination of 1,2,5-trimethylpyrrole was carried out at − 10°C with I_2/KI, the unstable 3-iodo-1,2,5-trimethylpyrrole was isolated. 5-Iodo-2,3,4-trimethylpyrrole has been described by Treibs and Kolm[153] as a fairly stable compound, decomposing readily in warm solution.

Mono- and dimethyl derivatives of 2- and 3-formyl and 2- and 3-ethoxycarbonylpyrroles have been transformed into their diiodo and, respectively, monoiodo derivatives by direct iodination with I_2/KI solution.[90,153] Doak and Corwin have studied the kinetics of such reactions with trisubstituted derivatives of pyrrole and 1-methylpyrrole **3.200** and **3.201** in aqueous dioxane buffered to pH 6.8–6.9[145] and have shown that the 2 position of pyrrole ring is 25 times more readily iodinated than is the 3 position and that the introduction of a methyl group at 1 position increased the reactivity of the pyrrole ring by about 8–15%. In the iodination reaction, both free iodine and hypoiodous acid appear to be involved, and Doak and Corwin excluded the presence of a pyrrolenine intermediate in the mechanism pathway.



3.200

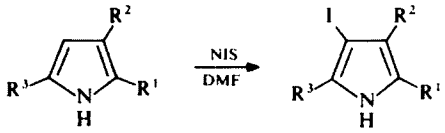
R = H, CH_3



3.201

N-Iodosuccinimide (NIS) in dimethylformamide has been recently used in the preparation of some aryl-3-iodopyrroles **3.202**.[81] The reaction is characterized

TABLE 3.3.19. MONOIODOARYLPYRROLES

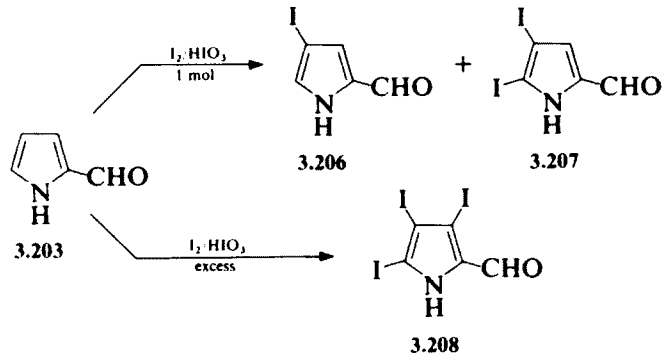


3.202

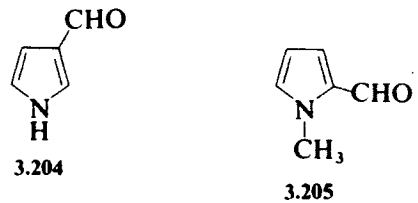
Iodopyrrole	R^1	R^2	R^3	Yield (%)	Conditions of Reaction: Time (h)	Conditions of Reaction: Temp. (°C)
3.202a	C_6H_5	C_6H_5	C_6H_5	71	6	−15
3.202b	CH_3	$CO_2C_2H_5$	C_6H_5	87	24	25
3.202c	C_6H_5	$CO_2C_2H_5$	C_6H_5	95	24	25
3.202d	CH_3	$COCH_3$	2-$NO_2C_6H_4$	90	24	25

by excellent yields under mild conditions with easy isolation of the product (Table 3.3.19).

The direct iodination of formylpyrroles **3.203**–**3.205** has been studied by Farnier and Fournari.[118,151] Treatment of **3.203** with an equimolar amount of I_2/HIO_3 afforded a mixture of 2-formyl-4-iodopyrrole **3.206** and 2-formyl-4,5-diiodopyrrole **3.207** in a ratio of 7:1. When I_2/KI and I_2/HgO were used, the 5-iodo- and, respectively, the 3,4-diiodo derivatives were also formed in trace amounts. Full iodination of 2-formylpyrrole with formation of **3.208** has been achieved with the use of an excess of I_2/HIO_3. Similar patterns of iodination are



3.206 3.207 3.203 3.208



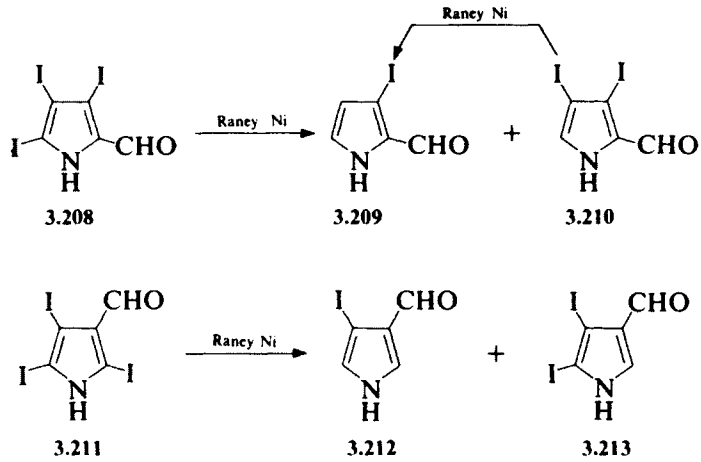
3.204 3.205

TABLE 3.3.20. IODINATION OF FORMYLPYRROLES **3.203–3.205**

Aldehyde	Iodinating System	Monoidopyrroles (%)	Diiodopyrroles (%)	Triiodopyrroles (%)
3.203	I_2/HIO_3 mol	4- (52)	4,5- (8)	—
3.203	I_2/HIO_3 excess	—	—	3,4,5- (55)
3.203	I_2/HgO	4- (33)	3,5- (2); 4,5- (6)	—
3.203	I_2/KI	4- (22); 5- (8)	4,5- (5)	—
3.203	*t*-BuOI	4-	4,5-	—
3.205	I_2/HIO_3	4- (30)	4,5- (5)	—
3.204	I_2/HIO_3	2- (1); 4- (5); 5- (16)	4,5- (1.5)	2,4,5- (1.5)
3.204	I_2/HIO_3 excess		—	2,4,5- (61)
3.204	I_2/HgO	4- (8.5); 5- (2)	4,5- (2.5)	2,4,5- (3)

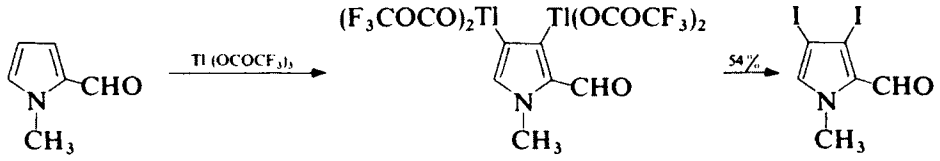
obtained with 2-formyl-1-methylpyrrole (Table 3.3.20). Iodination of 3-formylpyrrole is more complex.

Reduction of 2-formyl-3,4,5-triiodopyrrole **3.208** with Raney nickel afforded a mixture of 3-iodo- and 3,4-diiodo derivatives **3.209** and **3.210**; the latter compound is reduced under similar conditions to give 2-formyl-3-iodopyrrole **3.209**. Raney-nickel reduction of 3-formyl-2,4,5-triiodopyrrole **3.211** furnished the 4-iodo- and 4,5-diiodo derivatives **3.212** and **3.213**. This procedure is the method of choice for the preparation of 2-formyl-3-iodopyrrole **3.209**, formed in only trace amounts by direct iodination.



The 1-methyl derivative of **3.210** has been recently prepared from 2-formyl-1-methylpyrrole by reaction with a 10-fold excess of thallium(III) trifluoroacetate, followed by immediate conversion of the unstable intermediate into the iodinated compound.[154]

3-Iodopyrroles can seldom be obtained in useful preparative amounts by the direct iodination of the corresponding pyrroles. The best approach is analogous to that already described for the corresponding chloro and bromo compounds

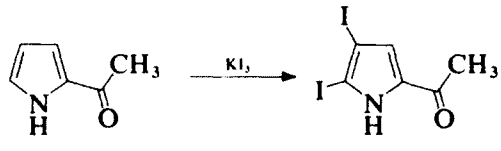


3.205 3.214

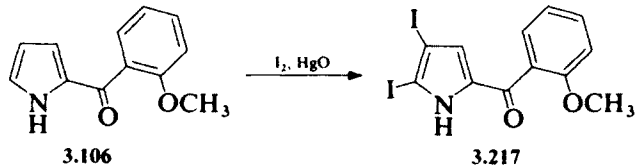
in which a readily removed electron-withdrawing group is located at the 2 position of the ring directing iodination to the 4 position.

To date, the use of bulky substituents at the 1 position to effect iodination at the 3 position does not appear to have been used.

As described above with the esters and aldehydes, a complex mixture, with relatively low yields of the 4-iodo compounds, is frequently obtained from the direct iodination of 2-substituted pyrroles. In a similar manner, the iodination of 2-acetylpyrrole **3.215** with alkaline potassium triiodide resulted in formation of 2-acetyl-4,5-diiodopyrrole **3.126** in 60% yield,[119] while the reaction of 2-(2-methoxybenzoyl)pyrrole **3.106** with I_2/HgO system in benzene at 20°C furnished 4,5-diiodo-2-(2-methoxybenzoyl)pyrrole **3.217** as the only product.[94]



3.215 3.216

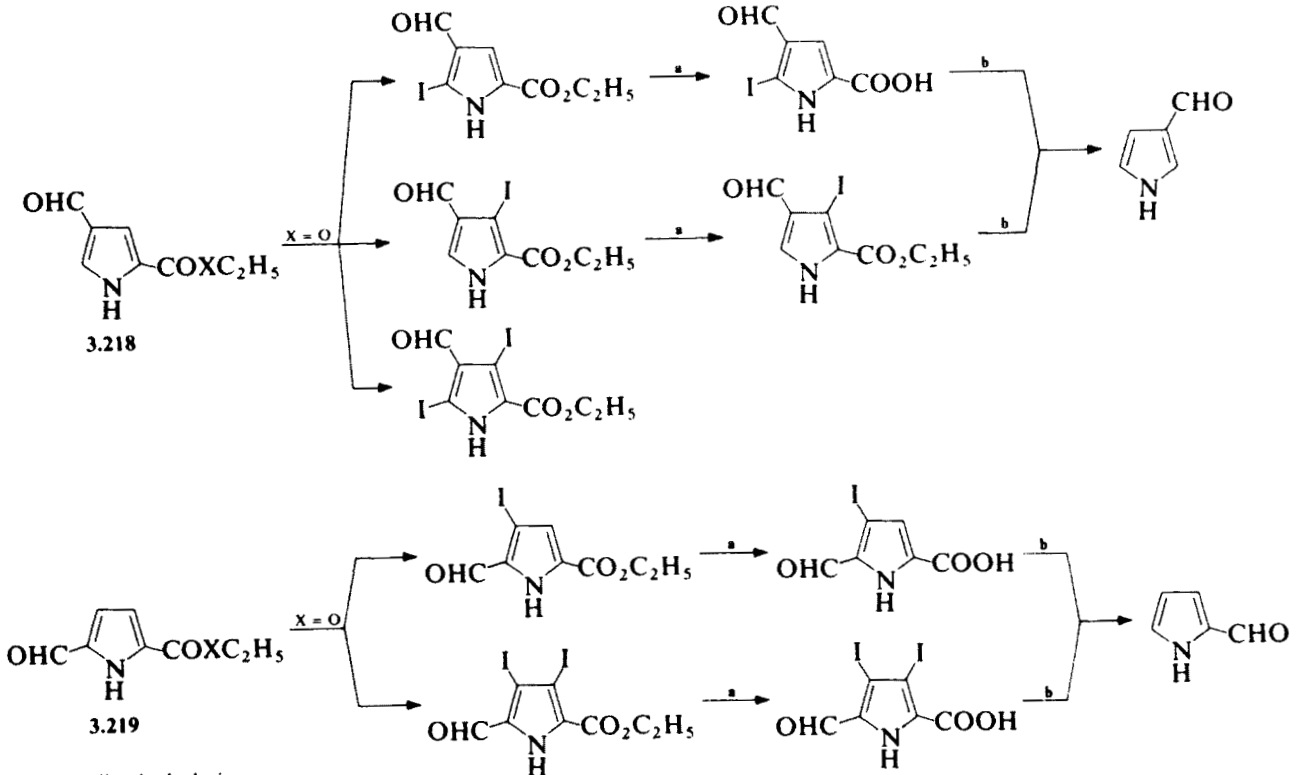


3.106 3.217

The direct iodination of ethyl 4-formyl- and 5-formylpyrrole-2-carboxylates and of the related thioesters has been investigated by Farnier and Fournari[118,151] using I_2/HIO_3 (Scheme 3.19 and Table 3.3.21). Alkaline hydrolysis of the iodinated esters provided the corresponding carboxylic acids, but

TABLE 3.3.21. IODINATION OF SOME ETHYL FORMYLPYRROLECARBOXYLATES AND RELATED THIOESTERS WITH I_2/HIO_3 SYSTEM

Formylpyrrole	X	Monoiodopyrroles (Yield %)	Diiodopyrroles (Yield %)
3.218	O	3- (23); 5- (42)	3,5- (2)
3.219	O	4- (82)	3,4- (13)
3.218	S	3- (10); 5- (25)	3,5- (2)
3.219	S	4- (15)	—

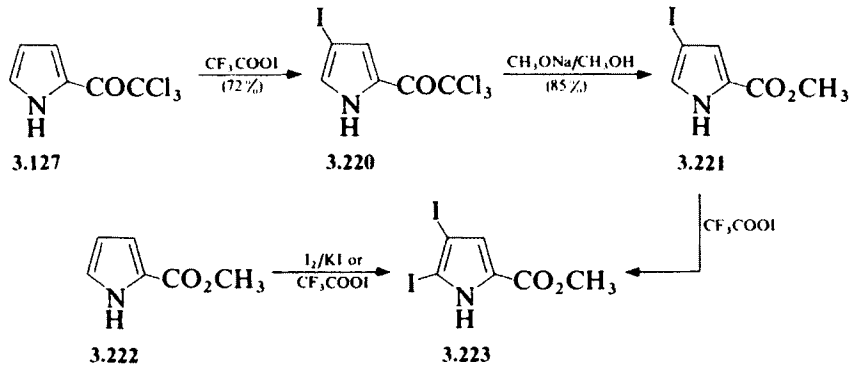


a. Alkaline hydrolysis.
b. Decarboxylation by treatment with copper powder and quinoline at reflux

Scheme 3.19

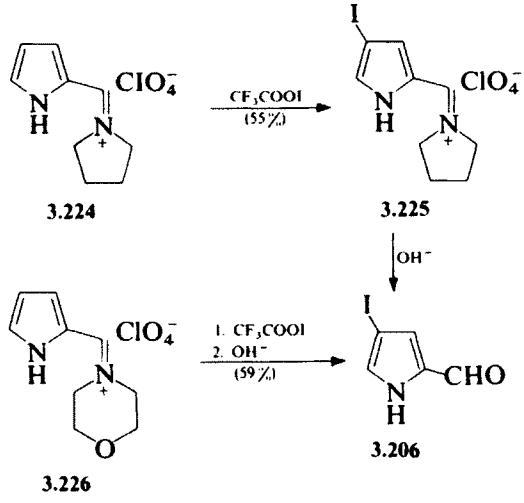
all attempts to prepare the formyliodopyrroles by decarboxylation proved unsuccessful because of the concomitant loss of iodine. Only the 2-formyl- and 3-formylpyrroles were isolated, as the main products, from these reactions.

The electrophilic iodination of 2-trichloroacetylpyrrole **3.127**[43] with trifluoroacetyl hypoiodite (from iodine and $AgOCOCF_3$) in chloroform at 22°C at the 4 position is more specific than it is for methyl pyrrole-2-carboxylate, and, with the facile conversion of the trichloroacetyl group into the ester, this is effectively the best route to 2-alkoxycarbonyl-4-iodopyrroles, for example, **3.221**. Direct iodination of methyl pyrrole-2-carboxylate **3.222** with I_2/KI or by the action of trifluoroacetyl hypoiodite furnishes primarily the 4,5-diiodo derivative **3.223**.



3.127 **3.220** **3.221** **3.222** **3.223**

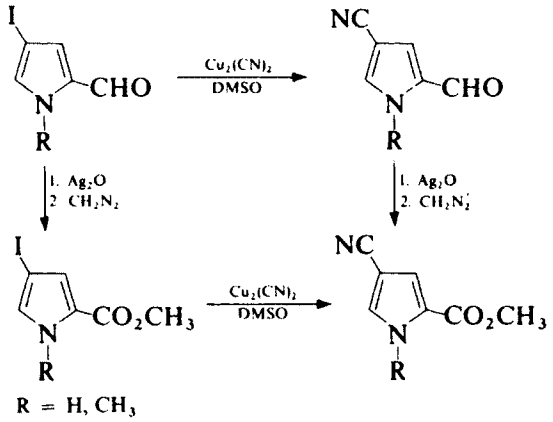
Virtually exclusive regioselective substitution at the 4 position has been achieved by Sonnet[44,155] using the pyrrolidinium salt **3.224** derived from 2-formylpyrrole. Subsequent hydrolysis of the iodinated derivative **3.225** yields 2-formyl-4-iodopyrrole **3.206** in an overall yield of 55%, with no evidence for the formation of the 5-isomer or of the 4,5-diiodo derivative. A slight improvement



3.224 **3.225** **3.226** **3.206**

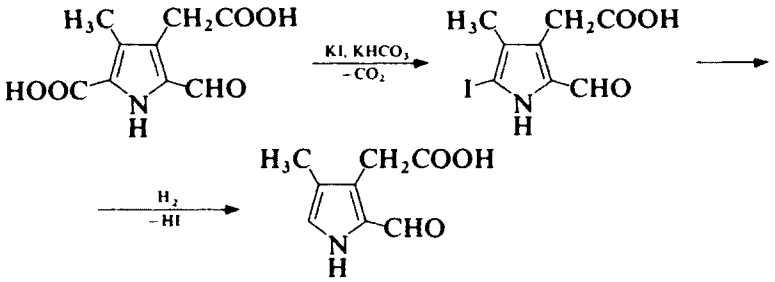
in yield (59%) was obtained when the morpholinium salt **3.226** was used. 2-Formyl-4-iodo-1-methylpyrrole was obtained in 55% yield by an analogous procedure. 2-Formyl-4-iodopyrrole can be converted into the corresponding ester, but the synthetic value of this overall procedure for the preparation of carboxylic esters is lost because of the number of steps involved in the conversion of the pyrrolidinium salt through to the iodinated ester.

As 2-formyl-4-iodopyrrole reacts easily with copper(I) cyanide in dimethyl sulfoxide, it is a valuable intermediate for the preparation of methyl 4-cyanopyrrole-2-carboxylate and its 1-methyl derivative (Scheme 3.20).[155]

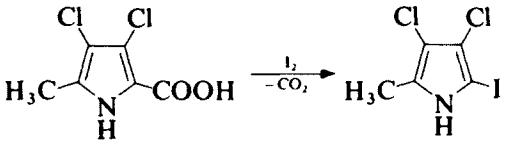


Scheme 3.20

Ipso-substitution by iodine[156–161] provides an effective procedure for the decarboxylation of pyrrolecarboxylic acids in which the ring is highly substituted by electron-withdrawing groups, with the iodo group being removed by



Scheme 3.21



Scheme 3.22

subsequent hydrogenolysis[156-161] (Scheme 3.21). This procedure has been used to prepare pyrroles containing both chlorine and iodine[90] (Scheme 3.22). Ipso-substitution of the iodo group may also occur during nitration of the ring[59] (see Section 3.3.2).

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3.4. ALKYLATION AND ACYLATION

Hugh J. Anderson and Charles E. Loader

Memorial University of Newfoundland
St. John's, Newfoundland
Canada A1B 3X7

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3.4.1. Introduction

Pyrrole and many of its derivatives react readily with a variety of electrophilic carbon atoms to give both alkylation and acylation products. Although acidic catalysts are still used, particularly for pyrroles that are deactivated by electron-withdrawing groups, it is often possible to carry out some reactions without a catalyst. Electrophilic reactions on pyrrole and 1-substituted pyrroles generally lead to 2-substitution, but there is usually some 3-substitution as well, especially when acid catalysis is used. Occasionally, the 3-substituted pyrrole may be the major product. There are also examples of 1-substitution as a major or minor product.

It is possible to activate the 1*H*-pyrrole nucleus toward very weakly electrophilic carbons by its conversion to the corresponding anion through the use of a variety of bases. However, this anion is an ambident one, and substitution may now take place on either a carbon atom, the nitrogen atom, or both, depending on the nature of the reactants and the conditions used.

When the 1 position is blocked, a pyrrolyl anion may often be prepared by either metal–hydrogen or metal–halogen interchange. While the former operation generally leads to 2-substitution of the anion on reaction with electrophiles, the latter procedure may be used to give a regiospecific product through ipso-substitution. The usual metal to be used in these exchange reactions is lithium, but several other metals may be used. The use of a palladium complex can also make alkenylation and arylation possible.

Several types of electrophilic carbon reagent produce intermediates that are not immediately those of alkylation or acylation but that, on workup, give products that belong in one of those categories. These reactions are included in the appropriate section of this chapter, if an alkyl or acyl product is easily obtained through a simple solvolytic workup.

Discussion of the alkylation and acylation of pyrroles considers in sequence the uncatalyzed substitution on the pyrrole nucleus, through the mild, non-acid-catalyzed reactions, to the Friedel–Crafts-type reactions, and then examines the reactions of pyrrolyl anions. Finally, attack on pyrroles by radicals is considerd.

3.4.2. Alkylation, Alkenylation, and Arylation on Carbon and Nitrogen

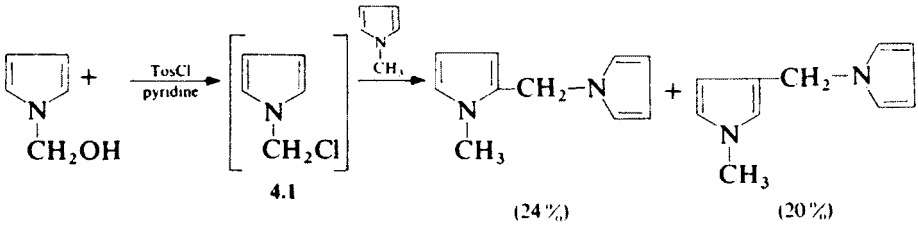
3.4.2.1. Uncatalyzed Electrophilic Substitution

Pyrrole and many of its derivatives are sufficiently nucleophilic to enter into uncatalyzed substitution reactions with a variety of electrophilic carbon compounds. Examples of Michael-type additions with compounds that possessed activated double or triple bonds arose from attempted[1] Diels–Alder reactions on the pyrrole ring. These reactions are in contrast to the cycloaddition structures commonly found with furans, and both mono- and disubstitution

products on the pyrrolyl carbon atom were obtained,[1] together with a small amount of the 1-substitution products.[2] When the reaction temperature was raised, several types of cycloaddition reactions were observed,[2] and this becomes the dominant pathway for 1-substituted pyrroles.[3]

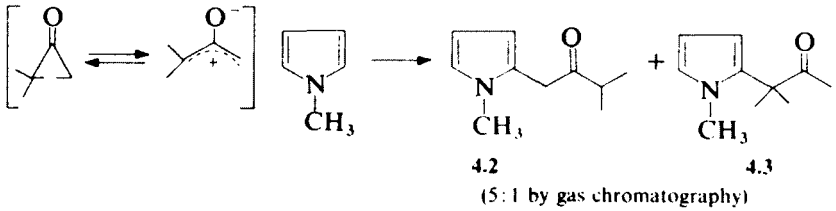
3.4.2.1.1. Reactions with Alkyl Halides and Related Electrophiles

Despite the electron-rich nature of pyrrole and some of its simple derivatives, there are relatively few direct nucleophilic substitution reactions by the ring on reagents in the absence of a catalyst. Typical examples of this type include those in which pyrrole reacts with the covalent tri(4-methoxyphenyl)methyl chloride to give 94% of the 2-substitution product,[4] while reaction with the more ionic triphenylmethyl tetrafluoroborate forms 2,5-ditritylpyrrole in 70% yield.[5] Scheme 4.1 shows how the reactive alkyl halide **4.1** is prepared in situ and reacts with 1-methylpyrrole.[6]



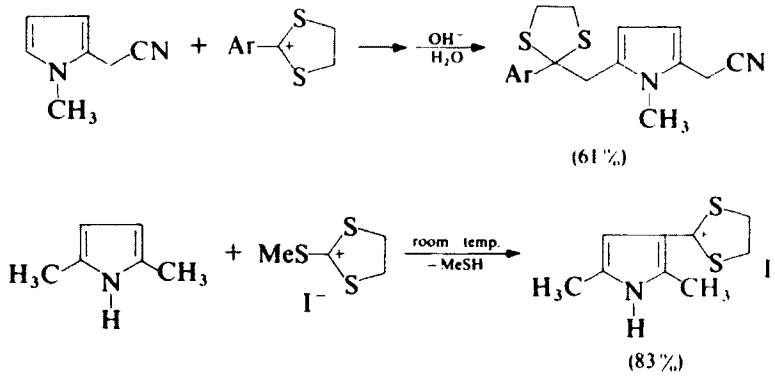
Scheme 4.1

In other examples, the electrophilic reagent owes its reactivity to the ring opening of β-propiolactone[7,8] to give 3-(pyrrol-2-yl)propanoic acid and the corresponding reaction with cyclopropanone[9] to form **4.2**, and **4.3**, as shown in Scheme 4.2.

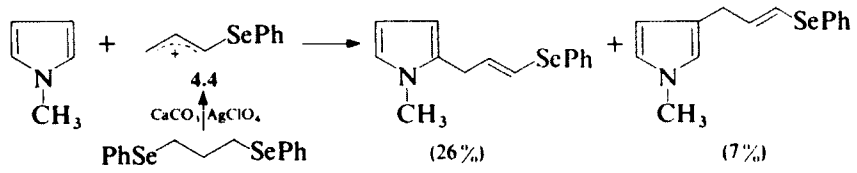


Scheme 4.2

A number of stabilized carbocationic reagents such as 2-aryl-,[10] 2-methylthio-,[5] dithiolium, benzodithiolium, benzoxathiolium,[11,12] and trithiolium salts[13] have been prepared, and a representative selection of their uses is shown in Scheme 4.3. Hydrolyses of the dithioketals[10] led to the corresponding carbonyl compounds. Selenium-stabilized allylic cations (e.g., **4.4** in Scheme 4.4), prepared as shown from 1,3-bis(seleno)propanes, gave a 4:1 mixture of 2- and 3-substituted 1-methylpyrroles in low to modest yield.[14,15]

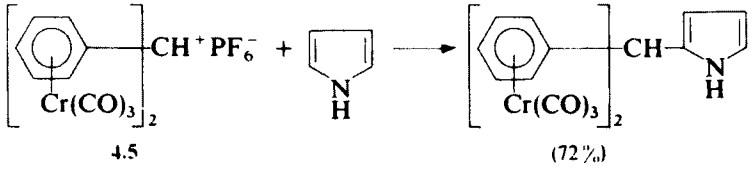


Scheme 4.3



Scheme 4.4

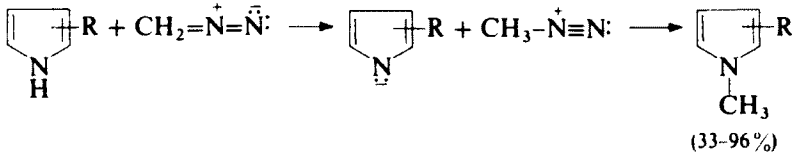
A more complex example of the stabilized carbocation reaction is illustrated in Scheme 4.5, in which the bis(tricarbonylchromium)adduct of diphenylmethyl hexafluorophosphate (**4.5**)[16] is used.



Scheme 4.5

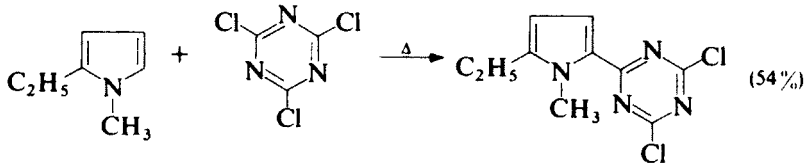
When carbocations were generated in the gas phase the reaction of the *tert*-butyl carbocation, for example, gave predominant 3-substitution and lesser amounts of 2- and 1-products with pyrrole and 1-methylpyrrole.[17–19] This is not a preparative method, however.

If the pyrrolyl NH is sufficiently acidic, it may be lost to diazomethane forming a cation with an excellent leaving group. The methylation then takes



Scheme 4.6

place (Scheme 4.6) on the 1 position.[20–22] Several authors have found that 1-methylation, in whole or in part, took place when diazomethane was used to esterify pyrrolecarboxylic acids[21,23] or to convert side-chain phenols to their methyl ethers.[24] The percentage of 1-methylation with substitution pattern in a variety of halogenated and other substituted methyl pyrrole-2-carboxylates has been suggested to be related to the acidity of the 1-hydrogen induced by the substituents on the pyrrole ring.[21] The results of other workers can be rationalized in the same way.[23–25] There are also a few examples of pyrrole acting as a nucleophile toward halogenated π-deficient heteroaromatics, as shown, for example, in Scheme 4.7, to give substitution products such as **4.6**.[26] Yields were improved by higher temperatures,[27] and were as good, or better, in the presence of aluminum chloride.[26] The use of a Lewis acid also avoided reaction with any ketone side chains[28] (see Table 3.4.1).



4.6

Scheme 4.7

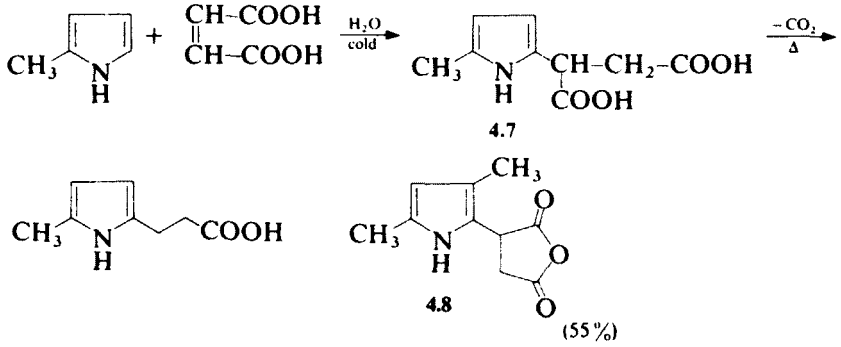
TABLE 3.4.1. PYRROLES PRODUCED BY UNCATALYZED *C*-ALKYLATION OR *C*-ARYLATION REACTIONS

R^1	R^2	R^3	R^4	R^5	Yield (%)	Ref.
H	$(CH_2)_2COOH$	H	H	H	NY	7
H	$(CH_2)_2COOH$	H	H	Me	NY	8
H	$(CH_2)_2COOH$	Me	H	Me	NY	8
H	$C(4\text{-}MeOC_6H_4)_3$	H	H	H	94	4
H	Trityl	H	H	Trityl	71	5
Me	CH_2CN	H	H	Thien-2-yl-1,3-dithiolan-2-yl	NY	10
Me	CH_2CN	H	H	2-(4-$CF_3C_6H_4$)-1,3-dithiolan-2-yl	NY	10
Me	CH_2CN	H	H	2-(4-ClC_6H_4)-1,3-dithiolan-2-yl	NY	10
Me	CH_2CN	H	H	2-(4-FC_6H_4)-1,3-dithiolan-2-yl	NY	10
Me	CH_2CN	H	H	2-(4-$MeOC_6H_4$)-1,3-dithiolan-2-yl	NY	10
Me	CH_2CN	H	H	2-(4-MeC_6H_4)-1,3-dithiolan-2-yl	61	10
Me	CH_2COOMe	H	H	2-(4-MeC_6H_4)-1,3-dithiolan-2-yl	17.4	10

3.4.2.1.2. Reactions with Alkenes

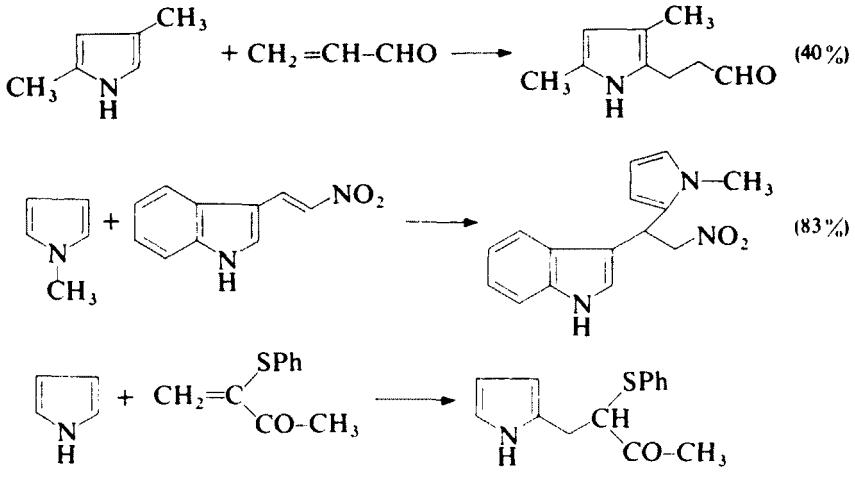
When Diels and Alder extended their examination of potential dienes for cycloaddition to the 5-membered heteroaromatics, they found that furan behaved as a diene toward dienophiles. However, pyrrole and its simple derivatives showed a variety of different reactions. Pyrrole itself was largely substituted and ring-opened by aqueous maleic acid,[1] although a small amount of pyrrole-2,5-dipropanoic acid was obtained. In contrast, 2-methylpyrrole reacted easily

with maleic acid, as shown in Scheme 4.8, to give 2-(5-methyl-2-pyrrolyl)butane-1,4-dioic acid **4.7** in good yield, and the product easily lost carbon dioxide on gentle warming.[1] Similar behavior was observed with 1-methylpyrrole, which gave the disubstituted addition–decarboxylation product. Maleic anhydride reacted with 2,4-dimethylpyrrole in benzene at room temperature[1] in a similar manner to give **4.8**. When 1-methylpyrrole and maleic anhydride were subjected to 15-kbar pressure at 40°C,[29] the results were the same as those obtained by Diels and Alder at atmospheric pressure, that is, quantitative Michael adduct formation, while pyrrole itself afforded the dicarboxylic acid (see also Section 3.4.3.1 for an example of an acylation reaction).



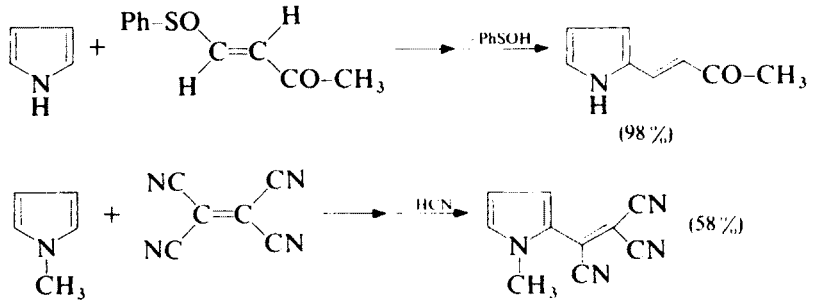
Scheme 4.8

A wide variety of other alkylations through uncatalyzed Michael-type additions to double bonds possessing strongly electrophilic carbons are now known. Most reagents are in the category of α,β-unsaturated acids and their derivatives,[1,30] aldehydes,[31] ketones,[32–34] nitriles,[35] and nitro compounds (Scheme 4.9).[36]

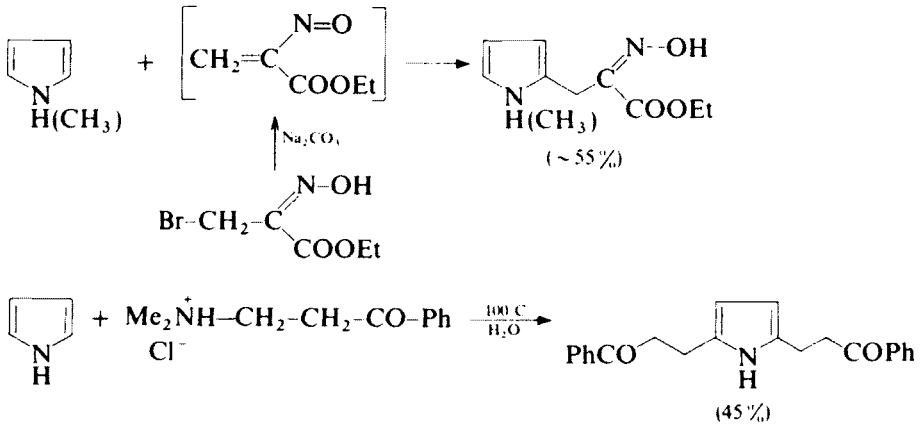


Scheme 4.9

Several other reactions follow the addition–elimination pathway (Scheme 4.10).[32,35,37] In some of the reactions the electrophilic reagent is prepared in situ (Scheme 4.11).[38,39] In contrast with these reactions, addition across the double bond of an enamine at < 100°C for a short time resulted in

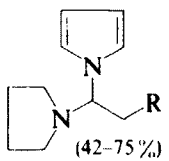


Scheme 4.10



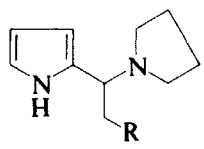
Scheme 4.11

1-substitution of the pyrrole ring to give **4.9**,[40] although at 110°C/12 h, regeneration of starting materials takes place, followed by 2-substitution leading[41] to a mixture of **4.10** and **4.11**.



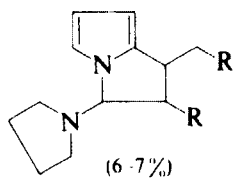
(42–75%)

4.9



(22–44%)

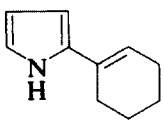
4.10



(6–7%)

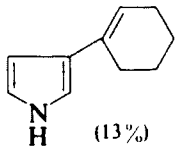
4.11

Still higher temperatures (150°C) can lead to elimination of the amine. For example, the enamine of cyclohexanone gave a mixture of **4.12**, **4.13**, and **4.14**,[42] as well as some 2,4-di(cyclohexen-1-yl)pyrrole and 2,5-di(cyclohexen-1-yl)pyrrole when treated this way.



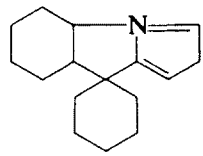
(15%)

4.12



(13%)

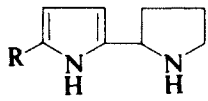
4.13



4.14

+ 10% disubstituted product

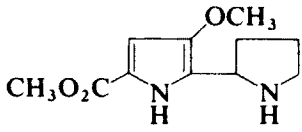
Direct addition to the carbon–nitrogen double bond[43] of 1-pyrroline led to potential 2,2′-bipyrrolyl precursors such as **4.15**.



R = H (48%)
R = CH_3 (79%)

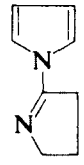
4.15

This method has been used to make **4.16** an intermediate used in a prodigiosin synthesis.[44] In another example of the Michael addition–elimination reaction, this time on the nitrogen, pyrrole yields **4.17**, when treated with 2-methoxy-1-pyrroline.[37]



(81% crude)

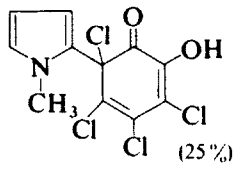
4.16



(34%)

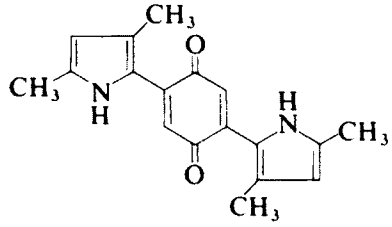
4.17

Michael addition of 1-methylpyrrole took place on 3,4,5,6-tetrachloro-*o*-quinone to give **4.18**,[45] while, in contrast, the initial 2:1 adduct of *p*-quinone and 2,4-dimethylpyrrole underwent further oxidation by the excess quinone present, affording **4.19**.[46]



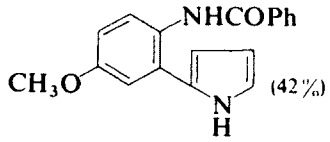
(25%)

4.18



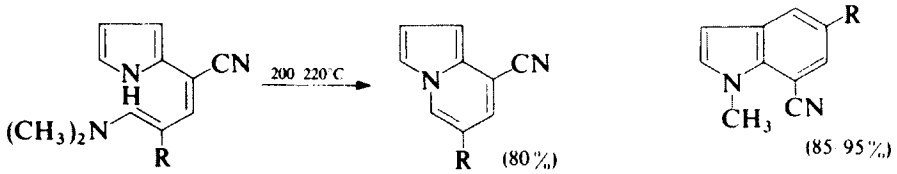
4.19

Addition and side-chain elimination on N-benzoyl-*O*-acetyl(4-methoxyphenyl)hydroxylamine[47] gave **4.20**.



4.20

What is possibly a variant of Michael addition led to **4.21** by ring closure followed by elimination of dimethylamine.[48] When the 1 position was blocked, ring closure occurred at the 3 position to give **4.22**.[48] (see Tables 3.4.2 and 3.4.3).



4.21 **4.22**

3.4.2.1.3. Reactions with Alkynes

In their paper exploring the reactions of dienophiles with pyrroles, Diels and Alder[1] reported that 2-methylpyrrole and dimethyl acetylenedicarboxylate gave a Michael adduct of melting point 111°C. Later, they isolated both the *E*- and the *Z*-isomers but did not assign their structures.[49] Since then a good deal of experimental work has been done to establish the structures of these, and other more complex products, obtained from the acetylenic diesters and acids and various pyrroles under neutral and acidic conditions.[2,50–53] We are here concerned only with alkenylation products produced under neutral conditions.

Recent work[2] has shown that pyrrole reacts with the acetylenic diester to give a mixture of 44% *Z* and 25% *E* Michael adducts at the 2 position and 6% of the *E*-isomer at the 1 position. This was the first record of such a reaction at position 1 under neutral conditions. Others[29] have found that this reaction, when conducted at 15-kbar pressure and at 40°C, gives similar results but lower yields, especially of the *Z*-isomer. 1-Methyl- and 1-benzylpyrrole also react with the acetylenic ester at the 2 position under pressure.[54] Evidence seems to favor the formation of a zwitterion **4.23** during addition that may be quenched by migration of the acidic NH, but, in its absence, the zwitterionic intermediate undergoes cycloaddition reactions as shown in Scheme 4.12.[55] These 1 : 1 products may be modified by further addition of the acetylenic ester or by elimination of acetylene. The correct steric assignment of the Michael adducts, derived from the acetylenic ester and 2-methyl-, 2,3-dimethyl-,[1,49] and 1,2-dimethylpyrrole[50] has now been made.[53] A 2 : 1 adduct[56] has also had its structure reassigned as **4.24**.[53] While most of the reactions with the acetylenic

TABLE 3.4.2. PYRROLES PRODUCED BY UNCATALYZED MICHAEL-TYPE ADDITION REACTIONS WITH ALKENES

R^1	R^2	R^3	R^4	R^5	Yield (%)[a]	Type[b]	Ref.
H	H	Cyclohexen-1-yl	H	H	13M	B	42
H	$CH(COOH)CH_2COOH$	H	H	Me	Good	A	1
H	$CH(COOH)CH_2COPh$	H	H	$CH(COOH)CH_2COPh$	10	A	30
H	$CH(COOMe)CH_2COPh$	H	H	$CH(COOMe)CH_2COPh$	73	A	30
H	CH(OH)COAr	H	H	H	38–80	C	59
H	CH(Pyrrolidin-1-yl)$CH_2CH_2CH_3$	H	H	H	44	B	41
H	CH(Pyrrolidin-1-yl)CH_2CH_3	H	H	H	20.5M	B	41
H	CH=CHCOMe	H	H	H	98	A	32
H	$CH_2CH(SPh)COMe$	H	H	H	94	A	33
H	CH_2CH_2CHO	Me	H	Me	40	A	31
H	CH_2CH_2CHO	Me	COMe	Me	NY	A	31
H	CH_2CH_2COMe	Me	Me	CH_2CH_2COMe	87	A	34
H	CH_2CH_2COOH	H	H	CH_2CH_2COOH	Very small M	A	1
H	CH_2CH_2COPh	H	H	H	5M	A	39
H	CH_2CH_2COPh	H	H	CH_2CH_2COPh	45M	A	39
H	COOMe	H	OMe	Pyrrolidin-2-yl	81cr	B	44
H	Me	H	H	$CH(COOH)CH_2COPh$	50	A	30
H	Me	H	H	Pyrrolidin-2-yl	79M	B	43

H	Me	CH(COOH)CH(Me)COOH anhydride	H	Me	30	A	1
H	Me	$CH(COOH)CH_2COOH$ anhydride	H	Me	~ 55	A	1
H	Me	COOEt	Me	CH_2CH_2CHO	~ 100cr	A	31
H	Me	Pyrrolidin-2-yl	H	Me	40	B	43
H	Cyclohexen-1-yl	H	H	H	15M	B	42
H	Cyclohexen-1-yl	H	H	Cyclohexen-1-yl	4M	B	42
H	Cyclohexen-1-yl	H	Cyclohexen-1-yl	H	5M	B	42
H	Piperidin-2-yl	H	H	H	74	B	43
H	Pyrrolidin-2-yl	H	H	H	48M	B	43
Me	CHOHCOPh	H	H	CHOHCOPh	55	C	60
Me	CH_2CH_2COOH	H	H	CH_2CH_2COOH	NY	A	1
Me	CH_2CH_2COPh	H	H	CH_2CH_2COPh	50	A	30
Me	Me	CHOHCOPh	H	Me	37	C	60
Me	Me	CHOHCOPh	CHOHCOPh	Me	39	C	60
Me	$C(CN)=C(CN)_2$	H	H	H	58	A	35

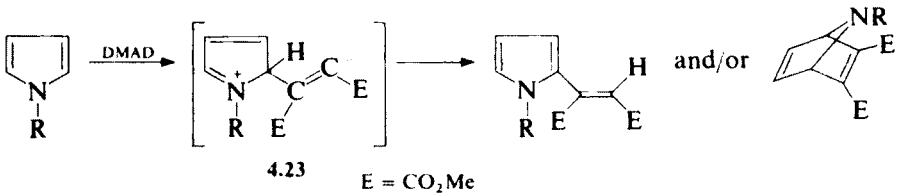
[a]M = component of mixture; cr = crude; NY = no yield.

[b]A = addition to C=C; B = addition to C=N; C = addition to C=O.

TABLE 3.4.3. *N*-ALKYLATION REACTIONS PRODUCED BY DIAZOMETHANE

R^1	R^2	R^3	R^4	R^5	Yield (%)	Ref.
Me	CN	H	H	NO_2	67	20
Me	COOMe	H	H	NO_2	57	20
Me	COMe	H	H	NO_2	70	20
Me	NO_2	H	H	NO_2	50	20
Me	NO_2	H	NO_2	H	82	20
Me	COOMe	H	Br	H	33	21
Me	COOMe	H	H	Br	63	21
Me	COOMe	H	H	Cl	92	21
Me	COOMe	H	Br	Br	93	21
Me	COOMe	H	Cl	Cl	96	21
Me	COOMe	Cl	H	Cl	96	21
Me	COOMe	H	H	COOMe	70	21
Me	COOMe	H	H	CHO	75	21
Me	COCOMorpholin-4-yl	H	H	NO_2	85	22
Me	$COCHCl_2$	H	H	NO_2	80	22
Me	$COCCl_3$	H	H	NO_2	77	22
Me	2,6-di$MeOC_6H_3CO_2$	H	H	H	NY	24
Me[a]	COOMe	COOMe	H	COOMe	70	25
Me[a]	COOMe	COOMe	H	H	32M	25
Me	COOH	H	3-Cl-2-$NO_2C_6H_3$	H	83	23

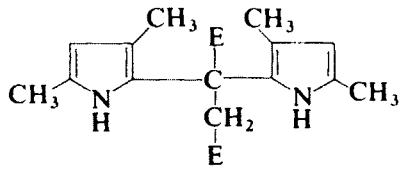
[a] Esterification accompanied *N*-methylation of the carboxylic acid.



4.23

E = CO_2Me

Scheme 4.12



4.24

diester gave mixtures that rendered them unsuited to useful preparations, some alkyne additions did give better results.[34,52,57]

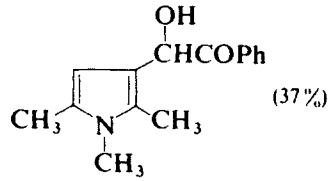
The reaction of benzyne with pyrrole is reported to give 2-phenylpyrrole, but in only 25% yield[58] (see Table 3.4.4).

TABLE 3.4.4. PYRROLES PRODUCED BY MICHAEL-TYPE ADDITION REACTIONS WITH ALKYNES

R^1	R^2	R^3	R^4	R^5	Yield (%)	Ref.
H	(E)C(COOMe)=CH(COOMe)	H	H	H	25M	2
H	(E)C(COOMe)=CH(COOMe)	H	H	Me	31M (NMR)	53
H	(E)C(COOMe)=CH(COOMe)	H	H	Me	M	49
H	(E)C(COOMe)=CH(COOMe)	H	H	Me	M	49
H	(E)C(COOMe)=CH(COOMe)	H	Me	Me	M	49
H	(Z)C(COOEt)=CH(COOEt)	Me	Me	OEt	83	52
H	(Z)C(COOMe)=CH(COOMe)	H	H	H	44M	2
H	(Z)C(COOMe)=CH(COOMe)	H	H	Me	31M (NMR)	53
H	(Z)C(COOMe)=CH(COOMe)	H	Me	Me	M	49
H	CH=CHCOMe	Me	Me	CH=CHCOMe	54	34
H	CH=CHCOMe	Ph	H	Ph	84	57
H	CH=CHCOOEt	Me	Me	H	76	34
H	CH=CHCOPh	Ph	H	Ph	87	57
H	C(COOMe)=CH(COOMe)	H	H	Me	NY	1
(E)C(COOMe)=CH(COOMe)	H	H	H	H	6M	2
CH_2Ph	(E)C(COOH)=CH(COOH)	H	H	H	41M	51
CH_2Ph	(E)C(COOMe)=CH(COOMe)	H	H	H	23M	53
CH_2Ph	(Z)C(COOH)=CH(COOH) anhydride	H	H	H	9.5M	51
CH_2Ph	(Z)C(COOMe)=CH(COOMe)	H	H	H	47M	53
COOMe	(E)C(COOH)=CH(COOH)	H	H	H	NY	50
Me	(E)C(COOMe)=CH(COOMe)	H	H	$CH=CH_2$	9M	503
Me	(E)C(COOMe)=CH(COOMe)	H	H	Me	59M	53
Me	(E)C(COOMe)=CH(COOMe)	H	H	Me	5M	503
Me	(Z)C(COOMe)=CH(COOMe)	H	H	$CH=CH_2$	20M	503
Me	(Z)C(COOMe)=CH(COOMe)	H	H	Me	20M	53
Me	(Z)C(COOMe)=CH(COOMe)	H	H	Me	23M	503
Me	(Z)C(COOMe)=CH(COOMe)	H	H	Me	40	50

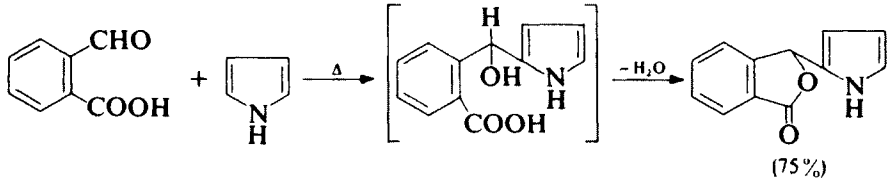
3.4.2.1.4. Reactions with Lactones and Some Other Carbonyl-Containing Compounds

Pyrrole and some of its derivatives add to carbonyl groups activated by a vicinal carbonyl system[59,60] to form products such as **4.25**.[60]



4.25

The uncatalyzed addition of pyrrole to an aromatic carbonyl group of the type shown in Scheme 4.13 has also been reported to take place, and the adduct was stabilized through lactone formation.[61]



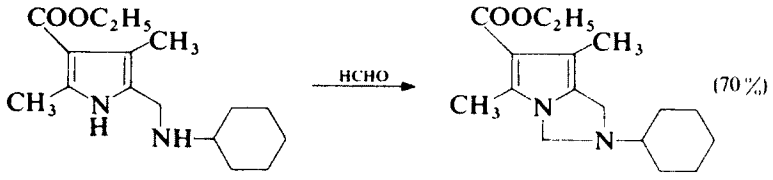
Scheme 4.13

There are, however, many more examples of carbonyl reactions of the pyrrole ring with carbonyl systems where acid catalysis is used (see Section 3.4.2.3.3).

3.4.2.2. Alkylation Using Iminium and Related Reagents

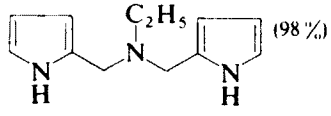
3.4.2.2.1. The Mannich Reaction

Pyrrole and many of its derivatives undergo the Mannich reaction with an aldehyde and primary or secondary amines, giving mono- or disubstituted products[62–75] in yields ranging from moderate to excellent. All the initial substitutions are on a ring carbon atom,[66] but, as it is possible for pyrroles to be hydroxymethylated on the nitrogen atom, the ring closure reaction to give **4.26** can take place[76] with a primary amine and an excess of formaldehyde, as shown in Scheme 4.14. With an excess of pyrrole, the Mannich reaction with a primary amine gave the product **4.27**.[65] Even the presence of electron-withdrawing groups does not prevent the occurrence of the Mannich reaction, as, for example, with the formation of **4.28**,[23] although such reactions appear to be slower.

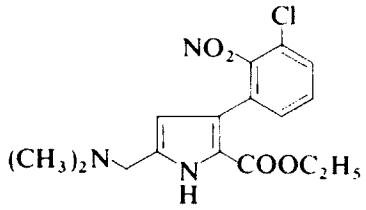


4.26

Scheme 4.14

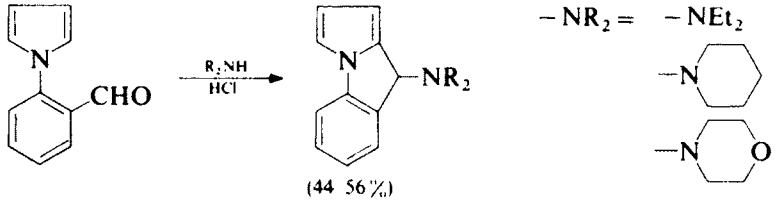


4.27

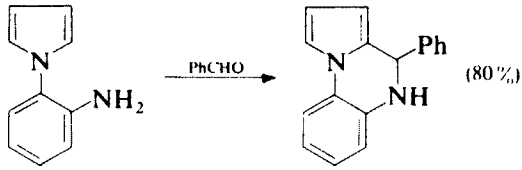


4.28

Advantage may be taken of the presence of an adjacent aldehyde group to induce a Mannich-type ring closure, as shown in Scheme 4.15.[77] Scheme 4.16 shows how a variation of the starting materials produced a similar intramolecular Mannich reaction but leading to a different ring system.[78]



Scheme 4.15



Scheme 4.16

Recent workers[79] reacted the Eschenmoser salt with 1-triisopropylsilylpyrrole to obtain, after cesium fluoride desilylation, 3,4-bis[dimethylaminomethyl]pyrrole in a 51% yield.

3.4.2.2.2. Other Iminium-Type Reactions

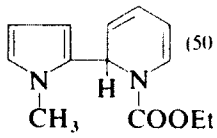
In addition to the Mannich reaction (Table 3.4.5), several other iminium cations aminoalkylate pyrroles. The pyridine–ethyl chloroformate combination

TABLE 3.4.5. MANNICH REACTION PRODUCTS

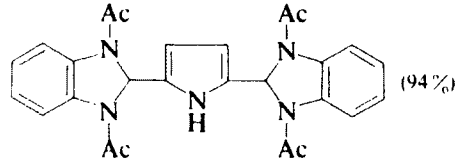
R^1	R^2	R^3	R^4	R^5	Yield (%)	Ref.
H	H	H	1-Me-4-COOMe-piperidin-2-yl	H	28M	86
H	1-Me-4-COOMe-piperidin-2-yl	H	H	H	53	86
H	CH_2morpholin-1-yl	H	H	H	25	62
H	CH_2morpholin-1-yl	H	H	H	95	64
H	CH_2morpholin-1-yl	H	H	CH_2morpholin-1-yl	95	64
H	CH_2piperidin-1-yl	H	H	H	20	64
H	CH_2piperidin-1-yl	H	H	H	50	62
H	CH_2piperidin-1-yl	H	H	CH_2piperidin-1-yl	85	64
H	CH_2piperidin-1-yl	Et	Et	H	72	74
H	CH_2NHEt	H	H	H	27	62
H	CH_2NHEt	H	H	H	61	65
H	CH_2NHMe	H	H	H	15	62
H	CH_2NHMe	H	H	H	51	65
H	CH_2NHcyclohexyl·HCl	H	H	H	66	76
H	CH_2NHi-Pr	H	H	H	44	65
H	CH_2NHt-Bu	H	H	H	61	65
H	CH_2NEt_2	H	H	H	40	62
H	CH_2NEt_2	H	H	H	64	75
H	CH_2NEt_2	H	H	H	81	73
H	CH_2NEt_2	H	H	CH_2NEt_2	16	75
H	CH_2NEt_2	H	H	CH_2NEt_2	30	64
H	CH_2NMe_2	H	H	H	77	62
H	CH_2NMe_2	H	H	H	95	75
H	CH_2NMe_2	H	H	CH_2NMe_2	48	64
H	CH_2NMe_2	2-NO_2-3-ClC_6H_3	H	COOMe	55cr	23
H	CH_2NMe_2	2-NO_2-3-ClC_6H_3	H	CH_2NMe_2	60cr	70
H	CH_2NMe_2	Et	Et	H	100cr	71
H	CH_2NMe_2	Et	Et	H	79	74
H	CH_2NMe_2	Me	Me	H	89	72
H	CH_2NMe_2.HCl	H	H	COMe	67	184

H	CH_2NMe_2.HCl	2-NO_2-3-ClC_6H_3	*COOEt*	Me	90cr	70
H	COOEt	2-NO_2-3-ClC_6H_3	H	CH_2NMe_2	76cr	23
H	COOEt	Me	CH_2NMe_2	Me	94	106
H	Me	H	CH_2pyrrolidin-1-yl	COOEt	69	504
H	Me	$(CH_2)_2COOH$	CH_2piperidin-1-yl	COOEt	88	497
H	Me	COMe	CH_2NMe_2	Me	44	176
H	Me	COMe	Me	CH_2NMe_2.HCl	57	69
H	Me	CH_2NEt_2.HCl	Me	COOEt	Quant.	69
H	Me	CH_2NMe_2	H	Me	92	66
H	Me	CH_2NMe_2	CH_2NMe_2	Me	90	66
H	Me	CH_2piperidin-1-yl	$(CH_2)_2COOEt$	COOEt	72	497
H	Me	COOEt	H	$CH_2N(Me)_2$.HCl	80	69
H	Me	COOEt	Me	CH_2NH *i*-Pr	39	76
H	Me	COOEt	Me	$CN_2N(Me)_2$.HCl	85	69
H	Ph	CH_2NMe_2	H	Ph	97.5	66
CH_2Ph	CH_2NMe_2	H	H	H	93	68
$CH_2NEt(CH_2$pyrrol-1-yl)	H	H	H	H	98	65
CH_2NMe_2	Me	H	H	Me	51	505
CH_2OCH_3	CH_2NMe_2	H	H	H	52	67
Me	1-Me-4-COOMe-piperdin-2-yl	H	H	H	38M	86
Me	CH_2NHEt	H	H	H	40	63
Me	CH_2NHMe	H	H	H	82	65
Me	CH_2NMe_2	H	H	H	70	68
Me	CH_2NMe_2	H	H	H	73	63
Me	CH_2NMe_2	H	H	H	NY	80
Me	CH_2NMe_2	H	H	CH_2NMe_2	78	63
Me	Me	CH_2NMe_2	H	Me	69	66
Me	Me	CH_2NMe_2	CH_2NMe_2	Me	72.5	66
Me	Me	COOEt	Me	CH_2NMe_2	NY	80
Ph	CH_2piperidin-1-yl	H	H	CH_2piperidin-1-yl	65	63
Ph	CH_2NMe_2	H	H	H	28	63
Ph	Me	CH_2NMe_2	H	Me	49.5	66
Ph	Me	CH_2NMe_2	CH_2NMe_2	Me	61	66

gave[80,81] **4.29**. A similar reaction of 2-methylpyrrole with pyrimidine and acetic acid gave the corresponding adduct,[82] as did the analogous addition to *N*-acyl salts of isoquinoline.[83] The 2,5-disubstituted pyrrole **4.30** is formed from the reaction of the benzimidazole–acetic acid combination with pyrrole.[84,85]

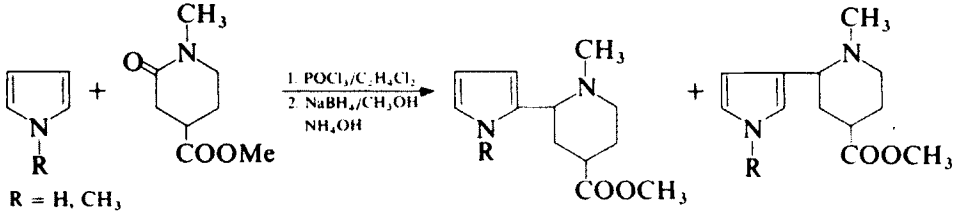


4.29



4.30

Another variation[86] of the iminium type is to be found with the in situ sodium borohydride reduction of the initially formed Vilsmeier–Haack acylation adduct (see Section 3.4.3.2.1) to give an aminomethyl product, as shown in Scheme 4.17.



Scheme 4.17

3.4.2.3. Friedel–Crafts Substitution

The reactivity of the pyrrole nucleus makes it possible to use a wide range of Lewis and Brønsted acid catalysts in alkylation reactions of the Friedel–Crafts type. Even the presence of strong electron-withdrawing groups does not prevent the reaction. Rearrangements of a kinetic to a thermodynamic product do occur, but less frequently than for acylations (see Section 3.4.3.3).

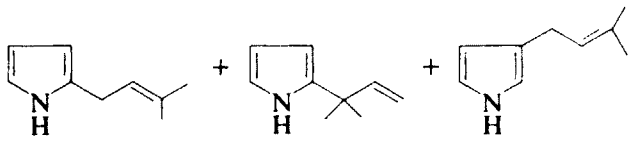
As well as the usual alkyl halides, alcohols, ethers, and alkenes, the electrophile may be created from alkynes, carbonyls, and other sources.* The acid-catalyzed reaction of carbonyl systems leads to hydroxyalkylated products, which often undergo further reaction such as dehydration, reduction, or the alkylation of a second pyrrole nucleus to form a dipyrromethane. Occasionally, acids may induce pyrrole ring opening and alkylation of a second pyrrole molecule yielding, eventually, an isoindole or an indolizine.

*Although the Lewis or Brønsted catalyzed attack by a dichloromethyl alkyl ether or an ortho ester falls into the alkylation category, the product isolated is the aldehyde and all discussion of these reactions has been placed under acylation (Section 3.4.3.3).

3.4.2.3.1. Alkylation with sp^3 Carbons

Lewis acid catalysts have not been widely used for alkylations of pyrrole and its simple alkyl derivatives. Whereas aluminum chloride is not a very successful[87] alkylation catalyst, the use of tin(IV) chloride has enabled the introduction of a 3-*tert*-butyl group on 2,5-di-*tert*-butylpyrrole in 72% yield.[88] Other *tert*-butylations using *tert*-butyl acetate with sulfuric, perchloric, or hydriodic acid catalysis gave poor results with ethyl 3,5-dimethylpyrrole-2-carboxylate.[89] In Section 3.4.2.1.1 we saw that $(4\text{-MeOPh})_3CCl$ alkylated the pyrrole ring without a catalyst. Similarly, trityl alcohol with acetic acid gave an excellent yield of 2-tritylpyrrole.[90]

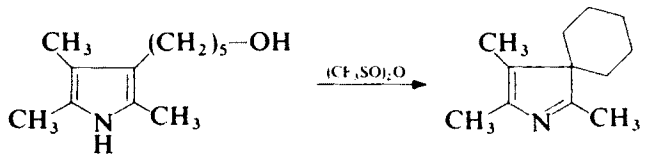
Boron trifluoride–diethyl etherate induces the prenylation of pyrrole by prenyl diisopropyl phosphate[91] but the product was found to be a mixture of **4.31**, **4.32**, and **4.33**.



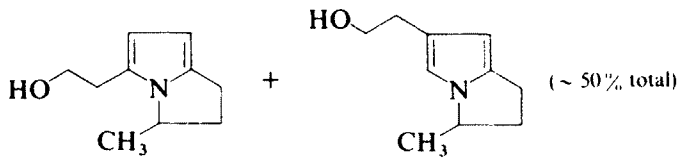
(34%) (10%) (6%)

4.31 **4.32** **4.33**

A rather unusual intramolecular alkylation[92] produced a spirocyclic product (Scheme 4.18). Another alkylation combination to have been used on 1,2-dihydropyrrolizines involves ethylene oxide and water;[93] the reaction being improved by acid catalysis, but producing an approximately 1 : 1 mixture of products (e.g., **4.34** and **4.35**) in modest yield.

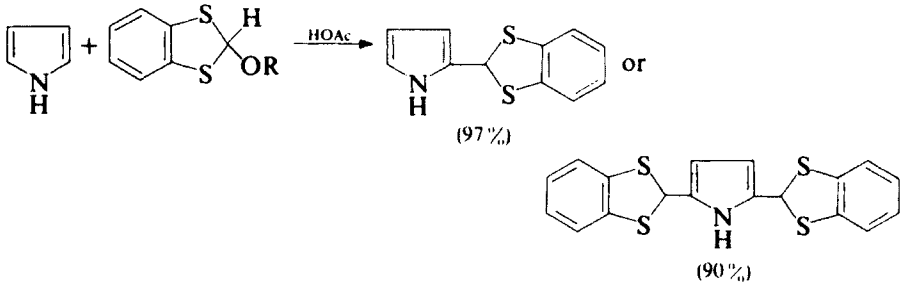


Scheme 4.18



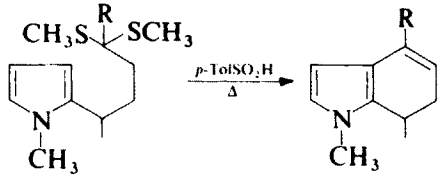
4.34 **4.35**

Several alkylations make use of the dithiolium cation that was referred to in Section 3.4.2.1.1. These ions may also be prepared in situ,[94] as indicated in Scheme 4.19.



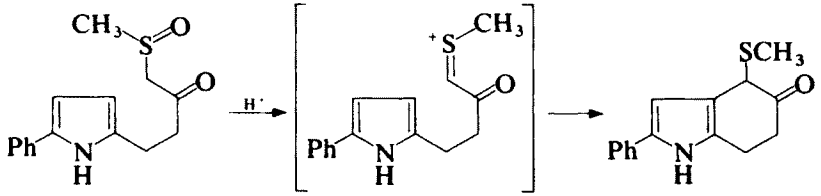
Scheme 4.19

A related reaction has been used to convert a pyrrole into an indole,[95] as shown in Scheme 4.20, where elimination and oxidation led to an excellent yield of the aromatic product.



Scheme 4.20

Two other ring-closure reactions have made use of β-ketosulfoxides and *p*-toluenesulfonic acid in an intramolecular Pummerer reaction,[96,97] as shown in Scheme 4.21.



Scheme 4.21

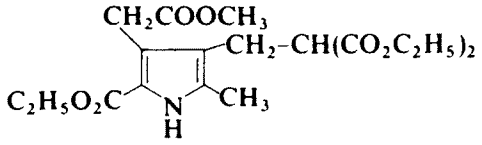
The presence of electron-withdrawing groups on the pyrrole ring generally requires the application of acid catalysis for successful alkylation. In many examples, however, more than one product is formed either directly or subsequently.

When 1-benzenesulfonylpyrrole was alkylated[98] with aluminum chloride, the results suggested that inter- or intramolecular rearrangements might be taking place, depending on the stability of the carbocations. There have been extensive studies of isopropylation and *tert*-butylation catalyzed by aluminum chloride and other Lewis acids on pyrroles with an electron-withdrawing group at the 2 position.[99–102] These indicated that the initial substitution took place princi-

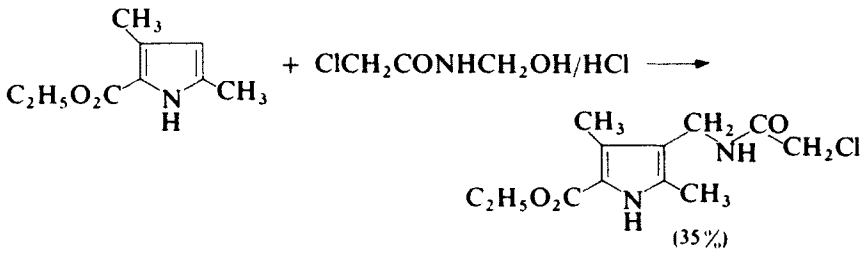
pally at the 4 position, followed by rearrangement to the 5 position and, possibly, a second alkylation to give the 4,5-dialkylated product. The rearrangement of the alkyl group was also influenced by the catalyst. Thus, gallium chloride and aluminum bromide produced less rearrangement, whereas iron(III) chloride and titanium tetrachloride did not catalyze alkylation.[99,102]

The aluminum-chloride-catalyzed isopropylations of 3-acetylpyrrole and methyl pyrrole-3-carboxylate[103] yielded only 5-substitution in about 60% yield. Most of these early alkylations made use of carbon disulfide as solvent, and a further possible complication was revealed when the less reactive ethyl group was introduced using aluminum chloride catalysis.[104] Small amounts of the dithio acid and of its ethyl ester were isolated together with a poor yield of the ethylation product. The use of dichloromethane or 1,2-dichloroethane over the past 20–30 years has produced fewer complications.

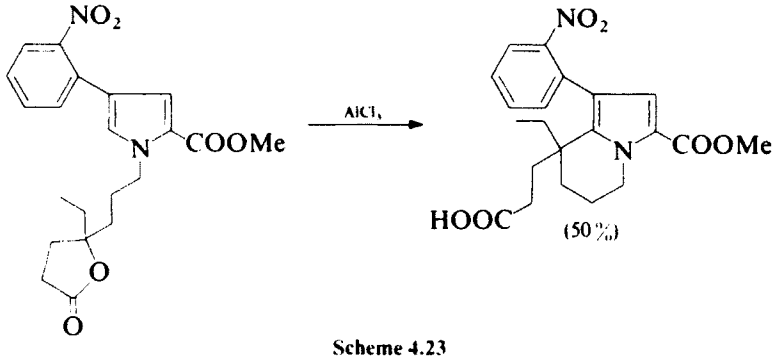
The importance of the propanoate side chain in naturally occurring pyrrolic systems has led to a number of papers that introduce that group by acid-catalyzed methods. An early technique made use of a dialkyl methoxymethylmalonate with hydrogen chloride[105,106] that afforded **4.36**. Tin(IV) chloride[107]



4.36



Scheme 4.22



Scheme 4.23

TABLE 3.4.6. PYRROLES PRODUCED BY LEWIS ACID-CATALYZED ALKYLATION REACTIONS

R^1	R^2	R^3	R^4	R^5	Yield (%)	Type[a]	Ref.
H	H	$CH_2CH{=}CMe_2$	H	H	6MGC	A	91
H	H	*t*-Bu	H	H	12MGC	B	87
H	$(CH_2)_2CN$	Me	H	Me	NY	A	8
H	$(CH_2)_2CONH_2$	Me	COOEt	Me	90	A	8
H	$(CH_2)_2COOH$	H	H	Me	NY	A	8
H	$(CH_2)_2COOH$	H	COOEt	Me	80	A	8
H	$(CH_2)_2COOH$	Me	H	Me	NY	D	8
H	$(CH_2)_2COOH$	Me	COMe	Me	73	A	8
H	$(CH_2)_2COOH$	Me	COOEt	CH_2COOEt	61	A	8
H	$(CH_2)_2COOH$	Me	COOEt	Me	73	A	8
H	$(CH_2)_2COOEt$	H	H	$(CH_2)_2COOEt$	31	A	8
H	$(CH_2)_2COOEt$	H	H	Me	36	A	8
H	$(CH_2)_2COOEt$	H	COOEt	Me	NY	A	8
H	$(CH_2)_2COOEt$	H	Me	Me	21	A	111
H	$(CH_2)_2COOEt$	Me	H	Me	55	A	8
H	$(CH_2)_2COOEt$	Me	COMe	Me	74	A	8
H	$(CH_2)_2COOEt$	Me	COOEt	CH_2COOEt	NY	A	8
H	$(CH_2)_2COOEt$	Me	COOEt	Me	66	A	8
H	$(CH_2)_2COOEt$	Me	Et	Me	NY	A	8
H	$(CH_2)_2COOMe$	H	H	$(CH_2)_2COOMe$	27	A	8
H	$(CH_2)_2COOMe$	H	H	Me	NY	A	8
H	$(CH_2)_2COOMe$	H	COOEt	Me	75	A	8
H	$(CH_2)_2COOMe$	Me	H	Me	NY	A	8
H	$(CH_2)_2COOMe$	Me	COMe	Me	72	A	8
H	$(CH_2)_2COOMe$	Me	COOEt	CH_2COOEt	NY	A	8
H	$(CH_2)_2COOMe$	Me	COOEt	Me	70	A	8
H	$(CH_2)_2COOMe$	Me	Et	Me	NY	A	8
H	$CHOHCCl_3$	H	H	H	40	C	122

H	$CH_2CH{=}CMe_2$	H	H	H	34MGC	A	91
H	$C(Me_2)CH{=}CH_2$	H	H	H	10MGC	A	91
H	CN	H	H	*t*-Bu	34	B	102
H	CN	H	*t*-Bu	H	36M	B	102
H	CN	H	*t*-Bu	H	56	B	102
H	CN	H	*t*-Bu	H	93	D	102
H	COOMe	H	H	*t*-Bu	NP	B	102
H	COOMe	H	*t*-Bu	H	NP	B	102
H	Me	H	Me	*t*-Bu	Trace	B	87
H	Me	$CH_2CH(COOMe)_2$	H	COOEt	NY	E	107
H	Me	COOEt	H	Et	16	B	104
H	Me	Me	H	Me	20GC	B	87
H	Me	*i*-Pr	H	Me	26GC	B	87
H	Me	*t*-Bu	H	Me	40GC	B	87
H	*i*-Pr	H	H	H	NY	B	99
H	*i*-Pr	H	COMe	H	62	B	103
H	*i*-Pr	H	COOMe	H	59	B	103
H	*t*-Bu	H	H	H	15MGC	B	87
H	*t*-Bu	*t*-Bu	H	*t*-Bu	72	E	88
COOMe	(E)C(COOMe)=CHCOOMe	H	H	H	36M	B	120
COOMe	(Z)C(COOMe)=CHCOOMe	H	H	H	36M	B	120
COOMe	$CH_2CH{=}CHCHO$	H	H	H	62	E	117
COOMe	CH_2CHO	H	H	H	54	E	117
COOMe	CH_2COPh	H	H	H	57M	E	117
Me	$(CH_2)_2COOMe$	H	COOEt	Me	30	A	110
Me	$CHOHCCl_3$	H	H	H	26	C	122
SO_2Ph	H	*t*-Bu	H	H	80	B	98
SO_2Ph	Et	H	H	H	26M	B	98
SO_2Ph	*i*-Pr	H	H	H	23M	B	98

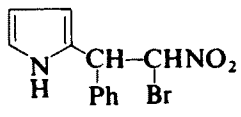
[a] A = $BF_3 \cdot Et_2O$; B = $AlCl_3$; C = $ZnCl_2$; D = $GaCl_3$; E = $SnCl_4$ or $SnCl_2$.

has also been used. A few methoxyacetic acid derivatives have been used to alkylate pyrroles; one such example is methoxyacetamide/HCl.[105] A more complex alkylation introduced the *N*-chloroacetyl derivative of the aminomethyl group,[108] as shown in Scheme 4.22, and the intramolecular alkylation ring closure in a synthesis of the artifact rhazinilam[109] utilizes the lactone moiety (see Scheme 4.23 and Table 3.4.6).

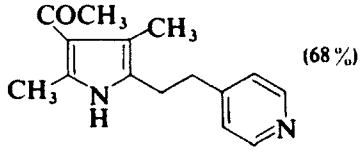
3.4.2.3.2. Alkylation and Alkenylation with Alkenes and Alkynes

The most widely used method for the introduction of acid-functionalized C_3 or C_4 side chains is of the Michael type. While boron trifluoride–diethyl etherate has been used on acrylates[8,110,111] to prepare 3-(pyrrol-2-yl)propanoates; zinc iodide has been found useful[112] for the addition of β-nitrostyrenes to give **4.37**.

More commonly, weak protic acids such as H_2SO_3 (SO_2 in H_2O/CH_3OH),[113–115] and CH_3COOH[116] have been used to catalyze this type of reaction. An example is the formation of the 4-vinylpyridine adduct[116] **4.38**.

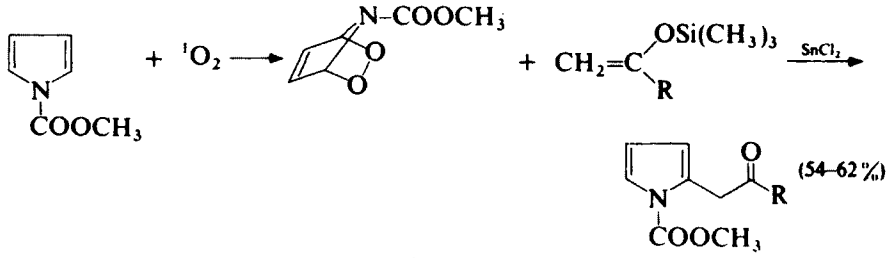


4.37



4.38

A quite different approach to Lewis acid-catalyzed alkylation is shown in Scheme 4.24.[117] 1-Methoxycarbonylpyrrole was converted with singlet oxygen into the endoperoxide, which was then reacted with the trimethylsilyl enol ethers of aldehydes and ketones in the presence of tin(II) chloride.

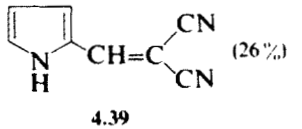


Scheme 4.24

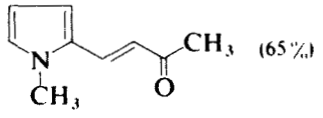
As in the uncatalyzed Michael addition (Section 3.4.2.1.2), there are examples of addition–elimination sequences such as the reaction of pyrrole with ethoxymethylenemalononitrile[118] to give **4.39** using acetic acid catalysis, or 1-methylpyrrole with *trans*-PhSOCH=CHCOCH$_3$/*p*-toluenesulfonic acid[32] to give **4.40**.

A more complex variation of the addition–elimination sequence was used[119] to effect the annulations shown in Scheme 4.25.

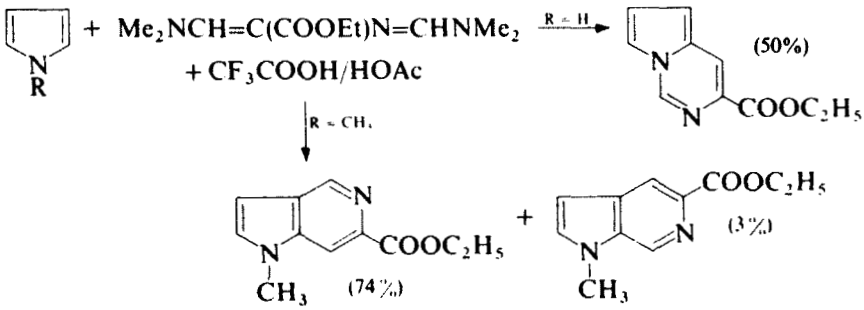
Aluminum chloride has been used to catalyze the Friedel–Crafts alkenylation of 1-methoxycarbonylpyrrole by dimethyl acetylenedicarboxylate,[120] when the



4.39

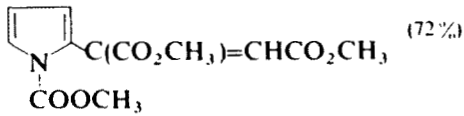


4.40



Scheme 4.25

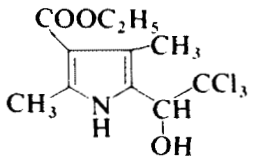
E and *Z* products (**4.41**) are formed in about a 1 : 1 ratio. Acetic acid has also been shown[53] to be a possible alkenylation catalyst, although the yield from 1-methylpyrrole was poor. In fact, better results were obtained in the absence of a catalyst (see Section 3.4.2.1.3). Aryl isonitriles have been added to the pyrrole ring in the presence of HCl to give[121] an anil side chain.



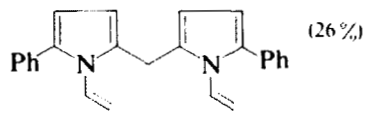
4.41

3.4.2.3.3. Alkylation and Alkenylation Using Carbonyl Compounds

There are several examples where simple hydroxyalkylation of pyrrole takes place using chloral in the presence of either zinc chloride[122] or hydrogen chloride.[69] In one example under the latter conditions, **4.42** was formed. When *vic*-dicarbonyl compounds were used, the products were acyloins[123] in 50–60% yield. More commonly, however, two pyrrole molecules are bridged by carbonyl group alkylation to form dipyrromethanes, such as **4.43**.[124]



4.42



4.43

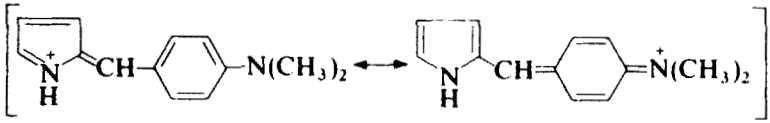
TABLE 3.4.7. PYRROLES PRODUCED BY BRØNSTED ACID-CATALYZED REACTIONS WITH ALKENES AND ALKYNES

R^1	R^2	R^3	R^4	R^5	Yield (%)	Type[a]	Ref.
H	$(CH_2)_2CO(CH_2)_{10}COOMe$	H	H	$(CH_2)_2CO(CH_2)_{10}COOMe$	44	A	114
H	$(CH_2)_2COCH_2COOMe$	H	H	$(CH_2)_2COCH_2COOMe$	NY	A	115
H	$(CH_2)_2COMe$	H	H	$(CH_2)_2COMe$	80	A	113
H	$(CH_2)_2$pyrid-4-yl	H	H	$(CH_2)_2$pyrid-4-yl	38	B	116
H	1,3-Benzodithiolan-2-yl	H	H	H	97	B	94
H	1,3-Benzodithiolan-2-yl	H	H	1,3-Benzodithiolan-2-yl	90	B	94
H	$CH{=}C(CN)_2$	H	H	H	26	B	118
H	$CH_2NHCOCH_2Cl$	H	COOEt	Me	31	C	108
H	$CH_2NHCOCH_2Cl$	$(CH_2)_2COOEt$	CH_2COOEt	COOEt	73	C	108
H	$CH_2NHCOCH_2Cl$	CH_2COOEt	$(CH_2)_2COOEt$	COOEt	69	C	108
H	CMeOHCOMe	H	H	H	50–60	B	123
H	COOEt	CH_2COOMe	$CH_2CH(COOEt)_2$	Me	65	C	106
H	Me	H	Me	$(CH_2)_2$pyrid-4-yl	79	B	116
H	Me	1,3-Benzodithiolan-2-yl	H	Me	96	B	94
H	Me	COMe	Me	$(CH^2)^2$pyrid-4-yl	68	B	116
H	Me	COMe	Me	*t*-Bu	12	B, C	89
H	Me	$CH_2CH(COOMe)_2$	Me	COOEt	90	C	105
H	Me	$CH_2NHCOCH_2Cl$	Me	COOEt	35	C	108
H	Me	COOEt	CH_2CONH_2	Me	NY	C	105

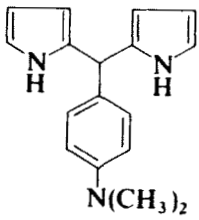
H	Me	COOEt	Me	$(CH_2)_2$pyrid-4-yl	46	B	116
H	Me	COOEt	Me	$CHOHCCl_3$	60	C	69
H	Me	COOEt	Me	*t*-Bu	22	D	89
H	Me	Et	Me	$(CH_2)_2$pyrid-4-yl	66	B	116
H	Me	*t*-Bu	Me	COOEt	30	A	89
H	Ph	Pr	Ph	H	NY	B	506
H	Trityl	H	H	H	100cr	B	90
$CH=CH_2$	CH_2(5-Ph-1-$CHCH_2$-2-pyrrolyl)	H	H	Ph	26	B	124
Me	$(CH_2)_2COMe$	H	H	$(CH_2)_2COMe$	48	A	113
Me	$(CH_2)_2$pyrid-4-yl	H	H	$(CH_2)_2$pyrid-4-yl	16	B	116
Me	(E)C(COOMe)=CH(COOMe)	H	H	H	12M	B	53
Me	(Z)C(COOMe)=CH(COOMe)	H	H	H	17M	B	53
Me	CH(1-Me-2-pyrrolyl)-CH_2COMe	H	H	H	19	E	32
Me	$CH(SO_2Ph)CH_2COMe$	H	H	H	74M	E	32
Me	CH=CHCOMe	H	H	H	65	E	32
Me	$CH=C(CN)_2$	H	H	H	15	B	118
Me	CMeOHCOMe	H	H	H	50–60	B	123

[a] A = H_2SO_4 or H_2SO_3; B = CH_3COOH; C = HI/Br/Cl; D = $HClO_4$ or $MgClO_4$; E = *p*-toluenesulfonic acid.

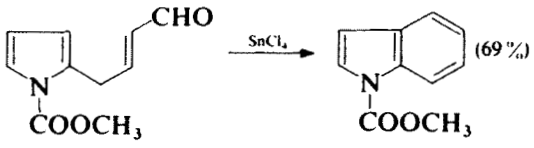
The initially formed hydroxyalkylated product may also undergo dehydration, particularly if conjugation or aromatization is possible. The Ehrlich reaction[125] is one pathway that dehydration can take. Here the intermediate from the pyrrole with *p*-aminobenzaldehyde and aqueous sulfuric or perchloric acid loses water to form the azafulvenium type salt (**4.44**), especially if electron donor groups are present. In contrast, the presence of an electron-withdrawing group tends to lead to the aryl dipyrromethane (**4.45**).[126] Some reactions where ring closure alkylation–dehydration led to aromatic products are shown in the formation of **4.46**,[117,127] and the analogous annulation reactions[128,129] are illustrated in Scheme 4.26.



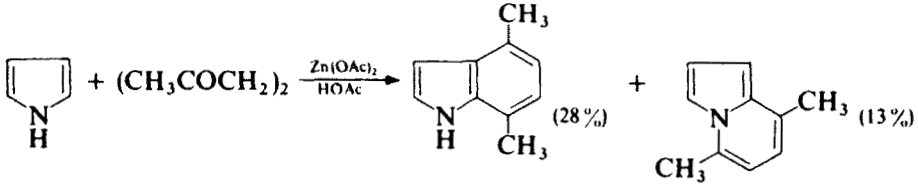
4.44



4.45



4.46



Scheme 4.26

Many other examples are found in the various ring closures of the Bischler–Napieralski[130] or Pomeranz–Fritsch[131–133] type where closures onto both carbon and nitrogen were observed in poor to good yields using a polyphosphoric acid or phosphorus oxychloride catalyst.

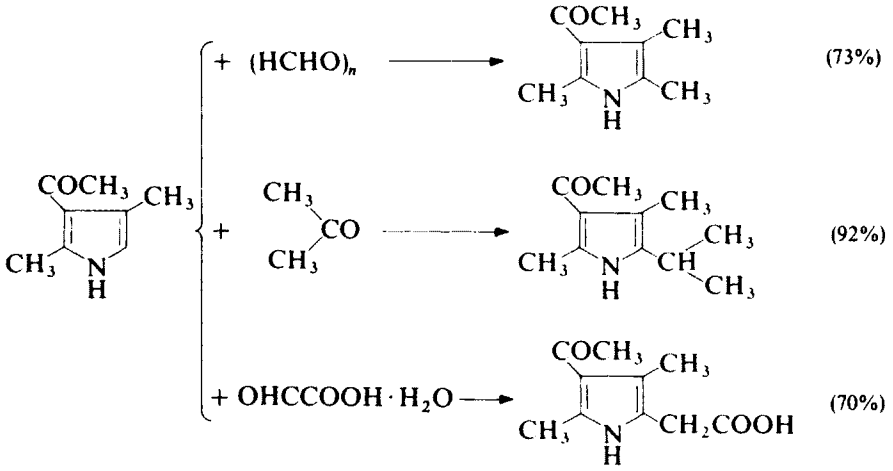
The combination of a Michael reaction with the Friedel–Crafts alkylation using α,β-unsaturated aldehydes and ketones[134] gave dipyrrolylpropenium salts with two molecules of the pyrrole derivative.

TABLE 3.4.8. PRODUCTS FROM THE REDUCTIVE ALKYLATION OF PYRROLES

R^1	R^2	R^3	R^4	R^5	Yield (%)	Ref.
H	$CHMe(CH_2)_2CHMe$(3,5-diMe-4-COMe-pyrrol-2-yl)	Me	COMe	Me	62	135
H	Me	COMe	Me	CH(Me)Ph	75	135
H	Me	COMe	Me	$CHMe(CH_2)_2COOH$	78	135
H	Me	COMe	Me	CHMeCOOH	59	135
H	Me	COMe	Me	$CHEt_2$	79	135
H	Me	COMe	Me	CH_2COOH	70	135
H	Me	COMe	Me	CH_2t-Bu	93	135
H	Me	COMe	Me	Et	58	135
H	Me	COMe	Me	Pr	59	135
H	Me	COMe	Me	CH_2Ph	85	135
H	Me	COMe	Me	Cyclohexyl	82	135
H	Me	COMe	Me	*i*-Pr	92[a]	135
H	Me	COOEt	Et	Et	53	135
H	Me	COOEt	Me	Me	75	135
H	Me	Me	COMe	Me	73	135
H	Me	Me	Me	COOEt	64	135
H	Me	Me	Me	Me	37, 50, 35, 68	135
H	Me	*i*-Bu	Me	COOEt	82	135

[a] $HBr/SnBr_2$ gave 77% and $H_2SO_4/Zn/Hg$ gave < 24% (crude) yield of product.

A further variation of the acid-catalyzed reaction of pyrroles with carbonyl compounds is the reductive alkylation achieved by the use of hydriodic acid–hypophosphorous acid or of zinc amalgam–hydrochloric acid.[135–138] A great many examples have been tabulated in these papers, illustrating the scope of this reaction, and a restricted selection from reference[135] is given in Scheme 4.27 (see also Table 3.4.8).



Scheme 4.27

3.4.2.4. Substitutions of the Pyrrolyl Anion

The first isolation and purification of pyrrole by Thomas Anderson[139] in 1857 was accomplished by lengthy reflux of a bone oil concentrate over excess solid potassium hydroxide followed by distillation and fusion of the residual product at red heat. When the melt was cooled and reacted with water, pyrrole was obtained. Thus the salt-forming ability of pyrrole was established at the very beginning of its history.

About 50 years later, Bernardo Oddo began his experiments using the pyrrolyl Grignard reagent,[140] eventually investigating its alkylations.[141] A variety of metal and related salts of 1*H*-pyrrole have since been prepared. Also, 1-substituted pyrroles have been converted to their anions by very strong bases, such as alkyllithiums.

While the spectral evidence supported 1-metallation in the salts of 1*H*-pyrrole,[142,143] their reactions indicated ambident anion behavior. An attempt has been made[144–146] to correlate alkylations at the carbon and nitrogen atoms of pyrrole with the concept of hard and soft acids and bases, as applied to the various counter cations, the solvent (including coordinating reagents), and the nature of the alkylating agent.

Briefly, nitrogen is the harder centre of the ambident anion and attracts hard cations such as magnesium. That tends to induce electrophilic substitution on

the carbon atom, because the nitrogen is blocked. With the successively softer cations: Li^+, Na^+, K^+, Tl^+, NR_4^+, there is increasing solvent separation of the ion pair and more *N*-alkylation takes place.[147,148] Reagents that coordinate the cation, such as HMPA or a crown ether, also tend to increase *N*-alkylation as do alkylating agents possessing the hard *p*-toluenesulfonate leaving group rather than the softer halide. The allyl group is softer than the alkyl group so allyl halides give more *C*-substitution, when mixtures of *C*- and *N*-alkylation are possible. If several of these factors are present, this complicates interpretations, but most of the observed results can be rationalized by the HSAB concept.[145] Substituents present on the ring will also strongly influence the N/C ratio.

3.4.2.4.1. Use of the Grignard Reagent

Until the 1950s much of the work on the alkylation of the pyrrolyl Grignard reagent suffered from the lack of good physical methods for separation and identification of the product mixtures. While it was realized from the beginning[141,149] that methylation of the pyrrolyl Grignard reagent gave both mono- and dimethylated products, the true nature of the product mixtures was finally sorted out in a series of papers.[143,147,150–153] The probable pathways for polymethylation are fully explored in Ref. 154, in which it has been concluded that Grignard exchange on methylated pyrroles is slow, but the product anions are more reactive to further alkylation.

The product mixture from the reaction with an alkyl halide under the usual conditions gave a poor yield of more 2- than 3-alkylpyrroles, together with small amounts of di- and polysubstituted products. A good deal of unreacted pyrrole was recovered, only a small amount of 1-alkylation occurred,[153,154] and some pentaalkyl-2*H*- and -3*H*-pyrrolenines were formed.[151,155] The use of the more reactive (and "harder") methyl *p*-toluenesulfonate gave, in a faster reaction, an increase in the 3-/2-isomer ratio and less polysubstitution.[154] Other authors using different alkylating agents have found similar results—low yields of a mixture containing mostly 2- and 3-substitution products.[143,156,157] It was also determined that, during Grignard *C*-alkylation, (-)2-bromobutane underwent S_N2 inversion.[158]

The use of the powerful coordinating agent, hexamethylphosphoric triamide (HMPA), led to a change from carbon to nitrogen alkylation.[159] Under these conditions, the hard coordinating agent strongly associated with the hard metal and separated the covalent bond, or ion pair, of the Grignard reagent.[145] Even then, there was still some *C*-alkylation and preparative yields of 1-alkylpyrroles were not easily obtained.

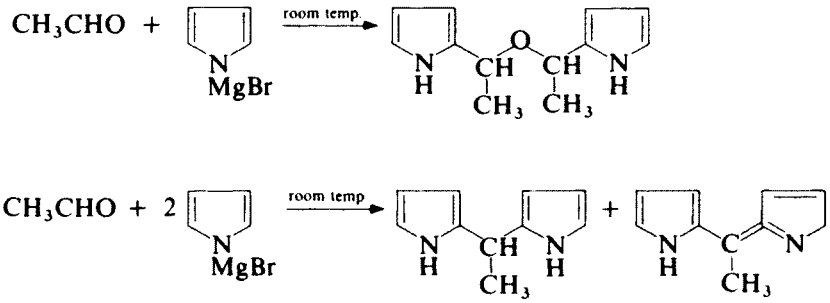
One apparent anomaly was the failure of HMPA to cause the dramatic change to *N*-substitution when allyl bromide was the alkylating agent.[159] The allylic group is much softer than the saturated isopentyl or methyl groups, however, and, consequently, attack at the softer ring carbons was largely maintained.

Another unexpected result was the greater proportion of 3- than 2-substitution that was observed[160] when the pyrrolyl Grignard reagent reacted with

oxirane. This observation contrasted with somewhat earlier work,[161] where the amounts of the two isomers obtained were reported to be about equal, but in very small yield. An aryloxirane afforded only 2-aryl-2-(2-pyrrolyl)ethanol, which was then reacted further.[162] On the other hand, reaction of the Grignard reagent with oxetane[157] gave about 40% yield of the expected 2-/3-isomer mixture in a 4:1 ratio.

The Sn(IV) ion is also a hard cationic species and produces results similar to those of the Grignard reagent. Bis(tributyltin) oxide reacts with pyrrole to give a 75% yield of the 1-$SnBu_3$ derivative,[163] which reacts with benzyl and allyl halides to give modest to poor yields of a mixture (about 2 : 1) of the 2- and 3-substituted pyrroles.

Unlike alkylation, hydroxyalkylation on nitrogen is reversible under basic conditions. As a consequence, the early literature of the reactions of the pyrrolyl Grignard and other metal salts with aldehydes is confused. The carbon of the carbonyl group is hard and might be expected to react at the pyrrolyl nitrogen atom. However, with formaldehyde, the Grignard reagent gave very little 1-substitution[164] and much more of the 2,5-dihydroxymethyl derivative.[165] Similarly, reaction with acetaldehyde in diethyl ether gave the complex results illustrated in Scheme 4.28.[166] The intermediate 2-hydroxyethyl compound could not be isolated, and no 1-substitution was observed. Thus the aldehyde group is not "hard" enough to displace the magnesium salt from the nitrogen and behaves like the alkyl group in Grignard reactions.



Scheme 4.28

1-Methyl-2-pyrrolylmagnesium bromide has been prepared (from 1-methyl-2-pyrrolyllithium) and its reactions[167] are discussed in Section 3.4.2.4.4.

Some examples of alkylation of the pyrrolyl Grignard reagent are listed in Table 3.4.9.

3.4.2.4.2. Use of an Alkali Metal or Its Salts

Following their proof that pyrrolylpotassium was allylated mostly on carbon but alkylated on nitrogen,[150] VanderWerf et al. explored the effects on the *N*/*C*-allyl substitution ratio[147] consequent to changes in the cation and medium. Any possible rearrangement of 1- to 2-allyl derivatives was ruled out, and later

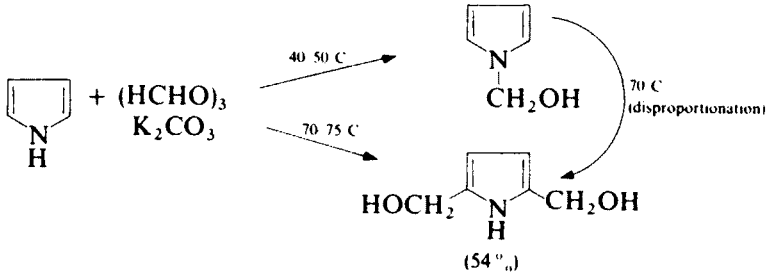
TABLE 3.4.9. REPRESENTATIVE EXAMPLES OF ALKYLPYRROLES OBTAINED FROM PYRROLYL GRIGNARD REAGENTS

R^1	R^2	R^3	R^4	R^5	Yield (%)	Ref.
H	H	$(CH_2)_2OH$	H	H	29.2M	160
H	H	$(CH_2)_2OH$	H	H	7–8M	161
H	H	$(CH_2)_2CN$	H	H	2.2MGC	143
H	H	$(CH_2)_3OH$	H	H	8M	157
H	H	Me	H	H	10CM	152
H	H	*i*-Pr	H	H	5CM	152
H	H	*s*-Bu	H	H	14CM	152
H	H	*t*-Bu	H	H	11M	156
H	H	*t*-Bu	H	H	NY	152
H	H	Allyl	H	H	NY	152
H	$(CH_2)_2OH$	H	H	H	7–8M	161
H	$(CH_2)_2OH$	H	H	H	9.8M	160
H	$(CH_2)_3CN$	H	H	H	9.8MGC	143
H	$(CH_2)_3OH$	H	H	H	32M	157
H	CH_2Ph	H	H	H	31cr	147
H	CH_2Ph	Me	Me	H	NY	507
H	CH_2Ph	Me	Me	CH_2Ph	59	507
H	Allyl	H	H	H	19	150
H	CH_2COOEt	H	H	H	NY	152
H	Me	H	H	H	16CM	152
H	*i*-Pr	H	H	H	10CM	152
H	*s*-Bu	H	H	H	34CM	152
H	*t*-Bu	H	H	H	28M	156
H	*t*-Bu	H	H	H	NY	152
H	Allyl	H	H	H	NY	152
H	Azlactone	H	H	H	56	508
$(CH_2)_2OH$	H	H	H	H	0.1M	161
CH_2OH	H	H	H	H	3	164
Me	Ph	H	H	H	78	167
Me	Pyridin-2-yl	H	H	H	71GC	167

work[168] confirmed the absence of thermal rearrangements. Variations in their reaction conditions included the use of solvents with a range of dielectric constant providing both heterogeneous and homogeneous conditions; the cations Li^+, Na^+, K^+, and $Ph(CH_3)_3N^+$; the effect of added $Bu_4N^+Br^-$; and change in reaction temperature. The results were explained on the basis of an increased dissociation of the ion pair favoring increased 1-substitution by allyl, crotyl, and benzyl halides. Later, these results, together with a further investigation of Grignard and phase-transfer alkylation under changing conditions, were interpreted using the concept of hard and soft acids and bases,[145] as discussed in the introduction to this section. Pyrrole was also allylated on carbon when Na_2CO_3 or K_2CO_3 in toluene or THF was used.[169]

As a consequence of the increasing softness of the alkali metal and alkylammonium salts of 1*H*-pyrroles, relatively few alkylations of the pyrrolyl anion take place on carbon unless the alkyl group is "softened" by other functionality.

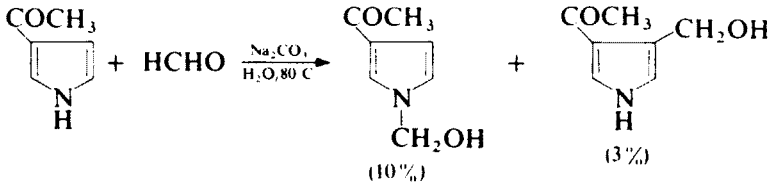
The results from the hydroxyalkylation reaction under basic conditions appear to be controversial and need further examination. Early workers,[170] using formaldehyde and aqueous potassium carbonate, found 2,5-disubstitution on both pyrrole and 1-methylpyrrole, whereas others[164] obtained a poor yield of the 1-hydroxymethyl derivative, when using aqueous calcium hydroxide. Later,[171] the probable sequence of events was clarified (Scheme 4.29).



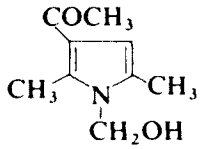
Scheme 4.29

It appears that in a highly polar solvent, such as water or pyrrole, at moderate temperatures, the ion pair is separated and 1-substituted pyrrole is the kinetic product. However, the alkanolamine is easily hydrolyzed under basic conditions in the polar solvent,[172] and at higher temperatures the thermodynamic *C*-substitution product may be obtained. This pathway has recently been confirmed.[173] Further evidence for this mechanistic rationalization is found in the hydroxymethylation of 3-acetylpyrrole (Scheme 4.30),[174] where a small amount of 1-substitution was obtained under the aqueous conditions shown, but when the reaction was conducted at room temperature in the much less polar tetrahydrofuran, the amount of 1-substitution was increased to 86%. Similarly, the 3,4-diester was converted into its 1-hydroxymethyl derivative, in 85% yield, using $PhCH_2NMe_3OH$ and formalin solution.[6,175] Other authors[176] have reported 1-substitution of 3-acetyl-2,5-dimethylpyrrole, when using aqueous base/formalin, to give **4.47**, but the corresponding reaction with the ester afforded the *C*-substituted product,[105] **4.48**, under similar conditions. Hence, in the presence of multiple groups on the ring, predictions appear risky, unless the exact conditions are known.

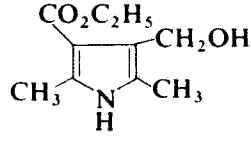
When a metal alkoxide and excess of the corresponding alcohol is heated with a pyrrole derivative to high temperature under pressure, alkylation takes



Scheme 4.30

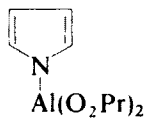


4.47

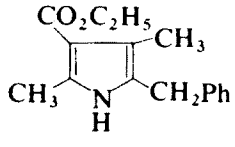


4.48

place.[177] For example, the methylation of 4-ethyl-2,3-dimethylpyrrole has been reported to give 5-methylation in 57% yield, but as the steam distillate from the reaction showed a weak aldehyde reaction, it appears that the alcohol also acted as a reducing agent. In a more recent example,[178] Al(O*i*-Pr)$_3$/*i*-PrOH/Raney nickel has been used to effect isopropylation of pyrrole to give 2,5-diisopropylpyrrole (34%), together with 1-isopropylpyrrolidine (40%). However, 2,5-dimethylpyrrole was isopropylated only on nitrogen affording the corresponding 1-substituted pyrrole (23%) and the pyrrolidine (62%). The authors of this work proposed a mechanism whereby the pyrrolyl anion displaces an alkoxide group to form **4.49** (thus placing the hard aluminum on the 1 position), which is then attacked by the carbonyl compound from Oppenauer oxidation of the alcohol leading to both *C*- and *N*-substitution.[178] The 1-alkylated pyrrole was readily reduced to the pyrrolidine (see Ref. 55, pp. 241–242).

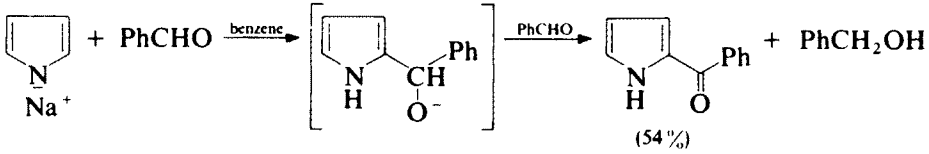


4.49



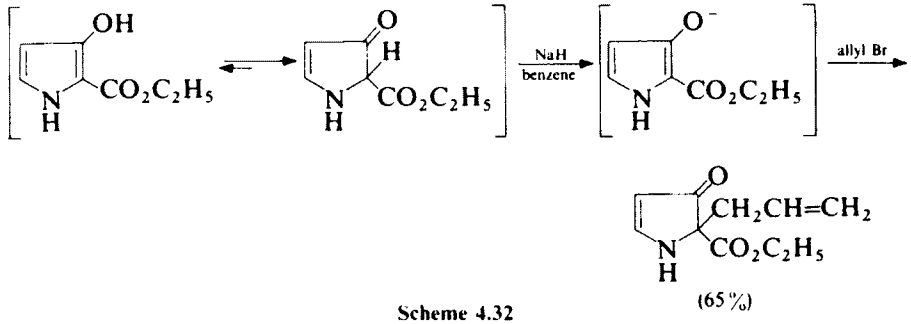
4.50

In contrast, the reverse reaction, with exclusive *C*-alkylation, is observed when pyrrolylsodium reacts with aromatic aldehydes to give 2-aroylpyrroles[179] (Scheme 4.31). A second molecule of benzaldehyde initiates an Oppenauer oxidation of the pyrrolyl alkoxide intermediate. In this reaction the aldehyde carbonyl was softened by attachment to the aromatic ring. Similarly, a benzylic carbon atom was softened by the attached phenyl group in the conversion of ethyl 2,4-dimethylpyrrole-3-carboxylate to **4.50**[80] using aqueous lithium hydroxide, benzyl chloride, and benzene under reflux with vibrator mixing. The same product was obtained (32% yield) from the corresponding Grignard reaction in ether.[80]



Scheme 4.31

A different mode of alkylation of the pyrrole ring takes place with some "hydroxypyrroles", which, under the basic conditions, react via the enolate anion as shown, for example, in Scheme 4.32[180,181] (see also Table 3.4.10).

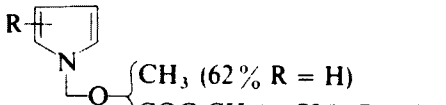


Scheme 4.32

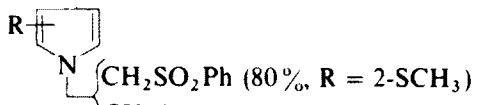
3.4.2.4.3. Substitution of the Pyrrolyl Anion on Nitrogen

Most of the base-catalyzed reactions of pyrrole and its derivatives have been directed toward 1-substitution, and so conditions were chosen to produce that result. Earlier workers used metallic sodium or potassium[80,150,182–184] in toluene or an ether, metal hydroxides or alkoxides in alcohol,[182,185–187] or an amide in liquid ammonia,[80] for alkylation or arylation on the nitrogen atom. Most of the recent workers have tended to use sodium hydride in tetrahydrofuran or dimethylformamide.[188–190]

Several types of base-catalyzed *N*-alkylations have been successful. Many of the substitution reactions give the simple 1-alkylation products of pyrrole derivatives, which possess a variety of ring functionality,[20,22,68,175,183,185,187,189,191–198] or connect the nitrogen atoms of two pyrrole rings[199–202] by a one, or more, carbon atom bridge. It has even proved possible to 1-benzylate the unstable 2-chloro- and 2-bromopyrroles using potassium in liquid ammonia.[156] The basic conditions used for 1-alkylation are also those that induce elimination. Thus, the results are best for primary, and poor (to failing) for tertiary halides.[145,148,203,204] Phosphate esters can also serve as alkylating agents.[205] Some alkylation reactions introduce substituted hydroxymethyl groups, which can be used as a protective substituent for the 1-position,[67,164,172,175,206–209] as illustrated by **4.51**. A number of other functionalized alkyl groups of the type of **4.52** have been described,[109,150,161,184,188,210–214] and protected glycosyl halides have been reacted with 2-cyano and 2,5-dicyanopyrrole using NaH–acetonitrile.[215]



4.51



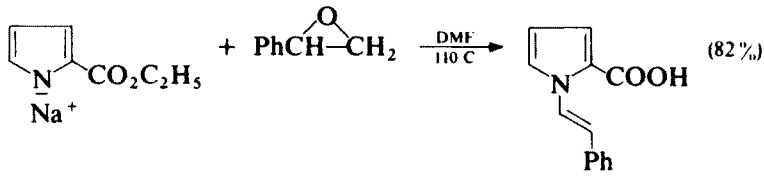
4.52

TABLE 3.4.10. TYPICAL BASE-CATALYZED *C*-ALKYLATION PRODUCTS

R^1	R^2	R^3	R^4	R^5	Yield (%)	Type[a]	Ref.
H	H	COMe	CH_2OH	H	3M	A	174
H	CH(CN)NHCO(3-MeC_6H_4)	H	H	H	44	C	509
H	allyl	H	H	H	30	B	150
H	CH_2OH	H	H	CH_2OH	NY	A	170
H	$C(SMe)_3$	H	H	H	70(84)[b]	C	13
H	$C(SMe)_3$	H	H	$C(SMe)_3$	93(86)[b]	C	13
H	Me	COOEt	CH_2OH	Me	NY	D	105
H	Me	COOEt	Me	CH_2OH	NY	D	105
H	Trityl	H	H	Trityl	7	B	311
SEM	Bu	H	H	H	27M	F	208
SEM	Bu	H	H	Bu	14M	F	208
SEM	COPh	H	H	H	75	F	208
SEM	Me	H	H	H	62M	F	208
SEM	Me	H	H	Me	21M	F	208
COO*t*-Bu	CHOHMe	H	H	H	47	F	245
COO*t*-Bu	CHOHPh	H	H	H	75	F	245
Me	$(CH_2)_3C(SMe)_2CH_3$	H	H	H	NY	F	95
Me	CH_2Ph	H	H	H	70	F	126
Me	CHO	H	H	Me	88	F	243
Me	Allyl	H	H	H	20	F	242
Me	CH_2OH	H	H	CH_2OH	NY	A	170
Me	$C(SMe)_3$	H	H	H	81(87)[b]	C	13
Me	$C(SMe)_3$	H	H	$C(SMe)_3$	53(65)[b]	C	13
Me	$CMeCH_2PhOH$	H	H	H	52	F	126
Me	$CMe(CH_2Cl)OH$	H	H	H	65	F	126
Me	CH_2SiMe_3	H	H	H	25	F	126
Me	CMe_2OH	H	H	H	73	F	126
Me	$CC_6H_4(4\text{-}MeC_6H_4)OH$	H	H	H	84	F	126
Me	$CC_6H_4(4\text{-}MeOC_6H_4)OH$	H	H	H	81	F	126
Me	$CC_6H_4(4\text{-}ClC_6H_4)OH$	H	H	H	85	F	126
Me	$C(4\text{-}MeC_6H_4)_2OH$	H	H	H	80	F	126
Me	CPh(Me)OH	H	H	H	91	F	126
Me	CPh_2OH	H	H	H	94	F	126
Me	Et	H	H	H	69	F	126
Me	Me	H	H	H	70	F	126
Me	C*t*-Bu(Me)OH	H	H	H	55	F	126
NMe_2	$CHOHC_6H_{13}$	H	H	H	75	F	244
SEM	$CHOHCH{=}CH_2$	H	H	H	52	F	207

[a] A = K_2CO_3; B = K; C = tertiary amine; D = NaOH; E = Na; F = Li.
[b] Tris(methylthio)methyl methanesulfonate (tris(methylthio)methyl tetrafluoroborate).

Epoxides are opened by the pyrrolyl anion and may give either the alcohol, in wet DMF, or the alkene, when heated in dry DMF.[216,217] At the same time, any ring ester groups may undergo hydrolysis,[216,218] as illustrated in Scheme 4.33.[218] However, an early report[219] of the reaction between chloromethyloxirane and pyrrolylpotassium found the product to be that of 1-alkylation, leaving the epoxide ring intact.



Scheme 4.33

In addition to these metal salt alkylations, other methods for *N*-alkylation have been investigated. Preparation and use of the "soft" thallium[I] salts,[148] phase-transfer-catalyzed reactions with quaternary ammonium salts (Table 3.4.11),[145,147,188,200,204,220–224] and with crown ethers[203,225,226] were

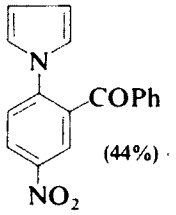
TABLE 3.4.11. PHASE-TRANSFER CATALYZED *N*-ALKYLATION AND *N*-ACYLATION PRODUCTS

R^1	R^2	R^3	R^4	R^5	Yield (%)	Type[a]	Ref.
$(CH_2)_2COMe$	COMe	H	H	H	97cr	A	230
$(CH_2)_2COMe$	CHO	H	H	H	68	A	230
$(CH_2)_2CN$	H	Me	H	H	60	B	231
$(CH_2)_2CN$	Me	H	H	H	63	B	231
$(CH_2)_2COOH$	H	H	H	H	80	B	233
$(CH_2)_2Cl$	COPh	H	H	H	89	A	188
$(CH_2)_2Cl$	CHO	H	H	H	94	A	188
$(CH_2)_2Cl$	SMe	H	H	H	93	A	188
$(CH_2)_2SO_2Ph$	COPh	H	H	H	87	A	188
2-Me-1,2-epoxypent-4-yl	H	H	H	H	40	C	510
2-Me-1,2-epoxybut-5-yl	H	H	H	H	34	C	510
CH_2Ph	H	H	H	H	60	A	223
CH_2Ph	H	H	H	H	90	C	225
CH_2Ph	H	H	H	H	90	C	511
CH_2Ph	CHO	H	H	H	86	A	224
Bu	H	H	H	H	82	C	225
Bu	H	H	H	H	82	C	511
Bu	H	H	H	H	92	C	203
COPh	H	CN	I	H	78	A	261
COPh	CHO	CH_2COOEt	I	H	91.5	A	261
CH_2pyrrol-1-yl	COPh	H	H	H	100	A	200
CH_2pyrrol-1-yl	CHO	H	H	H	98	A	200
CH_2pyrrol-1-yl	SMe	H	H	H	50	A	200
CH_2pyrrol-1-yl	H	H	H	H	20	A	200
CH_2OH	H	COOEt	COOEt	H	85	B	175
Et	H	H	H	H	75	C	225
Et	H	H	H	H	75	C	511
Et	H	H	H	H	83	C	203
Me	H	H	H	H	86–88	C	203
Me	COOEt	Me	Me	Me	81	B	220
Pr	H	H	H	H	91	C	203
i-Pr	H	H	H	H	34	C	203
Allyl	H	H	H	H	70	C	203

[a]A = quaternary ammonium salt; B = quaternary ammonium hydroxide; C = crown ether.

all successful, particularly for reactions with primary alkyl halides. The use of polyethylene glycols or their dialkyl ethers (PEG-1000, PEG-1000-Et_2, etc.)[221] gave results similar to those observed using a quarternary ammonium salt. The glycol ether was superior in that H-bonding to the hard pyrrolyl nitrogen atom by PEG, or water, tended to decrease 1-alkylation. Also, the softer allyl group gave less 1-substitution.

The nucleophilic substitution of an activated aryl chloride by the pyrrolyl anion gave **4.53**.[227]



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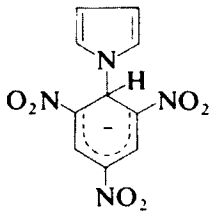
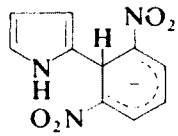


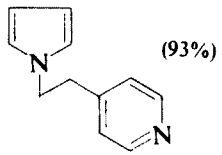
4.54



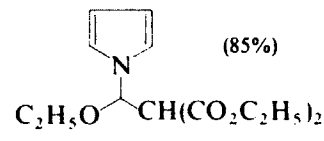
4.55

Although pyrrole and alkylated 1*H*-pyrroles did not react in DMSO with 1,3,5-trinitrobenzene, they did so in the presence of the methoxide ion.[228] Pyrrole gave a Meisenheimer salt **4.54**, which rearranged over an extended period (7 months) in solution to yield **4.55**. The alkylated pyrroles gave only *C*-substitution.

1-Substitution of the pyrrole ring can also be accomplished by Michael addition to various activated double and triple bonds. As indicated earlier (Sections 3.4.2.1.2 and 3.4.2.3.2), both neutral and acid-catalyzed Michael additions lead to carbon substitution but under base catalysis, including phase-transfer conditions, a variety of *N*-substituted pyrroles[39,186,217,229–233] have been prepared (e.g., **4.56**),[234] as well as the corresponding 2-pyridyl isomer,[235] from the reaction with the appropriate vinyl pyridine. As it can be removed easily,[236] the 2-(4-pyridylethyl) substituent may be used as a 1-protecting group. Occasionally, in the formation of **4.57** from ethyl ethoxymethylenemalonate under basic conditions[237] there is an accompanying elimination of ethanol to form the 1-alkenyl product. Acetylenes under pressure also underwent additions with the pyrrolyl anion to afford 1-alkenyl groups.[238,239]



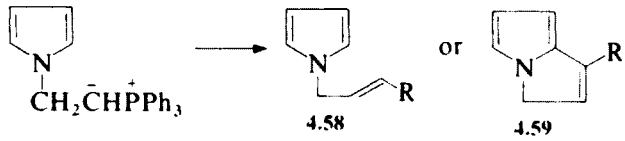
4.56



4.57

When the base-catalyzed Michael reaction is applied to vinyltriphenylphosphonium halide the intermediate carbanion becomes part of a new ylid, which can then react with a carbonyl group either externally to give compounds such

as **4.58**,[190] or internally to give the bicyclic type **4.59**,[30,240,241] as shown in Scheme 4.34 (see also Table 3.4.12).

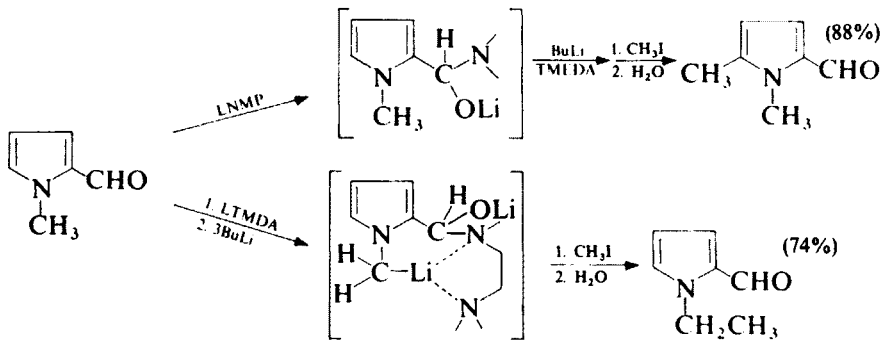


Scheme 4.34

3.4.2.4.4. Alkylation of 1-Substituted Pyrroles

As indicated earlier, *C*-alkylation of the pyrrolyl anion is not a satisfactory operation. However, when nitrogen is substituted with an inert group, metal–hydrogen interchange, almost always using an alkyllithium, first takes place at the 2 position. Subsequent alkylations of the 2-pyrrolyl anion have provided good results when methyl and primary halides were used.[95,126,208,242–244] Quite acceptable yields of 2-hydroxyalkyl derivatives have been obtained from the reaction of 1-substituted-2-pyrrolyllithium reagents with aldehydes and ketones,[126,244] and, while the 1-butoxycarbonyl blocking group has been successfully employed in this operation,[245] as it can removed easily, most of the removable protecting groups have been of the type **4.51** and **4.52**.

Dialkylation has occasionally been observed,[208] but a more detailed examination of dilithiation is discussed under acylation reactions (see Section 3.4.3.4.3). It has been possible to further alkylate 1-methyl-2-formylpyrrole by first reacting with lithium *N*-methylpiperazide (LNMP), followed by lithiation and alkylation, as shown in Scheme 4.35.[243] When an attempt was made to direct methylation to the 3 position using lithiated *N*,*N*,*N*′-trimethylethylenediamine (LTMDA) and excess *n*-butyllithium followed by methyl iodide, the product was 1-ethyl-2-formylpyrrole.[243] Thus, the proton was selectively removed from the 1-methyl group rather than from the 3 position.



Scheme 4.35

TABLE 3.4.12. PYRROLES OBTAINED BY BASE-CATALYZED *N*-ALKYLATION REACTIONS

R^1	R^2	R^3	R^4	R^5	Yield (%)	Type[a]	Ref.
$(CH_2)_{11}OH$	H	H	H	H	93	A	210
$(CH_2)_2CH(COOMe)_2$	Cl	Tos	H	H	90	B	512
$(CH_2)_2CN$	H	H	H	H	71	C	145
$(CH_2)_2CN$	Me	H	H	COOEt	NY	B	186
$(CH_2)_2CN$	Me	H	Me	H	38	B	186
$(CH_2)_2CN$	Me	H	Me	COOEt	50–80	B	186
$(CH_2)_2CN$	Me	CHO	Me	COOEt	55	B	186
$(CH_2)_2CN$	Me	COOEt	H	H	NY	B	186
$(CH_2)_2CN$	Me	COOEt	Me	COOEt	65	B	186
$(CH_2)_2CN$	Me	Et	Me	H	58	B	186
$(CH_2)_2CN$	Me	Me	H	COOEt	68	B	186
$(CH_2)_2CN$	Me	Me	COOEt	CHO	72	B	186
$(CH_2)_2COOEt$	H	H	H	H	22	A	211
$(CH_2)_2COOMe$	CHO	H	H	H	34	A	39
$(CH_2)_2NPhthal$	H	H	H	H	68	A	214
$(CH_2)_2OH$	H	H	H	H	45	A	161
$(CH_2)_2OH$	H	H	H	H	71	A	210
$(CH_2)_2OCOMe$	H	H	H	H	22	A	211
$(CH_2)_2SOPh$	COPh	H	H	H	86	B	188
$(CH_2)_2SO_2Ph$	CHO	H	H	H	84	B	188
$(CH_2)_2SO_2Ph$	SMe	H	H	H	80	B	188
$(CH_2)_2$pyrid-2-yl	H	H	H	H	89	B	235
$(CH_2)_2$pyrid-2-yl	Me	H	H	Me	53	B	235
$(CH_2)_3NMe_2$	H	COEt	H	H	60	A	184
$(CH_2)_3NMe_2$(tartrate)	COEt	H	H	H	55	A	184
$(CH_2)_3OH$	H	H	H	H	53	A	210
$(CH_2)_3OCOMe$	H	H	H	H	28	A	211
$(CH_2)_4Cl$	H	H	H	H	50.5	B	212
$(CH_2)_6OH$	H	H	H	H	78	A	210
$(CH_2)_2$pyrid-4-yl	H	H	H	H	93	B	234
(*E*)styryl	COOH	H	H	H	21	A	217

TABLE 3.4.12. (*Contd.*)

R^1	R^2	R^3	R^4	R^5	Yield (%)	Type[a]	Ref.
(*E*)styryl	COOH	H	H	H	82	B	218
2-C_6H_4CO-4-$NO_2C_6H_4$	H	H	H	H	44	B	227
2-OH-3-(pyrrol-1-yl)propyl	H	H	H	H	68	A	210
CH_2Ph	H	H	H	H	67	C	145
CH_2Ph	H	H	H	H	87	B	68
CH_2Ph	COOMe	H	H	H	25	A	187
2-$PhCH_2SC_6H_4CH_2$	H	H	H	H	77	A	194
2-$PhCH_2SC_6H_4CH_2$	CHO	H	H	H	99	A	194
Bu	H	H	H	H	25	C	145
Bu	H	H	H	H	33	C	145
Bu	H	H	H	H	84	C	145
COPh	Br	H	H	H	39	A	156
COPh	Cl	H	H	H	61	A	156
CHMeCOOEt	COPh	H	H	H	76	A	213
$CH(OEt)CH(COOEt)_2$	H	H	H	H	85	A	236
CH(Ph)CH(CN)COOEt	H	H	H	H	54	A	232
CH(Ph)CH(CN)COOMe	H	H	H	H	61	A	232
CH(Ph)CH(CN)COO*t*-Bu	H	H	H	H	81	A	232
CH(Ph)CMe(CN)COOEt	H	H	H	H	32	A	232
$CH(Ph)C(COOEt)_2$	H	H	H	H	58	A	232
Allyl	COOH	H	H	H	52	A	216,217
$CH{=}CH_2$	H	H	H	H	33	D	238
$CH{=}CH_2$	COOH	H	H	H	20	A	216,217
$CH{=}CH_2$	Ph	H	H	H	87	D	239
CH=C(CN)COOEt	H	H	H	H	70	A	236
$CH{=}C(CN)_2$	H	H	H	H	50	A	236
$CH_2CH(4\text{-}MeOC_6H_4)COOH$	H	H	H	H	51	A	229
$CH_2CH(4\text{-}NO_2C_6H_4)COOH$	H	H	H	H	NY	A	229
$CH_2CH(OH)Ph$	COOH	H	H	H	50	A	216,217
$CH_2CHOHCH_2OH$	H	H	H	H	48	A	210

$CH_2CHPhCOOH$	H	H	H	H	73	A	229
CH_2COOEt	H	H	H	H	17	A	211
CH_2COOEt	CHO	H	H	H	87	E	513
CH_2OH	H	COMe	H	H	10M	E	174
CH_2OH	Me	COMe	H	Me	65	C	176
$CH_2CH=CHMe$	H	H	H	H	61	A	150
SEM	H	H	H	H	85	B	208
SEM	COMe	H	H	H	91	B	208
SEM	CHO	H	H	H	98	B	208
SEM	COPh	H	H	H	94	B	208
SEM	H	H	H	H	83	B	207
CH_2OCOMe	H	H	H	H	22.5	A	164
CH_2OCH_2Ph	H	H	H	H	90	B	172
CH_2OBu	H	COOEt	COOEt	H	90	B	175
CH_2OCOt-Bu	H	H	H	H	78	B	209
CH_2OMe	H	H	H	H	62	B	67
CH_2pyrrol-1-yl	H	H	H	H	85	F	199
Et	H	H	H	H	28	C	145
Et	H	H	H	H	84	C	145
Et	H	H	H	H	85	D	204
Et	CONHPh	H	H	H	50	A	196
Me	H	H	H	H	30	C	145
Me	H	H	H	H	56	A	80
Me	H	H	H	H	68	C	145
Me	H	H	H	H	72	C	145
Me	H	H	H	H	86	D	204
Me	H	COt-Bu	H	H	77M	B	189
Me	COMe	H	H	H	30	B	20
Me	COMe	H	H	H	94	C	145
Me	COMe	H	H	NO_2	44	C	191
Me	COMe	H	NO_2	H	55	B	20
Me	COMe	H	NO_2	H	NY	C	191
Me	COPh	H	H	H	92	B	192
Me	CH=CHCHO	Et	Et	H	91	D	381

TABLE 3.4.12. (*Contd.*)

R^1	R^2	R^3	R^4	R^5	Yield (%)	Type[a]	Ref.
Me	CHO	H	H	H	33	D	193
Me	CHO	H	H	H	50	B	20
Me	CHO	H	H	H	77	C	145
Me	CHO	H	H	CHO	89.9	E	364
Me	CHO	H	H	NO_2	62	B	20
Me	CN	H	H	H	76	C	145
Me	CN	H	H	NO_2	NY	B	185
Me	CN	H	NO_2	H	45	B	185
Me	COCHOHPh	H	H	H	37	A	184
Me	COOEt	H	NO_2	H	89	F	514
Me	COOEt	Me	H	H	65	B	417
Me	COOMe	Br	Br	Br	67	B	197
Me	CO*t*-Bu	H	H	H	74M	B	189
Me	Cl	H	H	H	63	A	156
Me	Me	H	H	H	25	C	145
Me	Me	H	H	H	65	A	183
Me	Me	H	Me	H	NY	A	80
Me	Me	Me	H	H	86	D	204
Me	Me	Me	H	Me	67	A	183
Me	NO_2	H	H	H	32	C	20
Me	$COCH_2Ph$	H	H	H	49	B	192
Pr	H	H	H	H	85	D	204
i-Pr	H	H	H	H	5	C	145
i-Pr	H	H	H	H	60	D	204
Hexyl	H	H	H	H	70	C	145
Pentyl	H	H	H	H	81	C	145
Propargyl	H	H	H	H	27	A	150
Propyl	H	H	H	H	70	C	145
Styryl	COOH	H	H	H	21	A	216

[a]A = K; B = Na; C = NaOH; D = KOH; E = K_2CO_3; F = Li.

Similar lack of success was reported[246] for the attempted lithiation of 1-methyl-2-dimethylaminomethylpyrrole at the 3 position with *n*-butyllithium and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine, but treatment of the lithiated intermediate with benzophenone produced a 32% yield of the 5-substituted product. Lithiation of the analogous 1-benzenesulfonylpyrrole Mannich base led to mixtures arising from cleavage of the 1-group.[246] Somewhat more promising results were obtained with 2-(1-phenyl-2-pyrrolyl)-4,4-dimethyloxazoline[247] in which the oxazoline ring directed lithiation to give a 40–50% yield of an adduct with benzaldehyde in which the ratio of 3- to 5-substitution was about 4:1 to 6:1.[246] More success of directed substitution with an *ortho*-palladation procedure has been achieved with acylation reactions (see Section 3.4.3.4.3).

Metal–halogen interchange affords an approach to directed alkylation to the extent that the halogen can be directed into the desired position. In one successful approach, a 1-triisopropylsilyl group was used to block attack at the 2 position and direct bromination to the 3 position,[248] followed by exchange with a butyllithium and by alkylation,[249,250] which gave, among other products, the 3-methyl-, 3-octadecyl-, and 3-hydroxymethyl- derivatives in high yield, the 3-phenylhydroxymethyl derivative in moderate yield,[249] and a good yield of the 3-allyl compound.[250] In another approach,[251] a 1*H*-pyrrole was reacted first with sodium hydride before exchanging bromine with butyllithium and reaction with a ketone.

An approach to alkylation[252,253] involved treatment of 1-methyl-2-pyrrolyllithium with trialkylboron and iodine to give very good yields, as determined by gas chromatography, of the primary and secondary 2-alkyl compounds. When 1-methyl-2-pyrrolyllithium was converted into (2-dimethylaluminio)-1-methylpyrrole and reacted with glycopyranosyl fluorides, glycosylation took place at the 2 position of the pyrrole ring and configuration was retained at the anomeric carbon of the sugar moiety.[254]

3.4.2.4.5. Palladium and Other Metal-Assisted Substitution and Coupling Reactions

The use of palladium derivatives to assist alkylations, alkenylations, and arylations has generally made use of palladium(II) complexes. The reaction of pyrrole with butadiene used a mixed catalyst of $Pd(acac)_2/Ph_3P/AlEt_3$ in toluene at 100°C to give 2,5-bis(octa-2,7-dienyl)pyrrole in 90% yield, but only a 30% yield of a similar product from isoprene.[255] The palladium(II) acetate catalyzed reaction of styrene with 1-methylpyrrole gave a poor yield of a mixture of 2- and 3-*trans*-styryl-1-methylpyrroles.[256]

A much more successful approach[257] with palladium(II) acetate in boiling acetic acid in either a molar proportion, or a catalytic amount in the presence of a re-oxidant ($Na_2S_2O_8$ was best), has been used to introduce one or two acrylate groups as a mixture of *cis*- and *trans*-isomers, onto the 2- or 2,5-positions of 1-(2,6-dichlorobenzoyl)pyrrole in very good yields or onto 1-benzenesulfonylpyrrole in moderate yield (see Table 3.4.13).

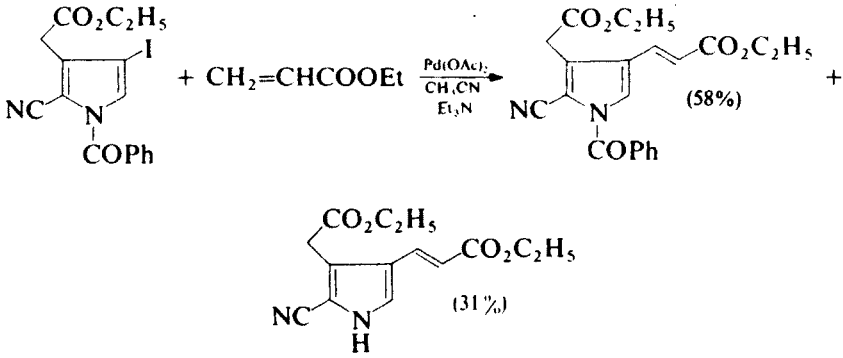
TABLE 3.4.13. ALKYLATION PRODUCTS OBTAINED FROM 1-SUBSTITUTED PYRROLES USING A TERTIARY AMINE OR NONALKALI METAL

R^1	R^2	R^3	R^4	R^5	Yield (%)	Type[a]	Ref.
H	H	*i*-Pr	H	H	NYM	A	515
H	*i*-Pr	H	H	H	NYM	A	515
$(CH_2)_2CN$	H	Me	H	H	60	B	231
$(CH_2)_2CN$	Me	H	H	H	63	B	231
$(CH_2)_2COOH$	H	H	H	H	80	B	233
Bu	H	H	H	H	82	C	148
CH_2OH	H	H	H	H	8	D	164
CH_2OH	H	COOEt	COOEt	H	85	B	175
Et	H	H	H	H	51	C	148
Me	H	H	H	H	98	C	148
Me	CHO	H	H	H	91	C	148
Me	COOEt	Me	Me	Me	81	B	220
Me	Pyridin-3-yl	H	H	H	66GC	E, F	167
Me	Thien-3-yl	H	H	H	73GC	E, F	167
Pr	H	H	H	H	68	C	148
i-Pr	H	H	H	H	95	C	148
t-Bu	H	H	H	H	15	C	148

[a]A = Ag(I); B = R_4NOH; C = Tl(I); D = $Ca(OH)_2$; E = Zn(II); F = Pd(II).

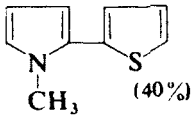
It was possible to alkenylate 1-methyl-2-pyrrolylmagnesium bromide with a haloalkene in the presence of a palladium(II) chloride complex in good yield.[258]

The Heck reaction[259] has been applied to introduce an acrylate group by ipso-substitution of halogen using palladium(II) acetate in acrylonitrile, as shown in Scheme 4.36.[260,261] It was generally found necessary to block the nitrogen, in order to obtain satisfactory results.

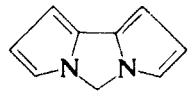


Scheme 4.36

Considerable interest has been shown in the metal-catalyzed aryl coupling of the pyrrole ring to other pyrroles or aromatic systems. Both intra- and intermolecular reactions have been successful. Early papers, for example, used



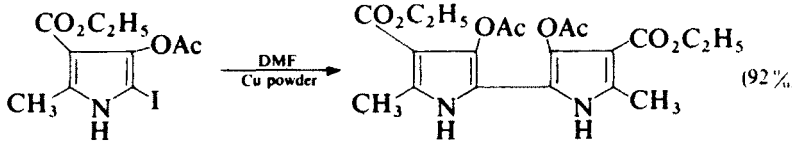
4.60



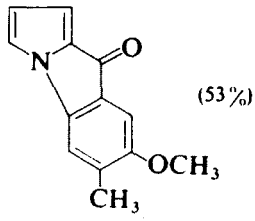
4.61

copper salt catalysis to induce the coupling. Thus, 1-methyl-2-pyrrolyllithium/CuBr and the heteroaryl iodide gave **4.60**,[262] and copper(II) chloride promoted intramolecular coupling of 1,1-dipyrrolylmethane to form **4.61**.[199]

The Ullmann reaction has been used successfully[263] to link substituted pyrroles bearing an iodo group. One such example is shown in Scheme 4.37.[264] Intramolecular *N*-arylation is also possible. Thus, when the sodium salt of a 2-(2-bromoaroyl)pyrrole was treated with copper(I) bromide, **4.62** formed.[265]



Scheme 4.37

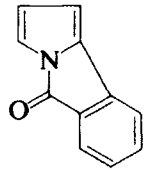


4.62

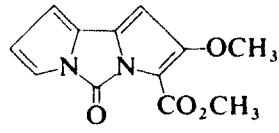
Other authors[266] have coupled 1-methylpyrrole oxidatively through the 2 position using several salts. Of these, nickel(II) chloride was found to be the best; the utility of the others, in decreasing order, was copper(II) chloride, cobalt(II) chloride, and manganese(II) chloride. Anhydrous iron(III) chloride in trifluoroacetic acid has also been used successfully in the efficient coupling of 2-cyanovinyl-3,4-dimethylpyrrole, whereas aqueous sodium dichromate in trifluoroacetic acid was found to be much less satisfactory.[267]

Palladium(II) salts have also been used in acetic acid for oxidative coupling of 1-benzoylpyrrole,[268] affording a 47% yield of the 2,2′-bipyrrole, but 1-methyl and 1-acetylpyrrole failed to react. When the reaction was conducted in the presence of benzene, 2,5-diphenylation of the ring occurred (25%), together with intramolecular ring closure to form **4.63**[269] (20%) as well as 8% of the 2,2′-bipyrrole. The ring-closure reaction could be avoided through the use of the 1-(2,6-dichlorobenzoyl) derivative when the yield of the 2,5-diphenyl derivative was increased to 80%.[270] When 1,1′-dipyrrolylmethanones were treated with

polymer-supported palladium(II) acetate, coupling through the 2,2′-positions occurred[271] and, hence, by using the appropriately substituted substrate, it is possible to obtain **4.64**, which can be hydrolyzed to give a 2,2′-bipyrrolyl building block for prodigiosin synthesis.



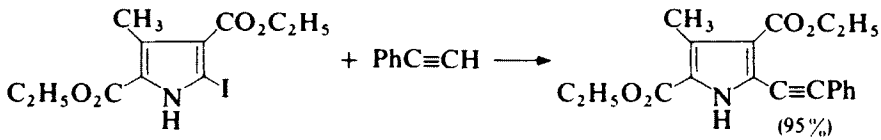
4.63



4.64

Some other metal derivatives have been made from 1-methyl-2-pyrrolyllithium, such as 1-methyl-2-pyrrolylmagnesium bromide and the corresponding 2-chlorozinc derivative.[167] These compounds have been oxidatively coupled using palladium(II) salts to give, for example, 1-methyl-2-phenylpyrrole (78%). The same product was obtained in 54% yield[272] using the palladium(II) catalyzed coupling of 1-methyl-2-trimethylstannylpyrrole and iodobenzene. Coupling with a halopyridine was also successful.[273]

Finally, a palladium(II)–copper(I) complex has been used in a type of Heck reaction to couple iodo-substituted pyrroles with acetylenes[274] as shown in Scheme 4.38. The reaction is compatible with most 1*H*-pyrroles and with acetylenic alcohols.



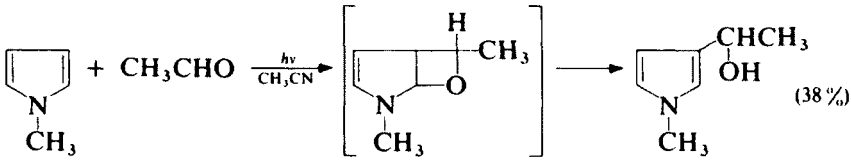
Scheme 4.38

3.4.2.5. Free-Radical Reactions

Most of the radical type reactions of pyrrole seem to have been directed to linking the system to other aromatic or heteroaromatic rings. There are relatively few examples of the simple substitution or addition type. The radicals are mostly photochemically generated, some chemically and one anodically. Yields range from miniscule to excellent.

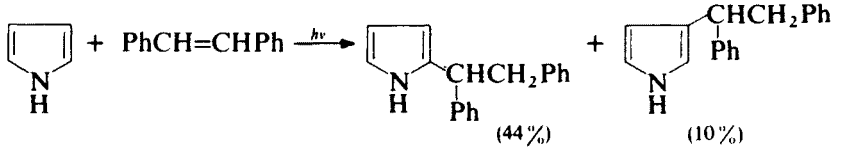
3.4.2.5.1. Photocatalyzed Substitutions and Additions

A very simple example of radical substitution is the photocatalyzed reaction with CF_3I, which gave about 35% yield of 2-substitution on both pyrrole and 1-methylpyrrole.[275] This photocatalyzed trifluoromethylation has been extended to more complex pyrroles.[276]



Scheme 4.39

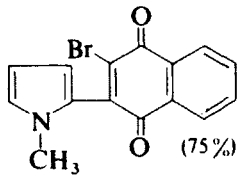
The photocatalyzed addition of the pyrrole ring to aldehydes and ketones has been rationalized in terms of a regiospecific [2+2] cycloaddition reaction to yield an intermediate oxetane, which ring-opens to produce the 3-hydroxyalkylproduct, as shown in Scheme 4.39.[277] Best results were obtained with 1-substituted pyrroles, although only moderate conversion was achieved with most reactions. Preparative reactions required lengthy illumination. It was also possible to obtain 3,4-dihydroxyalkyl derivatives in this way. The specificity of this reaction contrasts with the photoaddition of pyrrole to the carbon–carbon double bond of stilbene, which resulted in mixtures of 2- and 3-substituted products[278] (Scheme 4.40).



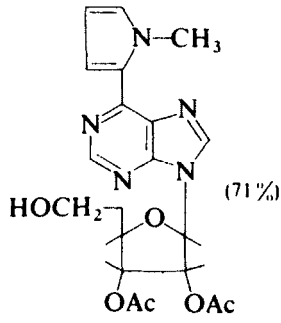
Scheme 4.40

Additions across the aromatic double bond are not common. Benzene gave 2-(2,5-cyclohexadien-1-yl)pyrrole in unspecified yield,[279] and the reaction with naphthalene produced a mixture of 2-pyrrolyl 1,4- and 1,2-addition products, also in unspecified yield.[280]

Photodimerization and photocyclization to other aromatic and heteroaromatic systems is widely used, as, for example, in the linking (e.g., **4.65**) of 1-methylpyrrole with several 2-substituted-1,4-naphthoquinones,[281] which



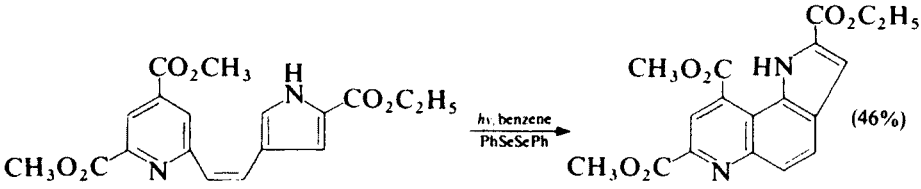
4.65



4.66

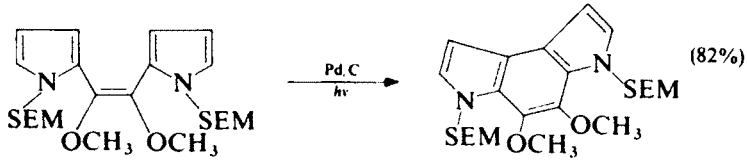
proceeds in variable yields. Similarly, the photoreaction of 9-substituted-6-iodopurines with 1-methylpyrrole gave **4.66**,[282] and other, simpler, examples involved the coupling of pyrrole or 1-methylpyrrole with 2- or 4-halopyridines,[283,284] or 3-iodopyridine,[285] or with chlorinated 5-iodopyrimidines,[286] all in moderate yields.

There are many recent examples of intramolecular photocatalyzed coupling to other aromatic or heteroaromatic systems, often with chemical assistance. Some of these have been used in the synthesis of important pharmaceuticals, as, for example, in a convergent approach to methoxatin (Scheme 4.41).[287]



Scheme 4.41

Five percent palladium on charcoal has been found to aid photocyclization under anaerobic conditions.[68,288–291] In the course of these studies, the skeleton of the benzo[1,2-*b*:4,3-*b*]dipyrrole unit, occurring in the antitumor antibiotic CC-1065 was constructed as shown in Scheme 4.42.[290]



Scheme 4.42

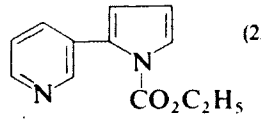
3.4.2.5.2. Anodic Alkylation

Only one paper[292] has described a direct anodic synthesis of an alkylpyrrole; 1-octylpyrrole was synthesized in 80% yield using the octyl halide in dimethylformamide with added tetraethylammonium *p*-toluenesulfonate. Cyanation on carbon has been accomplished electrochemically[293] in good yield on some 1-substituted pyrroles.

3.4.2.5.3. Chemically Induced Free-Radical Reactions

The simplest chemically induced radical alkylation is the methylation of 2-nitropyrrole using iron(II) ion and hydrogen peroxide in dimethyl sulfoxide to give 5-methyl-2-nitro (30%) and 3,5-dimethyl-2-nitropyrroles (12%) which were not separated.[294] It is of interest that dibenzylmercury and pyrrole in refluxing acetic acid produce 2-benzylpyrrole in an unstated yield,[295] but the free-radical tritylation of pyrrole is reported to give 2,5-dityrityl-3-pyrrolene.[296]

Free-radical arylation of 1-ethoxycarbonylpyrrole[297] gave 46% of the 2-phenyl derivative, but reaction with 3-pyridyl radical obtained from *N*-nitroso-*N*-(pyrid-3-yl-2-methylpropanamide) gave a poorer yield of **4.67**, which was converted to nornicotyrine. Attempted arylation of 1-methylpyrrole, in which the aryl radical is obtained from the diazonium salt, failed and gave the diazonium coupled product instead. In contrast, nitrophenyl and chlorophenyl radicals, obtained from the arylamine and pentyl nitrite in acetic acid gave satisfactory yields of the 2-substitution products with 1-ethoxycarbonyl, 1-methylsulfonyl, and 1-benzylpyrrole.[298]



(23%)

4.67

Direct free-radical coupling that is of any preparative value does not seem to have been accomplished. One example[299] produced 5-(2-pyrrolyl)-2-pyrrolidone in unspecified yield by the H_2O_2/acetic acid oxidation of pyrrole,

TABLE 3.4.14. FREE-RADICAL ALKYLATION PRODUCTS

R^1	R^2	R^3	R^4	R^5	Yield (%)	Type[a]	Ref.
H	H	$CHOH(CH_2)_3CH_3$	H	H	24C	A	277
H	H	CHOHMe	H	H	28C	A	277
H	H	$CHPhCH_2Ph$	H	H	10M	A	278
H	H	CMe_2OH	H	H	6C	A	277
H	2,5-Cyclohexadiene -1-yl	H	H	H	NY	A	279
H	2-Clpyrimidin-5-yl	H	H	H	49	A	286
H	$CHPhCH_2Ph$	H	H	H	44M	A	278
H	CH_2COOEt	H	COOEt	Me	44	B	25
H	CF_3	H	H	H	33GC	A	275
H	NO_2	H	H	Me	30M	C	294
H	NO_2	Me	H	Me	12M	C	294
H	Pyrid-2-yl	H	H	H	41	A	283
H	Pyrid-3-yl	H	H	H	12	A	285
H	Pyrid-4-yl	H	H	H	56	A	284
H	Pyrrolid-2-one-5-yl	H	H	H	NY	D	299
$(CH_2)_2CN$	H	$CHOH(CH_2)_2CH_3$	H	H	85C	A	277
$(CH_2)_2CN$	H	CMe_2OH	H	H	52C	A	277
CH_2Ph	1,4-Naphthoquinon-2-yl	H	H	H	50	A	281
COOEt	$3\text{-}ClC_6H_4$	H	H	H	48	E	298
COOEt	$3\text{-}NO_2C_6H_4$	H	H	H	75	E	298
COOEt	$4\text{-}ClC_6H_4$	H	H	H	52	E	298
COOEt	Ph	H	H	H	29	E	298
COOEt	Ph	H	H	H	46	E	297
COOEt	Pyrid-3-yl	H	H	H	23	E	297

[a]A = photoaddition; B = Cu/diazo; C = H_2O_2/Fe(II)/DMSO; D = H_2O_2/HOCOMe; E = N-nitrosoamides and triazenes.

while in another report,[300] di-*tert*-butyl peroxide has been used to produce, in very small amounts, a variety of products arising from attack of the 1-pyrrolylmethyl radical on 1-methylpyrrole. Pyrrole and di-*tert*-butyl peroxide is reported to give about 1.5% 2-(2-pyrrolin-2-yl)pyrrole.[300] (See Table 3.4.14.)

3.4.3. Acylation on Carbon and Nitrogen

Pyrrole and its alkyl derivatives are sufficiently electron-rich to be acylated without a catalyst by the usual reagents—acid chlorides and anhydrides, and, when electron-withdrawing groups are present on the pyrrole ring (or even with the reactive pyrroles), these same reagents have been used in conjunction with many Lewis and Brønsted acid catalysts in Friedel–Crafts acylations. In an alternative approach, pyrrole and its derivatives have been converted into the corresponding anions, which are acylated with the same, or milder, acylating agents. A number of heterocumulenes, such as ketenes and isocyanates, also acylate pyrroles directly.

In a number of these reactions it is necessary to solvolyze the immediate reaction product to reveal the desired acylated pyrrole. In other reactions, the acylated product has a reactive function which may be converted, if desired, to produce another acyl derivative before isolation.

3.4.3.1. Uncatalyzed Electrophilic Acylation

Most of the studies of the uncatalyzed acetylation of pyrrole have been carried out with acetic anhydride in sealed reaction vessels at temperatures of up to 300°C.[301–304] It soon became evident that both 1- and 2-acetylpyrrole were formed, but that, above 250°C, there was a rearrangement of the 1-acetylpyrrole into the 2-isomer.[305] The rearrangement process was later confirmed by other workers.[306] Recent authors[303] have shown that the presence of a base, such as the acetate ion, when used in conjunction with acetic anhydride, increases the proportion of 1-substitution; while the addition of triethylamine leads to an 80% yield of 1-acetylpyrrole at 130°C. Other workers have[304] found that, at 300–320°C, both 2-acetyl- (39%) and 3-acetylpyrrole (8.5%) are formed.

It has been suggested[307] that the basic workup method used by many authors cleaves the 1-acyl group from the initially formed 1,2- and 1,3-diacylated pyrroles to leave the mixture of 2- and 3-acyl products. It is also possible that the variable amount of 1-sustitution may be the result of the presence of small amounts of amine impurities in the pyrrole, which was available to several of the earlier workers. The effect of base on the acylation reaction will be discussed further in connection with reactions of the pyrrolyl anion (see Section 3.4.3.4).

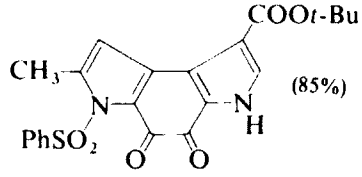
The reaction of pyrrole with trifluoroacetic anhydride in benzene at 0°C gave 66% of 2-trifluoroacetylpyrrole.[308] An examination of the steric effects of 1-substituents on the reaction has been carried out,[300] and the results were similar

to those found for the corresponding Vilsmeier–Haack formylation reactions (see Section 3.4.3.2.1).[310] Thus, small 1-substituents led exclusively to acylation at the 2 position, as determined by proton NMR spectral analysis, whereas medium size groups produced small amounts of the 3-isomer, and large (*tert*-butyl and adamantyl) groups caused almost exclusive 3-substitution. Reaction of the very bulky 1-triphenylmethylpyrrole with trifluoroacetic anhydride gave an 86% yield of 1-triphenylmethyl-3-trifluoroacetylpyrrole.[311] Some comparative rate studies have also been carried out with trifluoroacetic anhydride on pyrrole, 1-methyl-, and 2-methylpyrrole,[312] together with furan and thiophene. The mixed acetic-trifluoroacetic anhydride tended to produce mixtures of 2-acylated and 2-trifluoroacylated pyrroles with pyrrole and 1-methylpyrrole.[313] The mixed anhydride, prepared in situ from a mixture of potassium cyanoacetate and methanesulfonyl chloride, 3-cyanoacetylated 2,5-dimethyl- and 1,2,5-trimethylpyrrole in good yield.[314]

Treatment of pyrrole with silicon tetraacylate, prepared from the (C_2 to C_6) acid and silicon tetrachloride, gave moderate yields of 2-acyl derivatives.[315] It was even found possible[316] to 1-acetylate 4-chloro-2-formyl-3-(2-nitro-3-chlorophenyl)pyrrole with hot acetic acid alone.

Although maleic anhydride tends to undergo Michael-type reactions with pyrroles at atmospheric and at high pressures in the absence of a catalyst (see Section 3.4.2.1.2), under 8-kbar pressure for 5 days at 35°C, the reaction of 3,4-dichloromaleic anhydride with both pyrrole and 1-methylpyrrole gave 2-acylated products in 12 and 36% yields, respectively.[317]

Most of the uncatalyzed acylations have made use of the more readily available acid chlorides. These reagents led to 2-substitution, often in excellent yield, despite the sensitivity of pyrrole to acids. Among the more useful of these acylations is the trichloroacetylation,[318–320] the product from which may be solvolyzed during, or following, workup to give the carboxylic acid, its esters, or its amides. The use of phosgene,[106,321] or oxalyl chloride,[25,192,320,322,323] also permitted a manipulative workup. The use of oxalyl chloride can lead to intermolecular linkage of pyrrole rings,[320,323] as well as the intramolecular ring closure to form **4.68**.[324] Carbamoyl chlorides give 60–90% yields of the



4.68

amides,[325] while thiophosgene has been used to form the thiocarbonyl chlorides,[326] and $CO(CN)_2$ to introduce the 2-COCN (56%) group.[327] Aroylations were also successful in varying yields,[328] as were acylations with long-chain acid chlorides.[192] (See Table 3.4.15.)

TABLE 3.4.15. ACYLATED PYRROLES OBTAINED USING CARBOXYLIC ACID ACYLATION REAGENTS

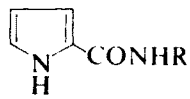
R^1	R^2	R^3	R^4	R^5	Yield (%)	Ref.
H	3-Meisoxazol-5-yl	H	H	$COCCl_3$	88	251
H	COMe	H	H	H	38M	304
H	COPh	H	H	COMe	20cr	516
H	CN	$(CH_2)_2COOEt$	H	CN	0.84	260
H	CN	$(CH_2)_2COOEt$	H	H	53	260
H	CN	H	$(CH_2)_2COOEt$	H	12	260
H	$COCH_2Ph$	H	H	H	42	192
H	$COCCl_3$	H	H	H	77–80	318
H	$COCCl_3$	H	H	H	78	320
H	$COCF_3$	H	H	H	66	308
H	$COCH_2COMe$	H	H	H	60	331
H	COCN	H	H	H	56	327
H	COCOOEt	H	COOEt	Me	86	25
H	COCOOH	Me	H	Me	65M	323
H	COCOOMe	H	H	H	22	320
H	$COC_{15}H_{31}$	H	H	H	33	192
H	COCCl=CClCOOH	H	H	H	12	317
H	CONHCOMe	H	H	H	11	335
H	$CONHCOCCl_3$	H	H	H	46	334
H	$CONHCOCCl_3$	H	H	H	NY	333
H	$CONH_2$	H	H	H	67	517
H	COOEt	Me	Et	$COCCl_3$	75	484
H	COOMe	H	$(CH_2)_2COOEt$	CN	84	260
H	H	COMe	H	H	8.5M	304
H	H	Me	H	CONHPh	NY	152
H	H	Pr	H	CONHPh	NY	152
H	H	Allyl	H	CONHPh	NY	152
H	Me	$COCCl_3$	H	Me	70	320
H	Me	$COCH_2CN$	H	Me	89	314
H	Me	$COCH_2COMe$	H	Me	60	331
H	Me	COCOCl	Me	COOEt	70	320
H	Me	COCl	Me	COOEt	NY	106
H	Me	$CONH_2$	H	COOEt	60–90 range	517
H	Me	$CONH_2$	Me	$CONH_2$	60–90 range	517

H	Me	$CONH_2$	Me	COOEt	60–90 range	517
H	Me	COOEt	COCOOH	Me	40M	323
H	Me	COOEt	H	$COCCl_3$	52	320
H	Me	COOEt	H	COCOOEt	56	320
H	Me	COOEt	H	$CONH_2$	60–90 range	517
H	Me	COOEt	Me	$COCCl_3$	NY	320
H	Me	COOEt	Me	COCOOEt	40	320
H	Me	COOEt	Me	COCOOH	57	320
H	Me	COOEt	Me	$CONH_2$	60–90 range	517
H	Me	COOEt	OH	CONHPh	84	395
H	Me	Et	Me	$COCH_2COMe$	NY	331
H	Me	H	H	$COCH_2COMe$	NY	331
H	Me	H	H	CONHPh	NY	152
H	Me	H	Me	$COCHPh_2$	NY	330
H	Me	H	Me	$COCH_2COMe$	75	331
H	Me	H	Me	COCOOH	58	320
H	Pr	H	H	CONHPh	NY	152
H	*t*-Bu	H	H	CONHPh	NY	152
H	Allyl	H	H	CONHPh	NY	152
$(CH_2)_2CN$	COCOCl	H	H	H	83	322
$(CH_2)_2CN$	COCOindol-3-yl	H	H	H	55	322
$COCHPh_2$	H	H	H	H	NY	329
Me	CH_2CN	H	H	$4\text{-}MeC_6H_4CO$	49	328
Me	CH_2COOEt	H	Me	$3,5\text{-}diClC_6H_3CO$	80	328
Me	CH_2COOEt	H	Me	$4\text{-}NO_2C_6H_4CO$	85	328
Me	$COCCl_3$	H	H	H	63	320
Me	$COCCl_3$	H	H	H	94	319
Me	COCOOEt	H	H	H	88	320
Me	COCOOH	H	H	H	63	320
Me	COCOindol-3-yl	H	H	H	57	322
Me	COCCl=CClCOOH	H	H	H	36	317
Me	Me	$COCH_2CN$	H	Me	75	314
Ph	Ph	Me	H	$CONH_2$	60–90 range	517
SO_2Ph	CN	H	*t*-Bu	H	37M	98
SO_2Ph	CN	*t*-Bu	H	H	56M	98
Trityl	H	$COCF_3$	H	H	89M	311

The major types of heterocumulene, which will add to pyrrole in uncatalyzed acylations, are the ketenes and the isocyanates. Diphenylketene has been reported[329] to react with pyrrole, affording 1-diphenylacetylpyrrole (m.p. 122°C) while the product from the corresponding reaction with 1-methylpyrrole is a disubstituted adduct [m.p. ca. 200°C (decomp.)], and 5-substitution occurs with 2,4-dimethylpyrrole.[330] Ketene itself also reacts with 2,4-dimethylpyrrole at the 5 position.[331] In view of these facts, the structure of 1-diphenylacetylpyrrole appeared improbable, but, more recently, it has been confirmed[332] through diphenylacylation of the tricarbonyl(η^5-pyrrole)manganese complex, which gave the same product, possessing the expected carbonyl stretching frequency. The 2-isomer[184] has a different melting point (104–106°C) and carbonyl stretching frequency.

Diketene is said to react with pyrroles without a catalyst to give *C*-acetoacetylations in good yields[331], but recent workers[251] found that pyridine catalysis was needed and suggested that earlier results arose from pyrrole being contaminated with a base. However, the earlier paper states that the diketene contained some acetic anhydride and, consequently, a Friedel–Crafts acylation also seems possible.

Many examples of the successful use of the heterocumulene-type isocyanate system, including phenyl,[333,334] acetyl,[335] trichloroacetyl,[333,334] trifluoroacetyl,[336] ethoxycarbonyl,[337] and *p*-toluenesulfonyl[337] derivatives lead to carbamoylation of the pyrrole ring at the 2 position (**4.69**). The last of these papers corrected the earlier report[338] of 3-substitution on pyrrole. The reaction with phenyl isocyanate has been used to characterize liquid alkyl pyrroles,[152,339] as has the corresponding reaction with phenyl isothiocyanate.[340–342]



4.69

Another useful reagent of this type is chlorosulfonyl isocyanate (see Table 3.4.16). The adduct from its reaction with pyrrole, on subsequent treatment with aqueous base, gave the 2-carboxamide in 74% yield, while warming the solution in dimethylformamide led to the 2-nitrile (73%).[343,344] Disubstitution was also easily accomplished, and, although most of the reported reactions were used to prepare the nitrile, the amide could have been obtained as easily.

3.4.3.2. Acylation Using Iminium-Type Reagents

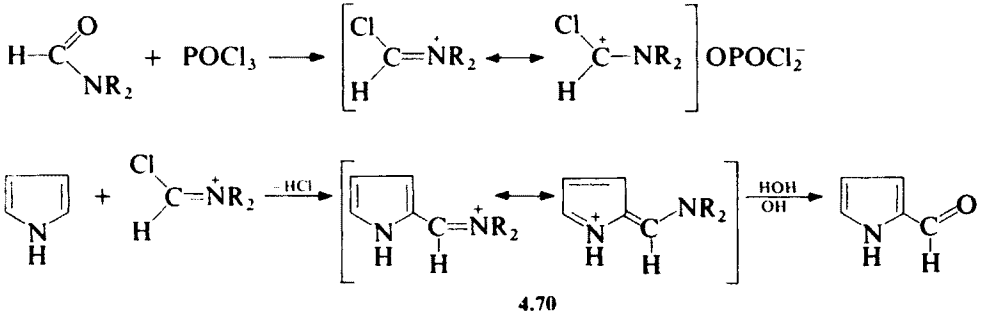
3.4.3.2.1. The Vilsmeier–Haack Reaction

Since its initial use on disubstituted pyrroles[345,346] and then on pyrrole itself[347,348] the Vilsmeier–Haack synthesis of formylpyrroles (Scheme 4.43) has

TABLE 3.4.16. ACYLATED PYRROLES DERIVED FROM REACTIONS WITH ISOCYANATES

R^1	R^2	R^3	R^4	R^5	Yield (%)	Ref.
H	H	CONHTos	Me	H	NY	337
H	COMe	H	H	CN	20.5M	344
H	COMe	H	CN	H	35.5M	344
H	CHO	H	CN	H	27	344
H	CN	H	H	H	40	343
H	CN	H	H	H	73	344
H	CN	H	H	5,5-diMe-1,3-dioxan-2-yl	63	518
H	CN	H	H	CN	2.5M	343
H	CN	H	CN	H	47	344
H	CN	H	CN	H	53M	343
H	CN	5,5-diMe-1,3-dioxan-2-yl	H	5,5-diMe-1,3-dioxan-2-yl	c.2	518
H	$COCCl_3$	H	CN	H	71	344
H	$CONHCOCCl_3$	H	H	H	46	334
H	$CONHCOCCl_3$	H	H	H	NY	333
H	$CONHCOCF_3$	H	H	H	66	336
H	CONHCOOEt	H	H	H	81cr	337
H	CONHPh	H	H	H	64	339
H	COOMe	H	H	CN	22M	344
H	COOMe	H	CN	H	45M	344
H	$CONH_2$	H	H	H	74	343
H	Me	H	H	CONHPh	85	339
H	Me	H	Me	$CONHCH_2Ph$	74	339
H	Me	H	Me	CONHPh	79	339
H	Me	CONHPh	H	Me	NY	339
H	Me	Et	Me	CONHPh	74	339
2-MePh	H	CONHTos	Me	H	33	338
COOEt	CN	H	H	H	58	343
Me	CHO	H	CN	H	53	344
Me	CN	H	H	H	58M	343
Me	CN	H	H	5,5-diMe-1,3-dioxan-2-yl	65	518
Me	CN	H	H	CN	2.5M	343
Me	CN	H	CN	H	2.8M	343
Me	CN	H	CN	H	50	344
Me	CN	5,5-diMe-1,3-dioxan-2-yl	H	5,5-diMe-1,3-dioxan-2-yl	18	518
SO_2Ph	CN	H	H	H	99	98

been one of the most widely used reactions in pyrrole chemistry.[349] It is mild, fairly selective, compatible with many functional groups, is easily carried out and often gives excellent yields. The reaction may be applied to the synthesis of ketones and to vinylogs of aldehydes and some rate studies have been carried out for the aroylation reaction.[350,351]



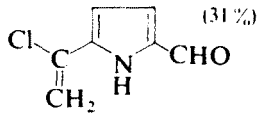
4.70

Scheme 4.43

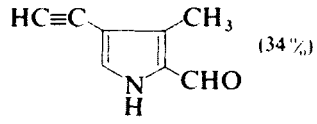
The reaction is remarkably tolerant of variations; the solvent for the reaction may, for example, be excess pyrrole,[352] excess dimethylformamide,[353] excess phosphorus oxychloride,[354] ethyl ether,[224] low-boiling petroleum,[355] or toluene,[355] as well as the usual dichloromethane or 1,2-dichloroethane. The electrophilic iminium salt is usually generated from the amide using phosphorus oxychloride, but other acid chlorides such as benzoyl chloride,[224,356,357] oxalyl chloride,[343,358] and a mixture of triphenylphosphine and bromine[359] may be used. Even perchloric acid has been used in the reaction with a vinylogous amide.[360]

The Vilsmeier iminium salt reagent is a bulky one, even for formylation, so substituents at the 1 position of the pyrrole ring cause a marked increase in 3-/2-isomer ratio, with this increased bulk.[310,361,362] Although most syntheses have been directed towards monosubstitution, it is possible to obtain diformyl by-products, although not in large amounts.[355,363–365] More of the 2,4-diformyl isomer than the 2,5-derivative is produced from pyrrole.[364] The Vilsmeier reaction has been used as a method of ring closure.[367] In another example,[367] formylation was accompanied by ring closure.

The compatibility of the reaction with a variety of sensitive functionality on the ring, and on the acylating reagents, is illustrated by the reaction of pyrroles substituted by cyclic ketals,[204] *S*-alkylthioesters and alkylthio groups,[368–371] trichloroacetyl,[319] 1-ethoxycarbonyl,[80,310] 1-dimethylamino groups,[67] and with chloropyrroles.[156] The reaction is not entirely satisfactory when enolizable ketone side chains are present. The acetyl group may be converted into a chlorovinyl group[372] as, for example, in the formylation of 2-acetylprrole which formed **4.71**,[373] or into the ethynyl group in the formation of **4.72** from 4-methyl-3-acetylpyrrole.[374] An oxime has been observed to be dehydrated to the nitrile during one aldehyde synthesis.[375]

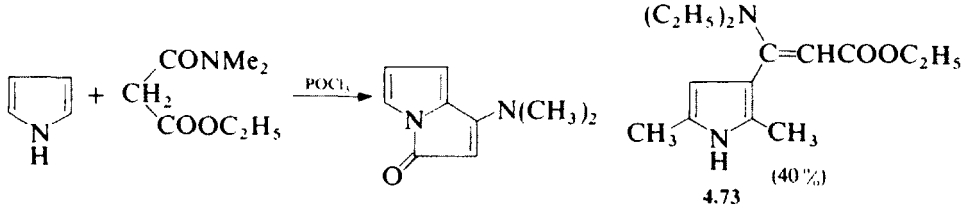


4.71



4.72

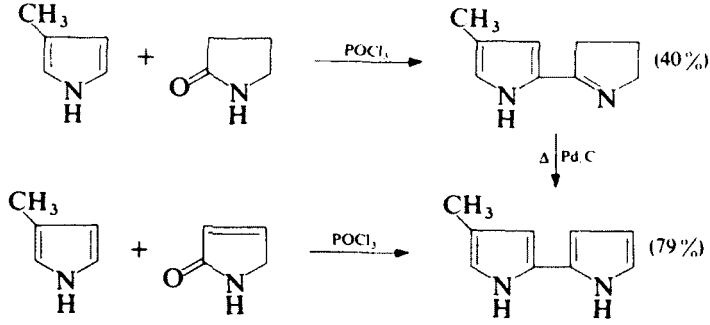
When the Vilsmeier acylation was carried out with amides derived from malonic acid some complications arose, which led to the formation of an oxopyrrolizine in about 30% yield (Scheme 4.44).[376] A 60% yield resulted when *N,N,N',N'*-tetramethylmalonamide was used.[354] The reaction of 2,5-dimethylpyrrole with the monoester–diethylamide gave compound **4.73**.[376]



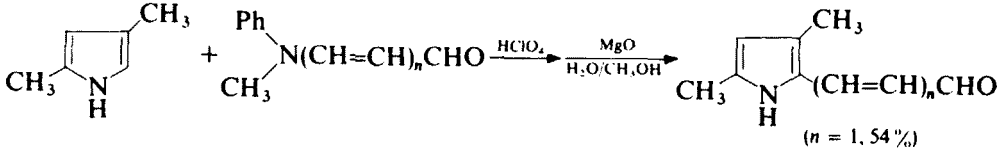
4.73

Scheme 4.44

While the aldehyde synthesis generally uses dimethylformamide, other *N,N*-disubstituted amides have been used, particularly for the acylation reaction.[151,192,350,353,376,377] In several examples cyclic amides of the pyrrolidin-2-one and 3-pyrrolin-2-one type have been used,[44,224,352,378,379] leading to dipyrroles,[379] or their precursors,[378] as shown in Scheme 4.45.



Scheme 4.45



Scheme 4.46

TABLE 3.4.17. VILSMEIER-HAACK FORMYLATION PRODUCTS

R^1	R^2	R^3	R^4	R^5	Yield (%)	Ref.
H	H	2-NO_2-3-ClC_6H_3	H	CHO	71	23
H	H	CHO	H	COCOOEt	0.4M	260
H	CH=CHCHO	H	H	H	17	382
H	CH=CHCHO	Et	Et	H	75	381
H	CH=CHCHO	Me	H	Me	54	360
H	CH=C(CN)COOEt	H	H	CHO	80	519
H	CH=CMeCHO	H	H	H	51	380
H	CHO	H	H	H	39M	364
H	CHO	H	H	H	78	349
H	CHO	H	H	H	80	520
H	CHO	H	H	$(CH_2)_3CN$	58	143
H	CHO	H	H	$(CH_2)_8CH_3$	81	521
H	CHO	H	H	1-Me-2-pyrrolyl	23M	224
H	CHO	H	H	1-Chlorovinyl	31	373
H	CHO	H	H	(2,4-di$NO_2C_6H_3$)S	42	187
H	CHO	H	H	2-CHO-furan-5-yl	14M	522
H	CHO	H	H	4-$NO_2C_6H_4$	70	523
H	CHO	H	H	5,5-diMe-1,3-dioxan-2-yl	56	524
H	CHO	H	H	CHO	0.5M	364
H	CHO	H	H	COCOOEt	1M	260
H	CHO	H	H	$COC_{15}H_{31}$	68	192
H	CHO	H	H	Cl	78	156
H	CHO	H	H	Me	57	525
H	CHO	H	H	Me	90	520
H	CHO	H	H	Me	97	526
H	CHO	H	H	Ph	65	523
H	CHO	H	H	SMe	64	370
H	CHO	H	H	Furan-2-yl	62M	522
H	CHO	H	2-$NO_2C_6H_4$	H	64M	109
H	CHO	H	5,5-diMe-1,3-dioxan-2-yl	H	36M	518
H	CHO	H	COMe	H	80	358

H	CHO	H	Am	Me	96	527
H	CHO	H	COPh	H	55	358
H	CHO	H	CHO	H	40	358
H	CHO	H	CHO	H	4M	364
H	CHO	H	CH_2COOEt	H	37.3M	261
H	CHO	H	COCOOEt	H	69M	260
H	CHO	H	COOMe	H	80	358
H	CHO	H	COSEt	H	62	358
H	CHO	H	Cl	H	50	358
H	CHO	H	Me	H	12MGC	528
H	CHO	H	NO_2	H	c.80	504
H	CHO	2-NO_2-3-ClC_6H_3	H	Me	75	393
H	CHO	2-NO_2-3-ClC_6H_3	COOEt	Me	73	393
H	CHO	2-$NO_2C_6H_4$	H	H	16M	109
H	CHO	5,5-diMe-1,3-dioxan-2-yl	H	H	42M	518
H	CHO	5,5-diMe-1,3-dioxan-2-yl	H	5,5-diMe-1,3-dioxan-2-yl	77	518
H	CHO	CH_2COOEt	H	H	59.5M	261
H	CHO	H	$C_{17}H_{35}$	H	NY	380
H	CHO	$C_{17}H_{35}$	H	H	NY	380
H	CHO	COOEt	Me	COOEt	59	353
H	CHO	COOEt	Me	Me	75	353
H	CHO	Cl	Cl	H	68	529
H	CHO	Cl	Cl	Me	96	529
H	CHO	Me	H	H	45	526
H	CHO	Me	H	H	48MGC	528
H	CHO	Me	H	H	60	530
H	CHO	Me	H	Me	75	520
H	CHO	Me	COMe	H	4M	374
H	CHO	Me	$COOCH_2Ph$	Me	37	356
H	CHO	Me	COOEt	H	72	353
H	CHO	Me	C≡CH	H	34M	374
H	CHO	Me	Me	H	74	531
H	CHO	Me	Me	H	75	530
H	CHO	Me	Me	H	79	520

TABLE 3.4.17. (*Contd.*)

R^1	R^2	R^3	R^4	R^5	Yield (%)	Ref.
H	CHO	Me	Me	Me	81	520
H	CHO	MeO	H	COOMe	59	527
H	CN	CH_2COOMe	$(CH_2)_2COOMe$	CHO	50	375
H	$COOCH_2Ph$	Me	H	CHO	72M	532
H	$COOCH_2Ph$	Me	CHO	H	28M	532
H	$COOCH_2Ph$	Me	Me	CHO	87	531
H	COOEt	H	H	CHO	14M	533
H	COOEt	H	H	CHO	63M	446
H	COOEt	H	CHO	H	26M	446
H	COOEt	H	CHO	H	50M	533
H	COOEt	$2\text{-}NO_2\text{-}3\text{-}ClC_6H_3$	H	CHO	65cr	23
H	COOEt	CHO	H	H	0.4M	446
H	COOMe	H	CHO	Thien-2-yl	85M	522
H	COSEt	H	H	CHO	59M	364
H	COSEt	H	H	CHO	69M	446
H	COSEt	H	CHO	H	23M	364
H	COSEt	H	CHO	H	26M	446
H	Me	H	Me	CHO	49M	534
H	Me	CHO	H	COSMe	85	368
H	Me	CHO	H	Me	18M	365
H	Me	CHO	H	Me	62	183
H	Me	CHO	H	Ph	80MGC, NMR	535
H	Me	CHO	$(CH_2)_2COOEt$	COOEt	87	536
H	Me	CHO	CHO	Me	10M	365
H	Me	CHO	COOEt	Me	93	353
H	Me	CHO	Me	CHO	2.5M	534
H	Me	CHO	Me	COOEt	96	534
H	Me	COOEt	Me	CHO	NY	534
H	Me	Et	Me	CHO	NY	534
H	Me	Me	Me	CHO	22	534
H	Ph	CHO	H	Me	20MGC, NMR	535

H	Ph	COOEt	H	CHO	62	523
H	$[CH=CH]_2CHO$	Me	H	Me	57	360
H	$[CH=CH]_2CHO$	Me	Et	Me	NY	360
2-MeC_6H_4	CHO	H	H	H	85	537
4-MeC_6H_4	CHO	H	H	H	75	537
COMe	CHO	H	H	H	61	310
CH_2Ph	H	CHO	H	H	12.5M	310
CH_2Ph	H	CHO	H	H	2.3	362
CH_2Ph	CHO	H	H	H	66.5M	310
CH_2Ph	CHO	H	H	H	74	362
COPh	CHO	H	H	H	74	310
CH_2Furan-2-yl	Me	CHO	H	Me	30 M	363
CH_2Furan-2-yl	Me	CHO	CHO	Me	15M	363
CH_2Furan-2-yl	Me	CHO	CHO	Ph	NY	363
Me	CHO	H	H	4-MeC_6H_4CO	50M	377
COOEt	CHO	H	H	H	73	310
COOEt	CHO	H	H	H	NY	80
COOEt	Me	H	Me	CHO	NY	80
Et	CHO	H	H	H	77	310
Me	H	CHO	H	H	c.6	447
Me	5,5-diMe-1,3-dioxan-2-yl	H	H	CHO	95	518
Me	CH=CHCHO	H	H	H	49	380
Me	CH=CMeCHO	H	H	H	13	380
Me	CHO	H	H	H	89	310
Me	CHO	H	H	H	95	520
Me	CHO	H	H	COOMe	60M	319
Me	CHO	H	H	Cl	89	156
Me	CHO	H	H	Me	79	520
Me	CHO	H	H	SMe	78	371
Me	CHO	H	H	SPh	78	371
Me	CHO	H	H	Pyrrol-2-yl	6M	224
Me	CHO	H	COMe	H	78	358
Me	CHO	H	CHO	H	61	358
Me	CHO	5,5-diMe-1,3-dioxan-2-yl	H	5,5-diMe-1,3-dioxan-2-yl	80	518

TABLE 3.4.17. (*Contd.*)

R^1	R^2	R^3	R^4	R^5	Yield (%)	Ref.
Me	CHO	Me	H	Me	65	520
Me	CHO	Me	Me	H	70	520
Me	Me	H	Me	CHO	NYM	365
Me	Me	CHO	H	Me	99	183
Me	Me	CHO	H	Me	NYM	365
Me	Me	CHO	CHO	Me	NYM	365
Me	Me	CHO	Me	CHO	NYM	365
NMe_2	CHO	H	H	H	56	67
Ph	H	CHO	H	H	4.5M	361
Ph	CHO	H	H	H	70M	361
Ph	Me	CHO	H	Me	73	355
Ph	Me	CHO	CHO	Me	13M	355
Ph	Me	Me	CHO	Me	83	355
Ph	Ph	H	CHO	Me	98	355
Ph	Ph	CHO	Me	Me	77	355
SO_2Ph	CHO	H	H	H	High	98
i-Pr	H	CHO	H	H	20M	310
i-Pr	CHO	H	H	H	59M	310
t-Bu	H	CHO	H	H	79M	310
t-Bu	CHO	H	H	H	4.5M	310
Trityl	H	CHO	H	H	87M	311
Trityl	CHO	H	H	H	13M	311

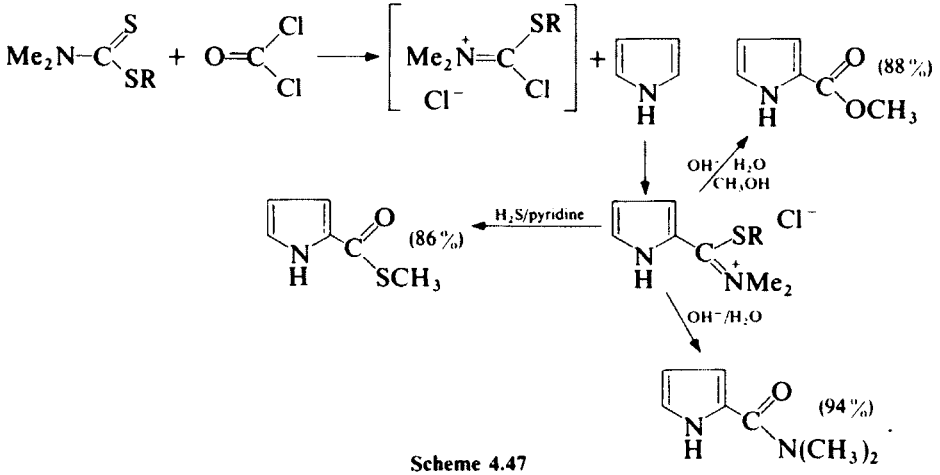
Several vinylogous Vilsmeier–Haack-type reactions have also been successful[380–382] in placing the -CH=CH·CHO group on the ring. Yields vary from poor to good; moderate yields are obtained in the example used in Scheme 4.46.[360] (See Tables 3.4.17 and 3.4.18.)

The initial product of the Vilsmeier–Haack reaction, the azafulvenium salt **4.70** (Scheme 4.43), is capable of several transformations in addition to simple hydrolysis to the carbonyl compound. Other reactions include direct conversion to a nitrile,[343] in moderate yield, and to thioacyl derivatives.

As the iminium side chain is strongly electron-withdrawing, the salt may also be used without isolation in Friedel–Crafts acylations[260,358] to afford 4-acyl-2-formylpyrroles (see other electrophilic reactions in Section 3.3.2). It has also proved possible to reduce the aroylation morpholinium salts with lithium borohydride to produce substituted benzylpyrroles in excellent yield.[383] When base is added to these salts the free azafulvene may then be induced to undergo several further reactions.[55,384] In some of these modifications, oxalyl chloride has been found to be superior to phosphorus oxychloride in the generation of the Vilsmeier reagent, since the only anion present is chloride.

In a different generation of the iminium salt,[385] boron trifluoride–diethyl etherate reacts with $ClCHFCF_2NEt_2$ to form $(ClCHFCF{=}NEt_2)^+BF_4^-$ which, on reaction with 1-methylpyrrole and workup, afforded a mixture of the 1-methyl-2-chlorofluoroacetyl (35%) and 1-methyl-3-chlorofluoroacetyl (35%) derivatives.

The chlorothioformamidinium salts,[386] formed as shown in Scheme 4.47, may be hydrolyzed to give *N*,*N*-dialkylcarboxamidopyrroles, but may also be used to form acids, esters, and *S*-alkylthioesters.



Scheme 4.47

3.4.3.2.2. The Gatterman and Houben–Hoesch Reactions

The Gatterman formylation reaction (see Table 3.4.19) using HCN/HCl in ether was introduced into pyrrole chemistry by Fischer and Zerweck[387] in 1922

TABLE 3.4.18. VILSMEIER-HAACK ACYLATION PRODUCTS

R^1	R^2	R^3	R^4	R^5	Yield (%)	Ref.
H	1-Pyrrolin-2-yl	H	H	H	80	352
H	1-Pyrrolin-2-yl	H	H	Me	78	378
H	1-Pyrrolin-2-yl	H	Me	H	40	378
H	1-Pyrrolin-2-yl	Me	H	H	40	378
H	1-Pyrrolin-2-yl	Me	COOEt	H	37	378
H	3,4-di$MeOC_6H_3CO$	H	H	H	81	192
H	3,4-MethylenedioxyC_6H_3CO	H	H	H	80	538
H	3,4-MethylenedioxyC_6H_3CO	H	H	$(CH_2)_2Ph$	29	192
H	5-COOMe-1-pyrrolin-2-yl	H	H	H	51	378
H	5-Me-1-pyrrolin-2-yl	H	H	H	84	378
H	5-Me-1-pyrrolin-2-yl	H	H	Me	78	378
H	COMe	H	H	H	50	539
H	COMe	H	H	H	75	540
H	COMe	H	H	H	87.5	303
H	COMe	H	H	Me	52	539
H	COMe	H	H	Me	NY	413
H	COMe	H	Me	Me	NY	413
H	COMe	2-NO_2-3-ClC_6H_3	H	Me	85	393
H	COMe	Me	H	Me	60	413[a]
H	4-$ClC_6H_4CH_2$	H	H	H	82	383[a]
H	4-$ClC_6H_4CH_2$	Me	COOEt	Me	90	383[a]
H	4-$MeOC_6H_4CH_2$	H	H	H	92	383[a]
H	4-$MeOC_6H_4CH_2$	Me	COOEt	Me	93	383[a]
H	4-$MeC_6H_4CH_2$	H	H	H	80	383
H	4-$MeC_6H_4CH_2$	Me	COOEt	Me	88	383
H	CH_2Ph	H	H	H	90	383
H	CH_2Ph	Me	COOEt	Me	93	383
H	$C(NEt_2)$=CHCOOEt	Me	Et	Me	36	376
H	CN	H	H	H	64	343[b]
H	COC_6H_{13}	H	H	H	89	540
H	$CO(CH_2)_2COOEt$	H	H	H	71	376
H	$CO(CH_2)_2Cl$	H	H	H	62	541
H	COBu	H	H	H	80	540
H	$COCH_2CONMe_2$	H	H	H	NYM	354

H	$COCH_2COOEt$	Me	COOEt	Me	61	376
H	$COCH_2Cl$	H	H	H	54	376
H	$COCH_2Cl$	Me	COOEt	Me	75	376
H	$COCH_2Cl$	Me	Et	Me	34	376
H	COMe	H	H	H	49	354
H	$COC_{11}H_{23}$	H	H	H	76	540
H	COC_9H_{19}	H	H	H	77	540
H	COEt	H	H	H	78	540
H	COC_5H_{11}	H	H	H	84	540
H	COPr	H	H	H	97	540
H	Me	H	Me	COMe	NY	542
H	Me	COMe	H	Me	NY	542
H	Me	COMe	Me	H	40	353
H	Me	COMe	Me	COMe	NY	542
H	Me	COPh	H	Me	NY	413
H	Me	$C(NEt)_2$=CHCOOEt	H	Me	40	376
H	Me	COOEt	Me	COMe	67	353
H	Me	COOEt	Me	COPh	62	353
H	Me	COOEt	Me	$CO(CH_2)_2COOMe$	40	353
H	Me	Et	Me	COMe	NY	542
H	SMe	H	H	$4\text{-}FC_6H_4CO$	54	369
H	SMe	H	H	COPh	79	369
H	[3,4-Bis(benzoyloxy)C_6H_3CO]	H	H	H	77	192
H	Pyrrol-2-yl	H	H	H	NY	379
H	Pyrrol-2-yl	H	Me	H	79	379
H	Pyrrol-2-yl	OMe	COOEt	H	65	379
CH_2Ph	Me	H	H	2-Pyrrolin-2-yl	21	224
Me	H	COMe	H	H	25M	376
Me	2-Pyrrolin-2-yl	H	H	H	34.5	224
Me	5-COOMe-2-pyrrolin-2-yl	H	H	H	33	224
Me	5-COOMe-1-pyrrolin-2yl	H	H	H	69	378
Me	COMe	H	H	H	59M	376
Me	COMe	H	H	H	NY	542
Me	CN	H	H	H	67	343[b]
Me	Me	H	H	2-Pyrrolin-2-yl	64	224

[a] Under reductive conditions.

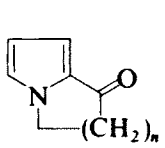
[b] In situ conversion to CN.

TABLE 3.4.19. FORMYLPYRROLES OBTAINED BY THE GATTERMAN REACTION

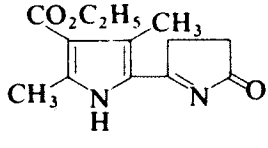
R^1	R^2	R^3	R^4	R^5	Yield (%)	Ref.
H	CHO	Me	H	Me	86	389
H	CHO	Me	Me	H	NY	543
H	CHO	Me	Me	CH=C(CN)COOMe	35	543
H	COOEt	H	H	CHO	28	455
H	COOMe	H	H	CHO	40	21
H	Me	CHO	H	COOH	NY	497
H	Me	CHO	$(CH_2)_2COOEt$	COOEt	41	106
$(CH_2)_2CN$	Me	CHO	Me	COOEt	74	186
Bu	CHO	H	H	H	61	455
Bu	CHO	H	H	H	66	389
Me	CHO	H	H	H	31	389
Me	CHO	H	H	H	31	455
i-Pentyl	CHO	H	H	H	62.5	455

and was used successfully for a number of years, and later in the Adams and Levine modification, using zinc cyanide,[388] until it was largely superseded by the Vilsmeier–Haack synthesis. A variant of the procedure used *sym*-triazine rather than hydrogen cyanide or zinc cyanide.[389] Occasionally ring halogens are displaced by this formylation reaction.[390]

The Houben–Hoesch acylation, also introduced by Fischer[391] is generally carried out using a nitrile under conditions similar to the Gatterman formylation. Sometimes boron trifluoride–diethyl etherate or zinc chloride have been added as catalysts.[212,392,393] Often the iminium salt, which precipitates from the ether solvent in both of these reactions, is isolated prior to aqueous workup. As well as the usual acylations and aroylations,[394,395] the reaction has been used extensively to introduce ketoesters and other functionalized ketoalkyl side chains,[396–398] especially the glyoxalate and the ketopropanoate groups,[186,399,400] although cyanogen gave a poor yield of the 2-COCN group.[391] Even 2- and 4-cyanopyridines reacted successfully to yield the corresponding pyridyl ketones.[401,402] Intramolecular cyclizations of 1-cyanoalkyl groups have led to compounds of the type of **4.74**.[212,231,392]



(*n* = 1, 2, or 3)



4.74 **4.75**

As might be expected, the presence of a second functional group on the new iminium side chain may cause further reactions on workup. An interesting example[397] of such a sequence is the formation of compound **4.75**, when ethyl 3-cyanopropanoate and ethyl 2,5-dimethylpyrrole-3-carboxylate were treated

with hydrogen chloride in ether and the resulting salt worked up using ammonia in chloroform.

In a variation[403] of the Houben–Hoesch reaction, the electrophilic reagent is prepared by alkylation rather than protonation of the nitrile, as shown in Scheme 4.48. Subsequent reaction with pyrrole in dichloromethane and hydrolysis then gave good yields of ketones, for example, 2-acetylpyrrole (92%).

Examples of the Houben–Hoesch acylation are found in Table 3.4.20.

$$R\text{–}C{\equiv}N + Me_3O^+BF_4^- \longrightarrow [R\text{–}C{\equiv}\overset{+}{N}\text{–}Me \longleftrightarrow R\text{–}\overset{+}{C}{=}N\text{–}Me]BF_4^-$$

Scheme 4.48

TABLE 3.4.20. ACYLPYRROLES OBTAINED BY HOUBEN–HOESCH REACTIONS

R^1	R^2	R^3	R^4	R^5	Yield (%)	Ref.
H	COCOOEt	2-NO_2-3-ClC_6H_3	H	Me	32	393
H	COOMe	H	*i*-Pr	COCOOEt	86	399
H	Me	H	Me	COPh	NY	394
H	Me	COCOOEt	H	COOEt	Quant	186
H	Me	COOEt	Me	$COCH_2COOEt$	86	398
H	Me	COOEt	OH	COMe	30–50	395
H	Me	Me	COOEt	$COCH_2COOEt$	61.5	398
CH_2Ph	CO4,6-diMepyrid-2-yl	H	H	H	75	402
CH_2Ph	$COCH_2Cl$	H	H	H	c. quant cr	396
Me	COpyridin-4-yl	H	H	H	NY	401
Ph	$COCH_2Cl$	H	H	H	NY	396

3.4.3.3. Friedel–Crafts Acylation

Friedel–Crafts acylation, which has been widely and successfully used in pyrrole chemistry, is another reaction which was introduced initially by Hans Fischer and co-workers.[404] Reaction at the 1 position is a rarity and, when it occurs, is usually catalyzed by Brønsted acids. Disubstitution does not usually occur. There are many Brønsted acid-catalyzed acylations and some of them produce subsequent rearrangements of the acyl groups. The reaction may be used for ring closures or to join aromatics intra- or intermolecularly.

As described in Section 3.4.3.1, the acylation of pyrrole and many simple alkyl derivatives may be accomplished without a catalyst. The presence of a Lewis acid catalyst causes polymerization of some of the more reactive pyrroles but enables the mono and disubstitution of others.[405] Tin(IV) chloride has been found to be superior to the more usually employed aluminum chloride for these acylations, but in substitutions where an electron-withdrawing group is present, aluminum chloride[102,192,358,404,406–409] is the reagent of choice. When compounds of intermediate reactivity are acylated, tin(IV) chloride,[28,186,405,410–412] zinc chloride,[191,413–415] and boron trifluoride–diethyl etherate[191,208,416–418] are often used successfully, and, as in

the benzene series, more than a catalytic amount of the Lewis acid is needed. As with alkylation reactions, much of the early work was conducted in carbon disulfide. Dichloromethane and 1,2-dichloroethane are now the solvents of choice for these reactions, thereby removing the occasional complication of dithiocarboxylation.[419]

Brønsted acid-catalyzed acetylation, using perchloric acid and acetic anhydride, has been found to give a mixture of 1- and 2-acetylpyrroles[420] in 36% yield, although the proportion of the 2-acetyl derivative increased with time at 70–80°C. Perchloric acid has been used in other *C*-acylation reactions,[264,368] although a comparative study[421] has shown that magnesium perchlorate is superior to perchloric acid as a catalyst for anhydride acylations. Polyphosphoric acid[111,422–426] and phosphorus pentachloride[427] have been used chiefly for the ring-closure reactions of side-chain acids or esters.

The Friedel–Crafts acylation of 1-methylpyrrole with methyl glutaroyl chloride and aluminum chloride gave 51% 2-substitution and 22% of the 3-isomer.[428] As mentioned above, however, many simple pyrroles tend to polymerize with alumium chloride, so most of the successful Lewis acid-catalyzed acylations have been carried out, from the beginning,[404] on deactivated pyrroles.

Although the aluminum chloride catalyzed acetylation of 1-benzoylpyrrole[98] gave only the 2-substituted product, the same reaction, when applied to 1-benzenesulfonylpyrrole and 1-(4-toluenesulfonyl)pyrrole, led to 3-substitution almost exclusively with a variety of acyl chlorides and anhydrides.[192,429–431] As the 1-benzenesulfonyl group is readily introduced and removed, this method constituted a useful approach to 3-acylpyrroles.[432] Changes in the Lewis acid catalyst,[408,433,434] or the proportion used,[429] have been shown to have a substantial influence on this regioselectivity. Thus, whereas 3-acetylation of the 1-arenesulfonylpyrrole also predominated with the use of titanium(IV) chloride and iron(III) chloride, the 2-acetyl derivative was the major product, when the tin(IV) chloride or zinc chloride was used as catalyst. It was found that boron trifluoride–diethyl etherate gave almost exclusively 2-substitution on 1-benzenesulfonylpyrrole.[408] A further limitation of the procedure is shown by the Friedel–Crafts formylation and cyanation reactions, which took place at the 2 position,[429] and, indeed, all attempts to introduce a one-carbon unit into the 3 position have failed,[408] except for the aluminum chloride-catalyzed reaction with *S*-ethyl chlorothioformate, which gives the *S*-ethyl pyrrole-3-thiocarboxylate product in 65% yield.[98]

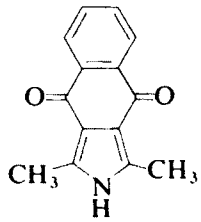
The 1-*tert*-butyldimethylsilyl[435] group also directs Friedel–Crafts acylation into the 3 position using aluminum chloride catalysis, but in only moderate yields. The trialkylsilyl group may be removed by fluoride ion in aqueous tetrahydrofuran, although some cleavage of that group during acylation results in the formation of the 2-acyl isomer as a by-product.

Brønsted acid-catalyzed rearrangements of the 2-acyl groups to the 3 position[436–438] have been observed for some 1-substituted pyrroles, and in some cases these have preparative significance. Additionally the polyphosphoric

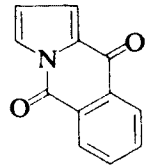
acid-catalyzed ring closure of some 3-(1-substituted pyrrol-2-yl)propanoic acids results in the migration of both the alkyl and acyl groups.[424] Acyl groups may also be lost under acidic conditions[439,440] (see Section 3.2).

The Friedel–Crafts acylation of pyrrole is compatible with a variety of carbonyl groups already attached to the ring or on the attacking electrophile despite the tendency of such groups to complex with Lewis acids. Thus, the 2-ester[102] 2-trichloroacetyl,[406] 2-*S*-alkyl thioester,[441] 2-iminium salt,[358,435] and the 2-cyano derivatives[407] have been acylated successfully, predominantly, or exclusively at the 4 position. When the 2-substituent is removable, this constitutes an approach to 3-acylpyrroles.[432] The linking of substituted pyrroles by long (8-, 9-, 10-, and 11-carbon) chains using the corresponding dicarboxylic acid chlorides and tin(IV) chloride in dichloromethane–nitromethane has been accomplished with high yields.[442] It should be noted that although oxalyl chloride has occasionally lost carbon monoxide in vigorous catalyzed reactions, leading to the introduction of the –COCl side chain,[407,408] without an acidic catalyst, the reaction can give the desired –CO·COCl grouping on reactive pyrroles.[320,322]

Electrophilic attack by acid chlorides has also included a number of dibasic acids in the form of their monoester acid chloride.[260,408,426,428,443] The boron trifluoride-catalyzed 3-acylation of 2,5-dimethylpyrrole with succinic anhydride has been reported to be successful (37%),[418] while the corresponding reaction with 2,4-dimethylpyrrole was found to proceed better in the absence of a catalyst than it did with either a Lewis or Brønsted acid.[397] Phthalic anhydride, in the presence of acetic acid, gave similar 3-acylation of 2,5-dimethylpyrrole[444] (60%) and, when heated strongly, cyclized onto the 4 position to give **4.76** (33%); when both the 1 and 2 positions were open, **4.77** was isolated in a low yield.[445]



4.76



4.77

The formylation procedures that use dichloromethyl alkyl ethers and a Lewis acid,[441] or trialkyl orthoformates with trifluoroacetic acid,[356] relate more closely to alkylation reactions. However, the product obtained on workup is the corresponding aldehyde. The process using the dichloromethyl ether gives better results when the solvent is a mixture of nitromethane and dichloromethane[319,441] and is especially useful when a deactivating group is present at the 2 position. Under the Friedel–Crafts conditions, the 4-formyl-2-substituted product is formed,[319,358,409,441,446,447] while the Vilsmeier–Haack conditions lead principally to the 5-formyl derivative.[448] A comparison of these

TABLE 3.4.21. ACYLPYRROLES OBTAINED FROM LEWIS ACID-CATALYZED FRIEDEL–CRAFTS REACTIONS

R^1	R^2	R^3	R^4	R^5	Yield (%)	Type[a]	Ref.
H	H	2,6-diMeOCOPh	H	H	4M	D	410
H	H	CHO	H	COCOOEt	0.4	A	260
H	2,6-di$MeOC_6H_3CO$	H	H	H	52M	D	410
H	2,6-di$MeOC_6H_3CO$	COOEt	Me	H	85	D	411
H	2,6-di$MeOC_6H_3CO$	COOMe	Ph	H	80	D	411
H	2,6-di$MeOC_6H_3CO$	Me	H	H	15 M	D	411
H	COMe	H	H	H	34	F	315
H	COMe	Me	Me	$COOCH_2Ph$	20	D	439
H	COPh	H	NO_2	H	41	A	504
H	COPh	Me	Me	COOEt	57	E	413
H	CHO	H	H	COCOOEt	1	A	260
H	CHO	H	$CO(CH_2)_2CHMe_2$	H	NY	A	409
H	CHO	H	COMe	H	22	A	103
H	CHO	H	COMe	H	77	A	544
H	CHO	H	COMe	H	80	A	358
H	CHO	H	COPh	H	55	A	358
H	CHO	H	CHO	H	40	A	358
H	CHO	H	$COCHMe(CH_2)_3CHMe(CH_2)_2CH_3$	H	NY	A	409
H	CHO	H	COCOOEt	H	69	A	260
H	CHO	H	$COC_{15}H_{31}$	H	NY	A	409
H	CHO	H	COOMe	H	80	A	358
H	CHO	H	COSEt	H	62	A	358
H	CN	H	COMe	H	71	A	103
H	CN	H	$COCCl_3$	H	48	A	407
H	CN	H	COOMe	H	84cr	A	407
H	CN	H	COSMe	H	71	A	407
H	$COCCl_3$	H	COMe	H	94	A	406
H	COEt	H	H	H	54	F	315
H	$COOCH_2Ph$	Me	Me	COMe	NY	D	531
H	COOEt	Me	Me	COMe	60	A	531
H	COOEt	Me	Me	COPh	53	A	531

H	COOMe	H	H	COMe	7.6M	A	103
H	COOMe	H	COMe	H	70M	A	103
H	COOMe	H	COPh	H	48	A	102
H	COOMe	H	$COCCl_3$	H	78	A	407
H	COOMe	H	COCOOEt	H	45	A	260
H	COOMe	Me	Me	COMe	NY	A	543
H	COC_5H_{11}	H	H	H	47	F	315
H	COPr	H	H	H	56	F	315
H	COSEt	H	COMe	H	54	A	441
H	COSEt	H	COPh	H	56	A	102
H	CO*i*-Bu	H	H	H	41	F	315
H	Me	3-$NO_2C_6H_4CO$	H	Me	52	B	416
H	Me	4-MeC_6H_4CO	H	Me	NY	B	416
H	Me	$CO(CH_2)_2COOH$	H	Me	37	B	418
H	Me	$CO(CH_2)_2COOH$	H	Ph	NY	B	418
H	Me	$CO(CH_2)_3CH_3$	H	COOEt	NY	A	527
H	Me	$CO(CH_2)_3Cl$	Me	COOEt	82	A	545
H	Me	$CO(CH_2)_2Ph$	Me	COOEt	92.5	D	546
H	Me	$COCH_2COOMe$	Me	COOEt	65	D	443
H	Me	COEt	Me	COOEt	NY	A	404
H	Me	COOEt	H	COMe	NY	A	404
H	Me	COOEt	Me	COEt	NY	A	404
H	Me	Me	COMe	COOEt	90	D	546
H	Me	Me	COMe	Me	NY	A	404
H	Me	Me	$CO(CH_2)_3Cl$	COOEt	55	A	545
H	Me	Me	COEt	Me	NY	A	404
H	NO_2	H	COPh	H	28.5	A	504
$(CH_2)_2CN$	Me	COMe	Me	COOEt	28	D	186
$(CH_2)_2CONH_2$	Me	COMe	Me	COOEt	NY	D	186
CH_2Ph	2-$COOHC_6H_4CO$	H	H	H	75	E	195
Me	H	$CO(CH_2)_3COOMe$	H	H	22M	A	428
Me	4,6-diCltriazin-2-yl	H	COMe	H	81	D	28
Me	4-ClC_6H_4CO	H	H	H	20	A	436
Me	4-ClC_6H_4CO	H	4-ClC_6H_4CO	H	12	A	436

TABLE 3.4.21. (*Contd.*)

R^1	R^2	R^3	R^4	R^5	Yield (%)	Type[a]	Ref.
Me	4-MeC_6H_4	COMe	H	H	60	A	377
Me	COMe	H	H	H	28	B	417
Me	COMe	H	H	H	30	B	191
Me	COMe	H	H	H	31	C	547
Me	COMe	H	H	H	40	E	191
Me	COMe	H	NO_2	H	60	B	191
Me	CHO	H	COMe	H	78	A	358
Me	CHO	H	COMe	H	83	A	358
Me	CHO	H	CHO	H	61	A	358
Me	CH_2CN	H	H	4-ClC_6H_4CO	21M	A	548
Me	CH_2CN	H	H	4-MeC_6H_4CO	25M	A	548
Me	CH_2CN	H	4-ClC_6H_4CO	H	7.4M	A	548
Me	CH_2CN	H	4-MeC_6H_4CO	H	6.5M	A	548
Me	CH_2COOMe	H	H	4-MeC_6H_4CO	15	D	328
Me	$CO(CH_2)_3COOMe$	H	H	H	51M	A	428
Me	Me	4-ClC_6H_4CO	H	Me	15	A	436
Me	NO_2	H	COMe	H	52	B	191
Ph	COMe	H	H	H	16	E	414
Ph	Me	4-$MeOC_6H_4CO$	H	Me	15M	A	405
Ph	Me	4-$MeOC_6H_4CO$	H	Me	27M	D	405
Ph	Me	4-$MeOC_6H_4CO$	4-$MeOC_6H_4CO$	Me	M	A, D	405
Ph	Me	COMe	COMe	Me	52	D, (40)A	405
Ph	Me	COPh	H	Me	46M	D	405
Ph	Me	COPh	COPh	Me	22 M	D, (38M)A	405
Ph	Me	COEt	COEt	Me	84	D, (23)A	405
Ph	Ph	H	COMe	Me	59	D, (52M)A	405
Ph	Ph	H	COPh	Me	49M	D, (39)A	405
Ph	Ph	COPh	COPh	Me	32M	D	405
Ph	Ph	COMe	COMe	Me	< 10	A	405
SO_2Ph	H	2-MeC_6H_4CO	H	H	NY	A	429

SO_2Ph	H	4-$MeOC_6H_4CO$	H	H	NY	A	429
SO_2Ph	H	COMe	H	H	99cr	A	408
SO_2Ph	H	COPh	H	H	99cr	A	408
SO_2Ph	H	COPh	H	H	NY	A	429
SO_2Ph	H	$CO(CH_2)_2COOH$	H	H	87Mcr	A	408
SO_2Ph	H	$CO(CH_2)_2COOMe$	H	H	98cr	A	408
SO_2Ph	H	$CO(CH_2)_3Cl$	H	H	92cr	A	408
SO_2Ph	H	$COCH_2Ph$	H	H	62	A	192
SO_2Ph	H	$COCHCl_2$	H	H	NYM	A	433
SO_2Ph	H	$COCH_2Cl$	H	H	NYM	A	433
SO_2Ph	H	$COCCl_3$	H	H	NYM	A	433
SO_2Ph	H	$COC_{15}H_{31}$	H	H	77	A	192
SO_2Ph	H	COSEt	H	H	65	A	98
SO_2Ph	H	COcyclopropanyl	H	H	99 cr	A	408
SO_2Ph	CO(1-SO_2Phpyrrol-3-yl)	H	H	H	37	A	408
SO_2Ph	COMe	H	H	H	83M	B	408
SO_2Ph	COMe	H	H	H	NY	A	98
SO_2Ph	COPh	H	H	H	75	B	408
SO_2Ph	$CO(CH_2)_2COOMe$	H	H	H	42M	B	408
SO_2Ph	$CO(CH_2)_3Cl$	H	H	H	56M	B	408
SO_2Ph	$COCHCl_2$	H	H	H	NYM	A	433
SO_2Ph	$COCH_2Cl$	H	H	H	NYM	A	433
SO_2Ph	$COCCl_3$	H	H	H	NYM	A	433
SO_2Ph	COCl	H	H	H	96cr	A	408
SO_2Ph	COcyclopropyl	H	H	H	69	B	408
SO_2Ph)	CN	H	H	H	99	A	98
t-$BuMe_2Si$	H	COMe	H	H	50	A	435
t-$BuMe_2Si$	H	COPh	H	H	46M	A	435
t-$BuMe_2Si$	H	$COCH_2Ph$	H	H	63M	A	435
Tosyl	$CO(CH_2)_2COOEt$	H	H	H	80	B	549

[a]A = $AlCl_3$; B = BF_3/Et_2O; C = $MgBr_2$; D = $SnCl_4$; E = $ZnCl_2$; F = $Si(OCOR)_4$.

TABLE 3.4.22. ACYLPYRROLES OBTAINED FROM BRØNSTED ACID-CATALYZED FRIEDEL–CRAFTS REACTIONS

R^1	R^2	R^3	R^4	R^5	Yield (%)	Type[a]	Ref.
H	COMe	H	H	H	48	A	421
H	COMe	H	H	COMe	c.19M	B	304
H	COMe	H	COMe	H	c.46M	B	304
H	CHO	Me	$(CH_2)_2COOEt$	Me	28	B	356
H	CHO	Me	$COOCH_2Ph$	Me	41	B	356
H	CHO	Me	COOEt	Me	48	B	356
H	CHO	Me	Me	Me	20	B	356
H	CN	H	H	COMe	20	A	335
H	CN	H	COMe	H	NY	A	335
H	COBu	H	H	H	35	A	421
H	$COCF_3$	H	H	H	6	B	304
H	COC_5H_{11}	H	H	H	32	A	421
H	COEt	H	H	H	55.3	A	421
H	$COOCH_2Ph$	Me	CHO	Me	82	B	356
H	COOEt	Me	CHO	Me	83	B	356
H	COO*t*-Bu	Me	CHO	Me	81	B	356
H	COPr	H	H	H	50	A	421
H	COSEt	H	H	COMe	NY	A	441
H	CO*i*-Bu	H	H	H	35	A	421

H	Me	H	Me	COMe	48	A	421
H	Me	H	Me	COEt	72	A	421
H	Me	2-$COOHC_6H_4CO$	H	Me	60	C	444
H	Me	COMe	H	COSMe	NY	A	441
H	Me	COMe	Me	COSEt	c.100	A	368
H	Me	COMe	OCOMe	COOEt	Quant.	D	395
H	Me	COOEt	Me	CH=NPh·HCl	NY	E	121
H	Me	COOEt	OH	2-$COOHC_6H_4CO$	80	C	395
2-NH_2Ph	Me	$COCF_3$	H	Me	20	B	550
CH_2Ph	COMe	H	H	H	34	E	422
Me	H	CHO	H	H	35	F	438
Me	COMe	H	H	H	40	A	421
Me	COEt	H	H	H	50	A	421
Me	Me	COOEt	OCOMe	COMe	81	A	264
Ph	COMe	H	H	H	77	A	421
Ph	COEt	H	H	H	56	A	421

[a] A = $HClO_4$ or $MgClO_4$; B = CF_3COOH or anhydride; C = CH_3COOH; D = H_2SO_4 or H_2SO_3; E = HI/Br/Cl; F = triflic acid.

two formylation procedures,[449] using titanium(IV) chloride as the catalyst for both reactions, showed that, when 1-(3-methylbutyl)pyrrole was used as the substrate, the reaction with methyl orthoformate gave more 2- than 3-formylation products (80:10), while the reaction with dichloromethyl ethyl ether gave more 3- than 2-formylation (50:10). Typical examples of Friedel–Crafts acylations are to be found in Tables 3.4.21 and 3.4.22, and examples of the formylation reaction are given in Table 3.4.23.

TABLE 3.4.23. FORMYLPYRROLES OBTAINED UNDER LEWIS ACID-CATALYZED CONDITIONS

R^1	R^2	R^3	R^4	R^5	Yield (%)	Type[a]	Ref.
H	CHO	H	CHO	H	43	A	409
H	CN	H	CHO	H	74	A	407
H	$COCCl_3$	H	CHO	H	3	A	406
H	$COCCl_3$	H	CHO	H	97cr	A	319
H	COOEt	H	H	CHO	1.5M	A	446
H	COOEt	H	CHO	H	82M	A	446
H	COOMe	H	CHO	H	86	A	498
H	COSEt	H	H	CHO	5M	A	446
H	COSEt	H	CHO	H	54	A	441
H	COSEt	H	CHO	H	83M	A	446
H	COSEt	H	CHO	H	c.88	A	447
CH(*i*-Bu)COOMe	H	CHO	H	H	10M[b]	C	449
CH(*i*-Bu)COOMe	H	CHO	H	H	50M[c]	C	449
CH(*i*-Bu)COOMe	CHO	H	H	H	10M[c]	C	449
CH(*i*-Bu)COOMe	CHO	H	H	H	80M[b]	C	449
Me	CHO	H	CHO	H	26	A	447
Me	$COCCl_3$	H	CHO	H	91	A	319
Me	$COOCH_2Ph$	H	CHO	H	98M	A	319
Me	COOMe	H	CHO	H	89	A	319
SO_2Ph	CHO	H	H	H	99cr	A	408

[a] A = $AlCl_3$; B = BF_3/Et_2O; C = $TiCl_4$.
[b] Formylating agent = $HC(OMe)_3$.
[c] Formylating agent = $CHCl_2OCH_3$.

3.4.3.4. Acylation of the Pyrrolyl Anion or Its Equivalent

3.4.3.4.1. Acylation of the Pyrrolyl Grignard Reagent

The first reactions carried out by Oddo on pyrrolylmagnesium iodide[140] were with carbon dioxide and ethyl chloroformate to give the 2-carboxylic acid and its corresponding ethyl ester, and he reported the separation of a heavy colored oil from the ether layer during the preparation of the pyrrolyl Grignard reagent. His next papers[450,451] reported acylation reactions with acyl and aroyl halides,

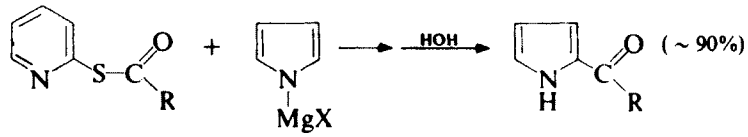
all of which gave 2-substitution in moderate to excellent yields. Not long after, Chelintzev, who had found[452,453] that the reaction with esters also gave 2-acylpyrroles, reported[454] the isolation of the 1-ethoxycarbonylpyrrole and, as a by-product, the 1,1′-dipyrroly ketone from the reaction of the pyrrolyl Grignard with ethyl carbonate.

For several years chloroformate esters were used to introduce a *C*-alkoxycarbonyl group,[455–457] but it was then found[458] that the reaction also gave both 1- and some 1,2-substitution products and that alternate additions of ethylmagnesium halide and ethyl chloroformate (in molar excess) gave 65% of the 1,2-diester, 26% of the 1-ester, and only 1.5% of the 2-ester. The presence of all three compounds in the reaction product was confirmed,[459] and, in addition, some 3-ester and 1,3-diester were also obtained.[99,341] Later, the 2,2′-dipyrrolyl ketone and the 2,1′-dipyrrolyl ketone were also detected.[103] It is probable that the hydrolytic workup used in the earlier work caused the cleavage of the 1-alkoxycarbonyl group and created the controversial reports.

It was subsequently established that hardly any 1-substitution occurred in the reaction between the pyrrolyl Grignard and *S*-ethyl chlorothioformate[441] and a number of thio- and thiolcarbonate esters,[460] although reaction with the carbonate ester itself gave almost exclusively the 1-ester. In order to determine whether migration was taking place from the 1 position to the 2 position in the Grignard-ester reactions, deuterium labelling experiments were carried out.[461] The reaction between pyrrolyl-d_4 magnesium bromide and methyl pyrrole-1-carboxylate as well as between pyrrolylmagnesium bromide and methyl pyrrole-d_4-1-carboxylate, both gave, as the main product, 1,2′-dipyrrolyl ketone, which on examination by mass spectrometry established that the ester probably reacted directly at the 2 position of the pyrrolyl Grignard, rather than at position 1 followed by rearrangement.

As demonstrated in Section 3.4.2.4, it is possible to rationalize alkylation and hydroxyalkylation reaction through the use of the principle of hard and soft acids and bases. This method has been applied[146] to the acylation reactions discussed above, together with other available data, under standardized conditions using the pyrrolyl Grignard reagent and a number of other metal salts. The acylating agent was also varied, as was the solvent, and a complexing agent was either present or absent.

As with alkylation reactions, the nitrogen atom was the harder centre of the pyrrolyl ambident anion bonded to the hard halomagnesium ion. The carbonyl carbon atom is also hard and, if two oxygen atoms are also bonded to that carbon atom as in a carbonate ester, it will displace the magnesium and give 1-substitution. One or more hydrogen, carbon, chlorine, or sulfur atoms directly bonded to the carbonyl carbon atom softens it and increases *C*-substitution until, eventually, no 1-substitution is observed.[146] Similar results were obtained with the Grignard addition to the cyano and cyanate groups. Recently, advantage was taken[462,463] of the very carbon-selective acylation reactions, provided by the especially soft carbonyl of the *S*-alkyl thioesters to prepare ketones (Scheme 4.49).



Scheme 4.49

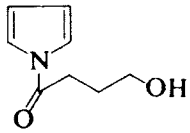
Alkali metal ions are softer than magnesium, and so 1-substitution takes place between most acylating agents and these types of pyrrole salt. One apparent exception[464] is the reaction of pyrrole with carbon monoxide at 60°C under 50-bar pressure. It seems likely that the kinetic reaction on nitrogen is reversible and the thermodynamic carbon-substituted product is obtained. In the related Kolbe–Schmidt preparation of pyrrole-2-carboxylic acid (41%), soft carbon dioxide is used with potassium hydrogen carbonate in water at 100°C and 800 psig (pounds per square inch gauge).[465] However, when the hard magnesium methoxide was used as the base, but softened by DMF, the reaction with carbon dioxide gave 23% of the 1-carboxylic acid.[320]

In summary, it can be generalized that the pyrrolyl Grignard reagent is generally acylated at a carbon atom and alkali metal salts are acylated on the nitrogen atom. As for alkylation reactions, however, an alteration in other parameters can change the results.[146] Thus, a more strongly coordinating solvent such as TMED, HMPA, or DMF can separate the Grignard covalent bond, or ion pair, sufficiently to increase substantially 1-substitution of the ring. The magnesium is softened by a softer halide, so more 2-substitution occurs when, for example, *S*-ethyl chlorothioformate reacts with pyrrolylmagnesium iodide than with the corresponding chloride or bromide.

As expected, groups already present on the ring help to stabilize or destabilize the pyrrolyl anion. The 2-methyl group destabilized it, and, indeed, substitution took place only at the 5 position when ethyl chloroformate reacted with 2-methylpyrrolylmagnesium bromide.[21] The Grignard reagent from ethyl pyrrole-2-carboxylate, on the other hand, gave diethyl pyrrole-1,2-dicarboxylate with ethyl chloroformate.[146]

A comparison of leaving groups in Grignard acylations with respect to the 2-/3-substitution ratio has also been made.[466] The more basic (i.e., poorer) the leaving group, the less electrophilic is the carbonyl carbon atom and, hence, the more selective it is in the acylation reaction. Thus, acylation of pyrrole showed decreasing amounts of 3-substitution in the following order of acylating agents: $CH_3COCl \simeq (CH_3CO)_2O \gg CH_3COOEt$. Several authors[184,467–469] have reported mixtures of 2- and 3-acyl products from acylation with acid chloride with a 2-/3-isomer ratio in the range 5:1 to 7:1. Use of the formate esters provided a poor yield of the 2-aldehyde.[453,470]

Predictably, lactones acylated the pyrrolyl Grignard reagent (see Table 3.4.24),[471,472] (but see Scheme 4.23, where an analogous Friedel–Crafts reaction leads to alkylation of the pyrrole ring). Reaction at 25°C with the lactone of 4-hydroxybutanoic acid formed the hydroxyamide **4.78**, but, with an excess of the pyrrolyl Grignard at 100–110°C, the 2-substituted product **4.79**



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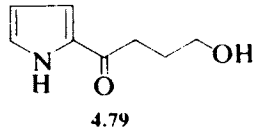


4.79

was formed;[471] yields of each product were about 90%.[472] This reaction has been applied to the synthesis of the ionophore antibiotic X14547A.[471,472] However, reaction with the lactone of 4-hydroxypentanoic acid, after refluxing in ether for 1 h, gave only the 2-acylated product in 71% yield.[473,474] Thus, any rearrangement from the 1 position to the 2 position must take place with considerable ease. It is conceivable that lactones tend to complex and soften the magnesium, thereby separating the ion pair before reaction on the 1 position.

TABLE 3.4.24. REPRESENTATIVE EXAMPLES OF ACYLPYRROLES OBTAINED FROM PYRROLYL GRIGNARD REAGENTS

R^1	R^2	R^3	R^4	R^5	Yield (%)	Ref.
H	H	COMe	H	H	4M	146
H	H	COMe	H	H	5M	468
H	H	COEt	H	H	4M	468
H	H	COEt	H	H	c.25M	467
H	H	COOMe	H	H	SomeM	341
H	H	CO*t*-Bu	H	H	12M	189
H	H	CO*t*-Bu	H	H	12M	469
H	2,6-di$MeOC_6H_3CO$	H	H	H	58	551
H	2-$COOHC_6H_4CO$	H	H	H	30M	195
H	3-$MeOC_6H_4CO$	H	H	H	65	213
H	4-$MeOC_6H_4CO$	H	H	H	44	213
H	COMe	H	H	H	NY	450
H	COMe	H	H	H	31	460
H	COMe	H	H	H	35M	146
H	COMe	H	H	H	36M	468
H	COMe	H	H	H	40	552
H	COMe	H	H	H	54	213
H	COMe	Me	Me	H	56	543
H	COMe	Ph	H	Me	75	553
H	COPh	H	H	H	52	450
H	COPh	H	H	H	70	554
H	COPh	H	H	H	75	213
H	COPh	H	H	H	91(93.4)[a]	463
H	COPh	H	H	H	92	462
H	COPh	Ph	H	Me	80	553
H	CHO	H	H	H	20	453
H	CHO	H	H	H	NY	470
H	2-$COOHC_6H_4CO$	H	H	H	38	445
H	CO(2-Clpyrid-3-yl)	H	H	H	65	555
H	$CO(CH_2)_2CHOHMe$	H	H	Bu	NY	473
H	$CO(CH_2)_3SPh$	H	H	H	95	462
H	$CO(CH_2)_7Me$	H	H	H	85	521

TABLE 3.4.24. (*Contd.*)

R^1	R^2	R^3	R^4	R^5	Yield (%)	Ref.
H	CO(furan-2-yl)	H	H	H	90	462
H	COpyridin-3-yl	H	H	H	41	213
H	COpyridin-4-yl	H	H	H	NY	213
H	COpyrrol-2-yl	H	H	H	83	146
H	COthien-2-yl	H	H	H	89	462
H	COBu	H	H	H	NY	450
H	COCHClMe	H	H	H	NY	467
H	$COCHEt_2$	H	H	H	61	213
H	COCH(tetrahydropyran-2-yl)Me	H	H	H	c.80	463
H	$COCH_2CH=CHEt$	H	H	H	90	462
H	$COCH_2$cyclohexyl	H	H	H	94.4(76.7)[a]	463
H	COCOpyrrol-2-yl	H	H	H	NY	451
H	COCOOEt	H	H	H	22M	146
H	COEt	H	H	H	NY	450
H	COEt	H	H	H	19M	468
H	COEt	H	H	H	c.25M	467
H	CONHPh	H	H	H	17M NI	196
H	COOH	H	H	H	20–30	140
H	COOEt	H	H	H	1.5M	458
H	COOEt	H	H	H	24	455
H	COOEt	H	H	H	44M	146
H	COOEt	H	*i*-Pr	H	40M	556
H	COOMe	H	H	H	18M	341
H	COOMe	H	H	H	25	99
H	COOMe	H	H	H	5.6M	459
H	COOMe	H	H	*i*-Pr	NY	99
H	COOMe	Me	Me	COMe	NY	543
H	COPr	H	H	H	NY	450
H	COSEt	H	H	H	42M	146
H	COSEt	H	H	H	56	441
H	COSEt	H	H	H	62	460
H	CO*t*-Bu	H	H	H	71M	189
H	CO*t*-Bu	H	H	H	71M	469
H	COcyclohexyl	H	H	H	92.7(71.3)[a]	463
H	CO*i*-Bu	H	H	H	NY	528
H	CO*i*-Bu	H	Me	H	17MGC	528
H	CO*i*-Bu	H	Me	H	17MGC	528
H	CO*i*-Bu	Me	H	H	33MGC	528
H	$CSNMe_2$	H	H	H	38	460
H	CSOEt	H	H	H	15	460
H	CSSEt	H	H	H	43	460
H	Me	H	H	COOEt	35	527
H	Me	H	Me	$COCHPh_2$	NY	330
H	Me	H	Me	COOH	73	457
H	Me	4-FC_6H_4CO	H	Me	88	416
H	Me	COMe	H	Ph	50M	553
H	Me	COPh	H	Me	NY	416
H	Me	COPh	H	Ph	58	553
H	Me	$COCH_2COOEt$	H	Me	68	457

TABLE 3.4.24. (*Contd.*)

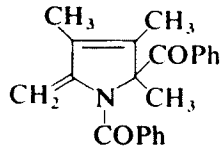
R^1	R^2	R^3	R^4	R^5	Yield (%)	Ref.
H	Me	COOH	H	Me	68	457
H	Me	COOEt	H	CONHPh	41	80
H	Me	COOEt	H	Me	71	457
H	Me	COOEt	Me	CH_2Ph	32	80
H	Me	COOEt	Me	CONHPh	24	80
H	Ph	COMe	H	Me	20M	553
H	Ph	COPh	H	Me	24	553
H	SMe	H	H	$COCHCl_2$	56	22
COpyrrol-2-yl	H	H	H	H	27	461
COpyrrol-2-yl	H	H	H	H	58–60	460
COMe	H	H	H	H	1M	146
SEM	H	H	H	H	70	206
$COCH_2COMe$	H	H	H	H	80M	146
COCOOEt	H	H	H	H	19M	146
CONHPh	H	H	H	H	67M NI	196
COOEt	H	H	H	H	19M	146
COOEt	H	H	H	H	26.4M	458
COOEt	H	H	H	H	46	460
COOEt	H	H	H	H	NY	454
COOEt	COOEt	H	H	H	65M	458
COOMe	H	H	H	H	20M	459
COOMe	H	H	H	H	42	460
COOMe	H	COOMe	H	H	2.5M	341
COOMe	COOMe	H	H	H	64M	459
COSEt	H	H	H	H	3M	146
Me	COpyrrol-2-yl	H	H	H	45	557
NMe_2	COCH(Me)cyclohexyl	H	H	H	84	244

[a]From reaction with RCOSR′ or (in parenthesis) RCOSeR′.

3.4.3.4.2. Acylation of Other Pyrrolyl Metal Salts

As mentioned in Section 3.4.2.4.1, 1-tributylstannylpyrrole, with its hard tin(IV), was alkylated and benzylated on the pyrrolyl carbon atom. The analogous acetylation affords the 2-acetyl and 1-acetylpyrrole in 43 and 2% yield, respectively.[163] On the other hand, the thallium(I) salt of pyrrole has a soft metal, and an excellent yield was obtained in the 1-acetylation of the thallium(I) salt of 2-formylpyrrole.[310]

The Schotten–Baumann reaction uses aqueous basic conditions and led, where this was possible, to 2-substitution in low to moderate yields on most alkylpyrroles;[475,476] 1-alkylpyrroles failed to react under these conditions. Possibly the 2-benzoylpyrrole is the thermodynamic product under these reaction conditions, although the carbonyl carbon atom of aroyl halides should be softened by its substituents. The Schotten–Baumann benzoylation of 2,3,4,5-tetramethylpyrrole afforded a compound whose structure was eventually established as **4.80**.[477] Other tetraalkylpyrroles behaved similarly.[478]



4.80

The "hardness" of the carbonyl carbon atom in the usual acylating agents makes it possible to obtain 1-acylation through the use of even mildly basic conditions (see Table 3.4.25) when the countercation is soft. Most authors have tended, however, to choose strong bases such as sodium hydride[209,257,271,479,480] mainly in THF or DMF or the isolated potassium salt in toluene, ether, or similar solvents,[3,80,413,475,481-483] to ensure the maximum yield of 1-acylation product. A comparison has been made of *N*- versus *C*-substitution for the alkali metal salts of pyrrole reacting with ethyl chloroformate with respect to results of the corresponding reaction using the Grignard reagent.[146] Weaker bases such as sodium and potassium carbonate and sodium acetate may give 1-,[80] 2-,[484] or 1,2-diacylation,[395] depending on the conditions used.

Among the many groups that have been used to block the 1 position of the pyrrole ring, the *tert*-butyloxycarbonyl (BOC) has been put in place using potassium *tert*-butoxide and di-*tert*-butyl carbonate,[485] sodium hydride/THF/phenyl *tert*-butyl carbonate,[209] pyrrolylpotassium/THF/*tert*-butyl azidoformate,[245,486] and di-*tert*-butyl carbonate/4-dimethylaminopyridine.[487]

Acylation has also been accomplished with the aid of phase-transfer reagents.[260,261] As discussed in Section 3.4.2.4.2, these reagents are very soft and 1-acylpyrroles were the exclusive products.

As mentioned in Section 3.4.3.1, pyrrole reacts with isocyanates to form 2-(*N*-substituted carboxamides). The pyrrolyl Grignard reagent in THF reacted with phenyl isocyanate, affording an unseparated 4:1 mixture of 1- and 2-carboxanilides in 67% overall yield,[196] whereas pyrrolylpotassium in THF or toluene gave 84% of the 1-isomer. Ethoxycarbonyl isocyanate behaved similarly with pyrrolylpotassium.[337] Grignard reagents, derived from pyrroles with electron-withdrawing groups, gave *C*-substitution products in low yields with phenyl isocyanate.[80] Recently, pyrrole has been converted to the (η^5-pyrrolyl)$(Ph_3)_2ReH_2$ complex, which reacted with acetyl and benzoyl chlorides. The acylated examples were easily converted to high yields of the 1-acylpyrroles.[488]

3.4.3.4.3. Acylation of 1-Substituted Pyrroles

As outlined in Section 3.4.2.4.4, 1-substituted pyrroles generally are lithiated at the 2 position, with *n*-butyllithium as the customary reagent,[262,414] and their dilithiation[414] has also been explored.[489-492] Analysis of the mono- and dilithiation reaction was accomplished by carbonation, followed by methylation with diazomethane, and proportions of the esters have been determined by NMR

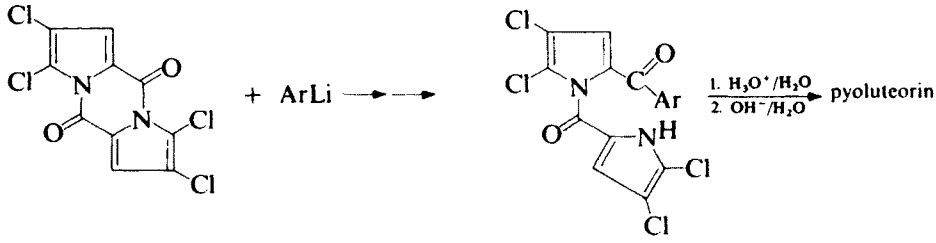
TABLE 3.4.25. ACYLPYRROLES OBTAINED UNDER WEAKLY BASIC CONDITIONS

R^1	R^2	R^3	R^4	R^5	Yield (%)	Ref.
H	H	2-NO_2-3-ClC_6H_3	H	COOMe	63crM	23
H	COPh	H	Me	Me	NY	413[a]
H	$COCH_2COMe$	H	H	H	36	251
H	$COCCl_3$	H	H	H	80	484
H	$COCF_3$	H	H	H	89	498
H	COCOpyrrol-2-yl	H	H	H	53	499
H	COCOOEt	H	H	H	64	240
H	COCOOEt	H	H	H	83	499
H	COCOOEt	H	H	H	96	499
H	COCOOEt	Me	COOEt	Me	92	499
H	COOEt	2-NO_2-3-ClC_6H_3	H	Me	NY	393
H	Me	H	H	COOEt	80–85	497
H	Me	H	H	COO*t*-Bu	75	497
H	Me	2-NO_2-3-ClC_6H_3	H	COOMe	80	23
COMe	H	H	H	H	80	303
COMe	CHO	H	H	H	80	500
COMe	CHO	COOEt	H	H	73	500
COMe	CN	H	H	H	35	335
COMe	Me	COOEt	H	H	91	500
COO*t*-Bu	$COCCl_3$	H	H	H	81	501
COO*t*-Bu	$COOCH_2Ph$	H	NHCOO*t*-Bu	H	80	501
COO*t*-Bu	$COOCH_2Ph$	H	NO_2	H	87	501
COO*t*-Bu	COOEt	H	H	H	85	501
COO*t*-Bu	COOEt	H	H	Me	94	501
COO*t*-Bu	COOEt	Me	H	Me	94	501
COO*t*-Bu	COOEt	Me	COOEt	Me	81	501
COO*t*-Bu	H	H	H	H	81	501
Me	COCOOMe	H	H	H	30	320
Me	Me	COPh	H	CH=C(Ph)(OCOPh)	12	496
SEM	COCO(1-SEMpyrrol-2-yl)	H	H	H	75	290
TMS	H	COCOOEt	H	H	70	248
COO*t*Bu	CH_2PPh_3I	H	H	H	97	68

[a] See Ref. 476 for a table of benzoylations using tertiary amines.

spectral studies. The addition of TMED has a very pronounced accelerating effect on the reaction and yields entirely 2-substitution products at room temperature and over the short term, but leads mainly to 2- and 2,5-disubstitution in boiling hexane. More 2,4-disubstitution of the ring took place in prolonged reactions and in the absence of TMED.[490] Increasing the bulk of the 1-substituent decreased the overall yield and increased the 2,4-/2,5-disubstitution ratio. As might be expected, metallation was aided by a solvent change from hexane to ethers and by the addition of complexing agents.[491] The ease of metallation was also increased by a change from *n*-butyllithium to *tert*-butyllithium. When 1-trimethylsilylpyrrole was treated with *n*-butyllithium in hexane and worked up and analyzed as before, the trimethylsilyl group was lost and the 2-ester consistently predominated.[492] With time, and excess of *n*-butyllithium, 2,5-disubstitution, and 3-substitution increases. A switch from hexane to ether or addition of TMED afforded only the 1-ester. All overall yields in these reactions were about 50% except at very low temperature. Esters possessing the 1-trimethylsilyl group were not detected.

Other 1-substituted pyrroles were lithiated and reacted with a variety of acylating agents[206,207,245,414] to give 2-substituted products. In a different approach to acylation (Scheme 4.50),[493] arylation of the pyrrocol, followed by hydrolysis, gives pyoluteorin.



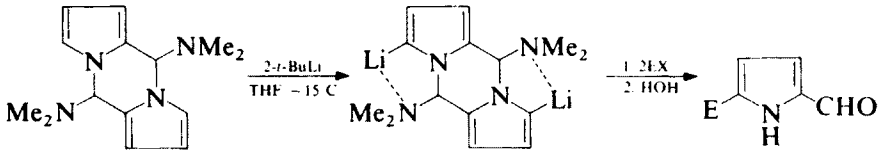
Scheme 4.50

The possibility of directed metallation to the 3 position has been explored using 1-methyl-2-(4,4-dimethyloxazolin-2-yl)pyrrole.[247] In a preparative experiment, its carbonation led to a mixture of the 3- and 5-carboxylic acids in 56 and 9% yield, respectively. The directed palladation of 1-benzenesulfonyl-2-dimethylaminomethylpyrrole has been effected using lithium tetrachloropalladate(II)[246] and, when followed by treatment with carbon monoxide in methanol, gave the 3-methoxycarbonyl derivative in 63% yield.

The discovery that the 1-triisopropylsilyl group directed electrophiles preferentially into the 3 position[248] permitted synthesis of the 3-bromo derivative and its subsequent conversion into 1-triisopropylsilylpyrrol-3-yllithium, from which several acylated products were obtained.[249,250] These included the 3-carboxylic acid, the 3-glyoxylic ester, the 3-aldehyde, the 3-acetyl, and the 3-benzoyl derivatives. In addition, the analogous availability of the 3,4-dibromo derivative

enabled two successive lithium–bromine interchanges to be carried out, and a subsequent sequence of reactions led to verrucarin E.[249]

An interesting and potentially valuable "one-pot" directed metallation approach is outlined in Scheme 4.51.[494] The available azafulvene dimer is used to introduce electrophiles into the 5 position of the pyrrole ring, and subsequent hydrolysis yields the 5-substituted-2-aldehydes in good yield. Use of the azafulvene dimer from 4-bromo-2-formylpyrrole enables lithium-bromine interchange. This is followed by acylation or alkylation to afford, on hydrolysis, 4-substituted-2-formylpyrroles in good yield.[495]



Scheme 4.51

3.4.3.4.4. Acylation of Pyrroles Using Amines

When tertiary amines are used to catalyze the acylation of pyrroles, the product is usually one of *C*-acylation, often in very good yield. The combination of reagents is generally triethylamine/acid chloride,[320,335,476,496] *N*,*N*-dimethylaniline/acid chloride,[23,393,497,498] and pyridine or 2,6-lutidine/acid chloride.[240,484,499] These reactions should be compared with the behavior reported in Section 3.4.2.2.2, in which the pyrrole ring reacts with the π-deficient heteroaromatic ring on treatment with ethyl chloroformate/pyridine.[80,81] Acylation reactions have been carried out using phosgene or oxalyl chloride, followed by treatment with an alcohol to afford the corresponding ester.

When the acid anhydride was used with a tertiary amine, however, the product was the 1-acyl derivative. Presumably, the conjugate anion from the anhydride removes the 1-proton, enabling 1-acylation. In many reactions, triethylamine has been used,[303,335] but in more recent work it has been replaced by 4-dimethylaminopyridine.[68,500,501] A similar reaction has employed 1-acetylimidazole and proved autocatalytic. The released imidazole aided the deprotonation to afford an almost quantitative yield of 1-acetylpyrrole.[502] This observation should be compared with the apparently analogous reaction with *N*-acetylbenzimidazole[85] (see Section 3.4.2.1.2).

3.4.4. References

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3.5. OXIDATION AND REDUCTION OF THE PYRROLE RING

Albert Gossauer and Petr Nesvadba

Institut für Organische Chemie der Universität Freiburg i. Ue. Switzerland

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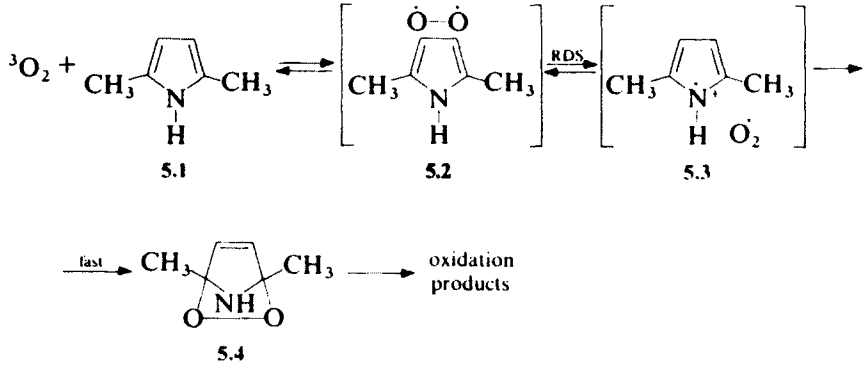
3.5.1. Autoxidation

Although the reaction of pyrroles with singlet oxygen has been studied intensively in the past, there has been relatively little interest in the autoxidation reaction with triplet molecular oxygen.[1–4] Early work showed, that pyrrole, on standing in air and light, autoxidizes to form dark-colored pigments, so-called pyrrole blacks.[5] Ciamician and Silber[6] reported that the autoxidation of pyrrole in water produces large amounts of a black polymer along with a minor quantity of succinimide and an unidentified product with empirical formula $C_{12}H_{14}N_2O_5$.

The first step in the autoxidation of pyrrole involves the formation of a complex between the latter and oxygen. In fact, a new absorption band at 296.5 nm develops in the UV spectrum of pyrrole during its saturation with oxygen. This band disappears again when oxygen is removed by evacuation or

nitrogen purging. (For a review of the oxidation of monocyclic pyrroles, see Ref. 1.) Further spectroscopic evidence for a molecular association complex between oxygen and 2,5-dimethylpyrrole in hexane or dodecane has been presented recently.[7] The formation of this complex seems to be completely reversible. Additionally, gas chromatographic (GC) and nuclear-magnetic resonance (NMR) analyses failed to indicate the development of any significant intermediate product in the oxygenated solutions of 2,5-dimethylpyrrole.

Beaver and co-workers have postulated the mechanism of autoxidation of 2,5-dimethylpyrrole **5.1** based on kinetic measurements.[8,9] As shown in Scheme 5.1, the rate-determining step (RDS) is the electron transfer from the pyrrole nucleus of the molecular association complex **5.2** to the lowest unoccupied molecular orbital (LUMO) of the oxygen atom to form the charge-transfer complex **5.3**, which is postulated to be in equilibrium with an endoperoxide **5.4** of the same type as formed in the photochemical dye-sensitized oxidation of pyrroles (see Section 3.5.2). Such a common intermediate for both sensitized photoxidation and autoxidation could account for the observation that many photochemical oxidations and autoxidations of pyrrole derivatives yield the same type of products.[9]



5.1 **5.2** **5.3** **5.4**

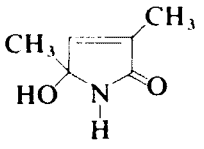
Scheme 5.1

The mechanism depicted in Scheme 5.1 explains qualitatively why electron-rich pyrroles autoxidize much faster than pyrrole itself or than pyrroles substituted with electron-withdrawing groups.[9] Scheme 5.1 accounts also for the observation that there exists a correlation between the pyrrole anodic oxidation potential and the pseudo-first-order rate constant for the autoxidation.[8,9]

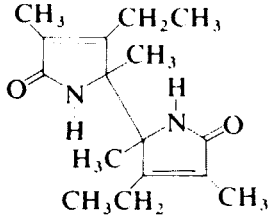
The influence of the solvent on the yield of simple pyrrole autoxidation products was studied by Metzger and Fischer.[10] They found that the best yields are obtained in mixtures of ethanol and diethylether. Acetic anhydride was found to speed up the reaction, probably through a catalytic effect.

The autoxidative reactions are very sensitive to the proton concentration in the reaction medium. They are, in general, accompanied by acid-catalyzed polymerizations under highly acidic conditions. The rate of autoxidation is quite

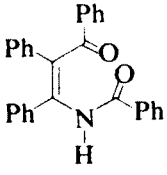
slow under neutral conditions and increases again with increasing pH values.[1-4,11,12] This demonstrates the greater susceptibility to autoxidation of the electron-rich pyrrole anion, formed in basic medium, compared with the neutral species. The same reasons probably account for the easy autoxidation of pyrrole Grignard reagents.[1,13] Hoft and co-workers have studied the autoxidation of some *C*-alkylpyrroles.[14,15] Thus, the autoxidation product of 2,4-dimethylpyrrole in benzene was identified as the hydroxypyrrolinone **5.5**. A similar autoxidation of 3-ethyl-2,4-dimethylpyrrole (kryptopyrrole) gave the dimeric compound **5.6**. The autoxidation of 2,3,4,5-tetraphenylpyrrole in benzene in the presence of potassium hydroxide yielded mainly the ketoamide **5.7** together with minor amounts of the enlactam **5.8**.[16] Smith and Jensen[17,18] have found that *N*-alkylpyrroles react with oxygen much slower than *C*-alkylpyrroles. The reactivity decreases with increasing steric demand of the 1-alkyl substituent.



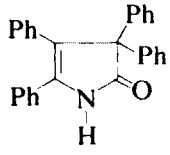
5.5



5.6



5.7



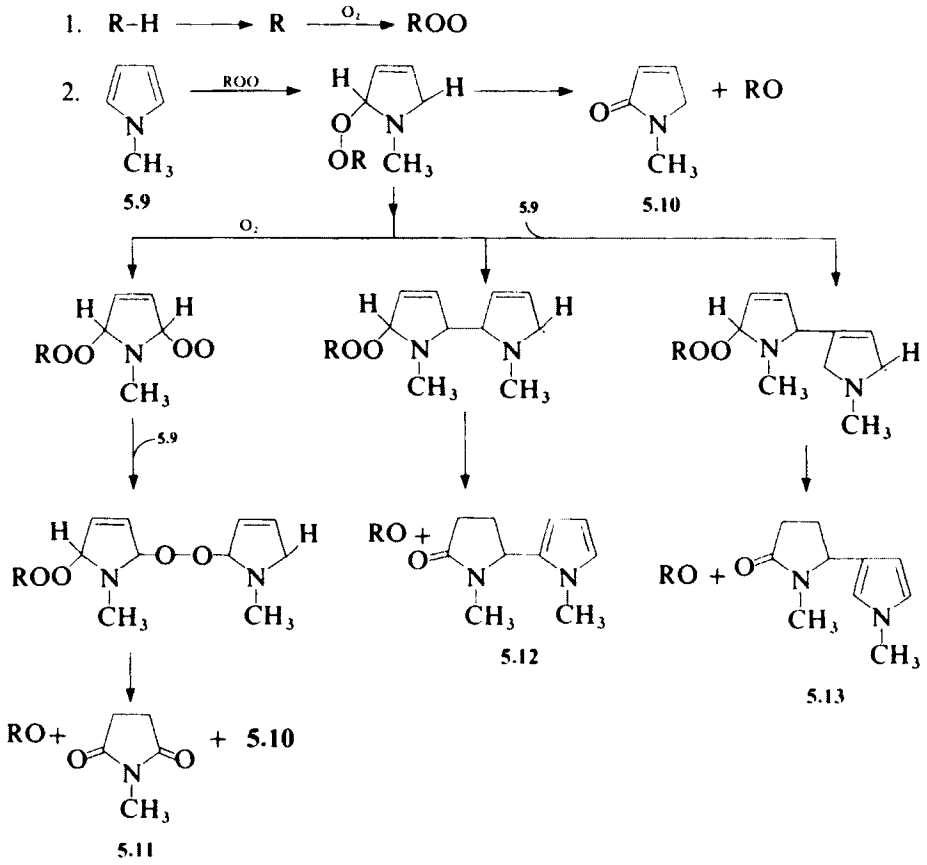
5.8

The experimental results suggested that *N*-alkylpyrroles undergo the reaction with triplet oxygen by a free-radical process. The autoxidation of *N*-alkylpyrroles exhibits, in fact, an induction period during which no oxygen consumption takes place.[17,18]

The mechanistic sequence, as outlined in Scheme 5.2, has been postulated for the formation of the four isolated simple autoxidation products **5.10**–**5.13** obtained from 1-methylpyrrole **5.9**.[18]

Other evidence for the free-radical character of the autoxidation of pyrroles was furnished by the fact that the autoxidation of pyrrole adducts, formed on bovine serum albumin on treatment with 2,5-hexandione, was inhibited by free-radical scavengers (e.g., ascorbic acid). Free-radical initiators, on the other hand, accelerated the autoxidation.[11]

It must be pointed out, however, that the autoxidation of 2,5-dimethylpyrrole is insensitive to the presence of sterically hindered phenols in the reaction



Scheme 5.2

medium.[8] The autoxidation of pyrroles was also studied in connection with important practical problems such as the storage stability[1,2,19] and burning[20] of petroleum-fuel-containing pyrroles.

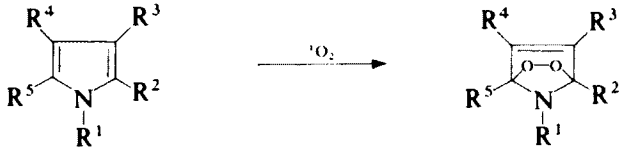
3.5.2. Photooxidation

Dye-sensitized photooxidation reactions of pyrroles have been intensively studied in the past quarter century. Several reviews[1,21,22] and monographs[2,3] dealing with this subject are available.

A Diels–Alder-type reaction of singlet oxygen with the dienic pyrrole system to form a 2,5-endoperoxide is generally believed to be the first step in most pyrrole photooxidations.

The 2,5-endoperoxides are normally not sufficiently stable to be isolated. However, Lightner and co-workers[23] have established, by the use of low-temperature ^{1}H NMR spectroscopy, the formation of the pyrrole endoperoxides

5.15a–i during the photooxidation of pyrroles **5.14a–i** at − 78°C in acetone-d_6. The *N*-phenylpyrrole endoperoxide **5.15c** prepared at − 78°C in acetone-d_6 or Freon 11 was observed to liberate singlet oxygen on warming to − 20°C, as proved by trapping with 2,3-dimethyl-2-butene to give 2,3-dimethyl-3-butene-2-hydroperoxide.[24]



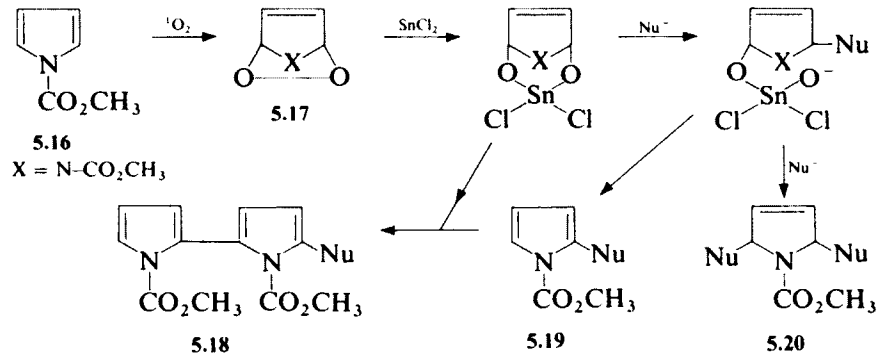
5.14a–i

a $R^1 = R^2 = R^3 = R^4 = R^5 = H$
b $R^1 = CH_3$, $R^2 = R^3 = R^4 = R^5 = H$
c $R^1 = Ph$, $R^2 = R^3 = R^4 = R^5 = H$

5.15a–i

d $R^1 = Bu$, $R^2 = R^3 = R^4 = R^5 = H$
e $R^1 = H$, $R^2 = CH_3$, $R^3 = R^4 = R^5 = H$
f $R^1 = R^2 = H$, $R^3 = CH_3$, $R^4 = R^5 = H$
g $R^1 = H$, $R^2 = t$-Bu, $R^3 = R^4 = R^5 = H$
h $R^1 = R^2 = H$, $R^3 = t$-Bu, $R^4 = R^5 = H$
i $R^1 = R^2 = CH_3$, $R^3 = R^4 = H$, $R^5 = CH_3$

The unstable, but reactive, pyrrole endoperoxides were used as useful intermediates for the introduction of various functional groups into the pyrrole ring.[25,26] Thus, the endoperoxide **5.17**, prepared by low-temperature oxidation of the pyrrole **5.16**, was condensed with various nucleophiles using $SnCl_2$ as a catalyst to afford 2-substituted pyrroles **5.19**, as the major products, along with the 2,2-bipyrroles **5.18** and 3-pyrrolines **5.20**. The proposed mechanism[25] is depicted in Scheme 5.3.



5.16
X = N–CO_2CH_3

5.17

5.18

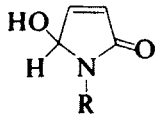
5.19

5.20

Scheme 5.3

It is generally accepted that the various products of photooxidations of pyrroles result from decomposition of the initially formed endoperoxides.[1–4,21,22] The reaction conditions are very important and may significantly affect the nature of the products. A key role is played by the dilution of the reaction mixture.[21] Normally, pyrrole photooxidations are not very useful as preparative reactions, since they usually lead to mixtures of products.

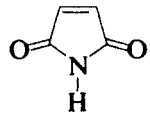
In an early work, Bernheim and Morgan[27] reported the isolation of a crystalline product from the methylene-blue-sensitized photooxidation of pyrrole in water. This product was shown later by Mayo and Reid[28] to be 5-hydroxy-3-pyrrolin-2-one (**5.21a**). 1-Methylpyrrole behaves similarly,[28] giving **5.21b**. However, the photooxidation of pyrrole in methanol does not yield any hydroxypyrrolinone **5.21a** but only maleimide (**5.22**) and 5-methoxy-3-pyrrolin-2-one (**5.23**).[29]



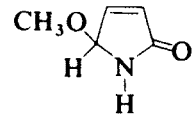
5.21a, b

a. R = H

b. R = CH_3

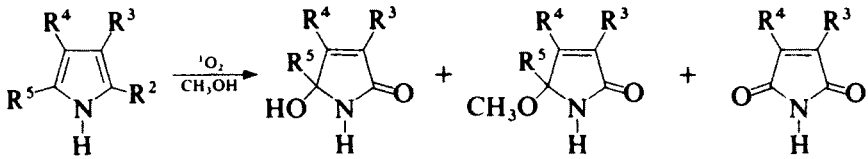


5.22



5.23

The photooxidation of *C*-alkylpyrroles **5.24a–h** in methanol was extensively studied by Lightner and co-workers. The reaction generally follows a common reaction pathway to give three major products (**5.25a–h**, **26a–h**, and **27a–h**) in varying amounts, as summarized in Table 3.5.1.

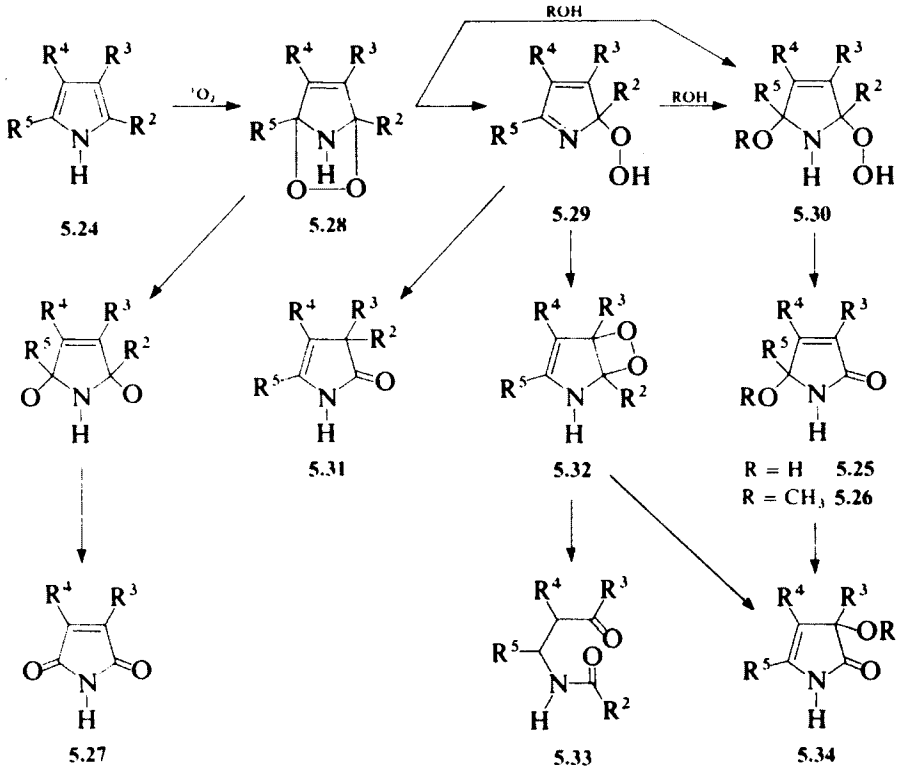


5.24a–h **5.25a–h** **5.26a–h** **5.27a–h**

TABLE 3.5.1. OXIDATION OF *C*-ALKYLPYRROLES (**5.24a–h**) WITH SINGLET OXYGEN

Compound		Yield (%)			Ref.
		5.25	**5.26**	**5.27**	
5.24a	$R_2 = H, R_3 = R_4 = C_2H_5, R_5 = CH_3$	40	11	3	30
5.24b	$R_2 = R_5 = H, R_3 = R_4 = C_2H_5$	0	33	34	29
5.24c	$R_2 = R_4 = H, R_3 = R_5 = CH_3$	48	16	0	31
5.24d	$R_2 = R_3 = R_4 = H, R_5 = CH_3$	15	20	0	31
5.24e	$R_2 = H, R_3 = R_5 = CH_3, R_4 = C_2H_5$	16	14	3	32
5.24f	$R_2 = R_4 = R_5 = H, R_3 = CH_3$	10	22	13	33
5.24g	$R_2 = R_3 = R_4 = H, R_5 = (CH_3)_3C$	12	23	0	34
5.24h	$R_2 = R_4 = R_5 = H, R_3 = (CH_3)_3C$	11	34	31	34

The formation of the compounds **5.25–5.27** and other photooxidation products may be rationalized in terms of the mechanistic pathways presented in Scheme 5.4. The precursors of the pyrrolinones **5.25** or **5.26** are the hydroperoxides **5.30**. However, it is difficult to ascertain whether **5.30** is formed directly by



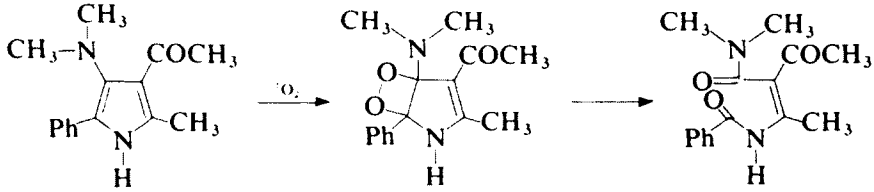
Scheme 5.4

nucleophilic attack of the solvent ROH on the endoperoxide **5.28** or through formation of **5.29** as an intermediate. Direct incorporation of water during the formation of hydroxylactams **5.25** was established by Lightner[23] using $H_2{}^{18}O$. In nonaqueous solvents, however, the major route for the formation of **5.25** is via the rearrangement, in preference to the hydrolysis of the endoperoxides **5.28**.[23]

The α-hydroperoxides **5.29** are generally unstable; however, under favorable conditions, such as where bulky substituents R^2 and R^5 prevent the formation of the endoperoxide **5.28**, they have been isolated.[16,35] Their rearrangement leads to the formation of the 4-pyrrolin-2-ones **5.31**[35] (cf. Scheme 5.5).

The dioxetanes **5.32**, formed from the hydroperoxides **5.29**, rather than by direct 1,2-addition of singlet oxygen,[23] are the most probable precursors for both open-chain amides **5.33**[36] and the 3-oxygenated derivatives **5.34**.[23]

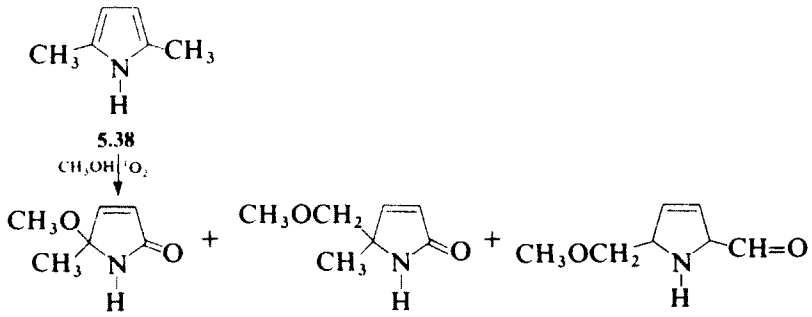
Tarzia and co-workers[37] have recently studied the photooxidation of some 4-aminosubstituted pyrroles. In the case of the pyrrole **5.35**, the exclusive isolation of the amide **5.37** suggests the formation of a dioxetane intermediate **5.36**. This remarkably selective formation of the dioxetane contrasts sharply with the generally observed 1,4-addition of singlet oxygen to form 2,5-endoperoxides.



5.35 5.36 5.37

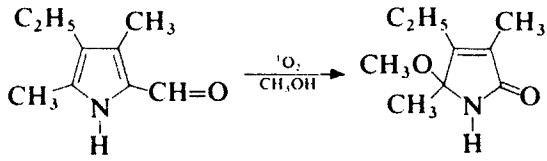
Tarzia explained this observation in terms of the enamine character of the 4,5-double bond of the pyrrole **5.35**.

A partial oxidation of α-methyl groups, which cannot be straightforwardly explained in terms of the Scheme 5.4, has been reported several times.[36,38] Thus, photooxidation of 2,5-dimethylpyrrole (**5.38**) in methanol yields a mixture of the 5-methoxylactam **5.39** 5-methoxymethyl lactam **5.40** and aldehyde **5.41**.[38]



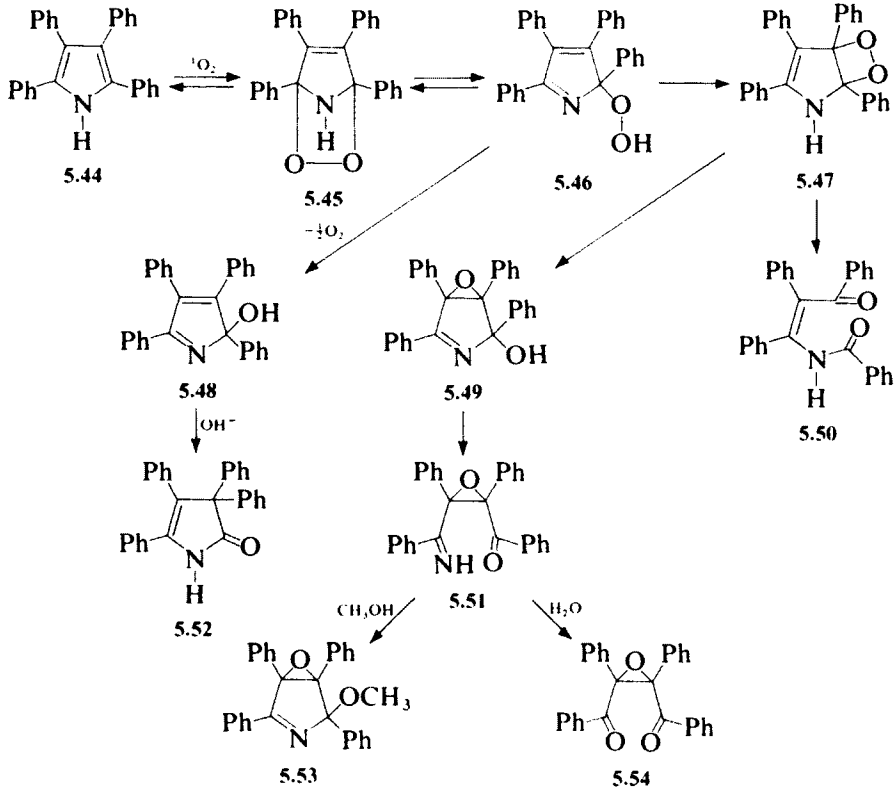
5.38 5.39 5.40 5.41

Pyrroles substituted with electron-withdrawing groups react with singlet oxygen considerably slower than do simple alkyl pyrroles. No recognizable products have been obtained from the 2-formylpyrrole.[39] On the other hand, 4-ethyl-3,5-dimethylpyrrole (**5.42**) yields 53% of the pyrrolinone **5.43**.[39] Apparently, the photooxidation is facilitated when the electron-attracting effect of the formyl group is partly compensated by the electron-donating effect of the alkyl groups.



5.42 5.43

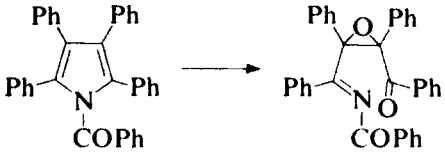
Photooxidation of polyarylpyrroles has been better investigated than that of alkylpyrroles because the products obtained are more stable and easier to characterize. The mechanistic pathways for the different products formed during the photooxidation of 2,3,4,5-tetraphenylpyrrole (**5.44**) in methanol are presented in Scheme 5.5. Thus, Wasserman and Liberles[40] have found that the



Scheme 5.5

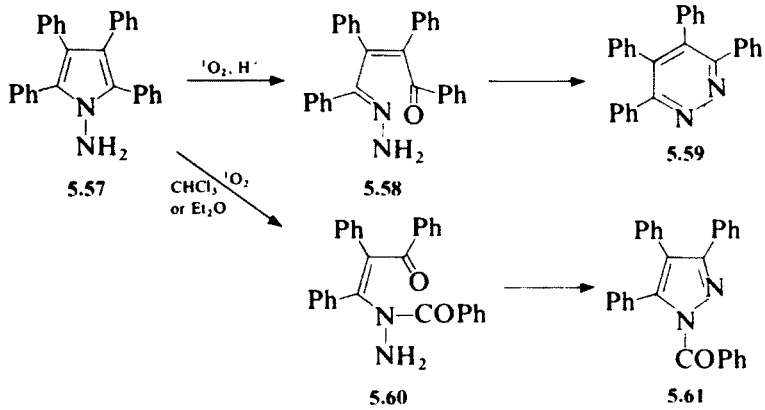
methylene-blue-sensitized photooxidation of **5.44** gave a mixture of the cleavage product **5.50** and the cyclic epoxide **5.53**. The same reaction in methanol containing potassium hydroxide gave the rearranged product **5.52**, probably formed from the intermediate **5.48**. The key intermediate **5.46**, formed by ring opening of the primarily formed endoperoxide **5.45**, was isolated somewhat later.[16] Its cyclization leads to the dioxetane **5.47**, which, in turn, undergoes cleavage of the 2,3-bond, thereby yielding **5.50**. On heating in benzene, **5.46** regenerates the starting pyrrole **5.44** and oxygen. In boiling methanol, on the contrary, the hydroperoxide **5.46** yields a mixture of the cleavage product **5.50**, the hydroxyepoxide **5.49**, the methoxyepoxide **5.53**, and the dibenzoylstilbene oxide **5.54**. Probably the open-chain compound **5.51**[16,41-43] is formed as a precursor of **5.53** and **5.54**.

Pentaphenylpyrrole does not behave very differently.[44] Anomalous oxidative cleavage of the 1,2-bond explains the formation of the epoxide **5.56**, which is the major product of photooxidation of 1-benzoyl-2,3,4,5-tetraphenylpyrrole **5.55**.[45] An analogous 1,2-cleavage occurs during photooxidation of 1-amino-2,3,4,5-tetraphenylpyrrole (**5.57**) in acidic media.[46] The so formed monohydrazone of 1,2-dibenzoylstilbene (**5.58**) cyclizes readily, according to Scheme



5.55 5.56

5.6, to give the pyrazine **5.59**. In chloroform or ether, however, cleavage of the 2,3-bond dominates, giving the *N*-acylhydrazine **5.60**, whose cyclization leads to the pyrazole derivative **5.61**.



5.57 5.58 5.59 5.60 5.61

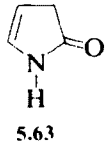
Scheme 5.6

3.5.3. Oxidation by Chemical Reagents

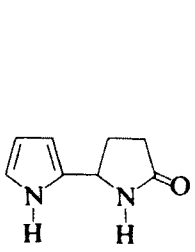
3.5.3.1. Hydrogen Peroxide, Peracids, and Other Peroxides

Angeli and Alessandri[47] reported in their early work that, in acetic acid, pyrrole polymerizes by the action of hydrogen peroxide to give ill-defined oxygenated material; so-called pyrrole black. Since this observation, the hydrogen peroxide oxidation of pyrroles attracted the attention of numerous research groups and has been subject of several reviews.[1-4] The study of the hydrogen peroxide oxidation of unsubstituted pyrrole in buffers at various pH values (1.1–9.0) has shown that pyrrole blacks are formed only in strongly acidic medium. In neutral media, 3-pyrrolin-2-one (**5.62**) is always formed, together with its isomer **5.63** in a ratio of about 9 : 1.[45-48] The pyrrolinones **5.62** and **5.63** are the probable precursors[49] for the dimeric,[52] trimeric,[53,54] and tetrameric[49] compounds **5.64–5.66**, which have been also isolated from the reaction mixtures. The mechanism of their formation is outlined in Scheme 5.7.[3] The best yields of

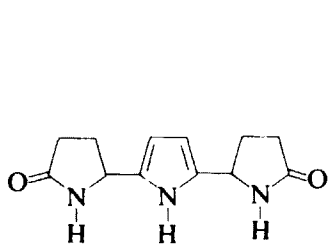
5.62



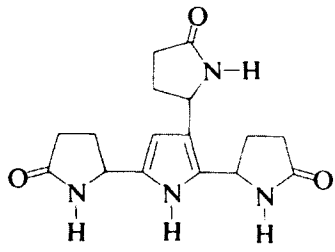
5.63



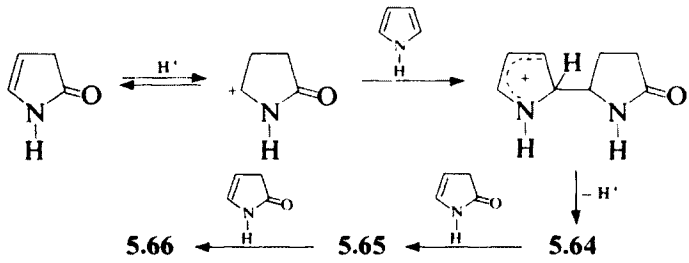
5.64



5.65



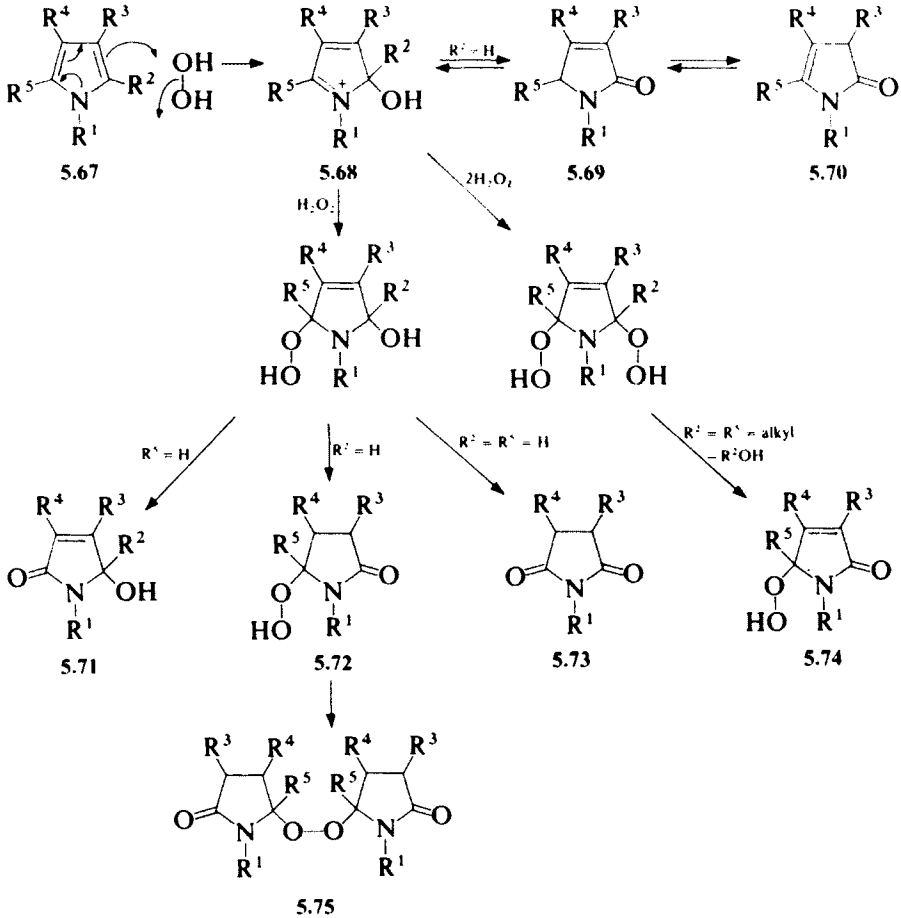
5.66



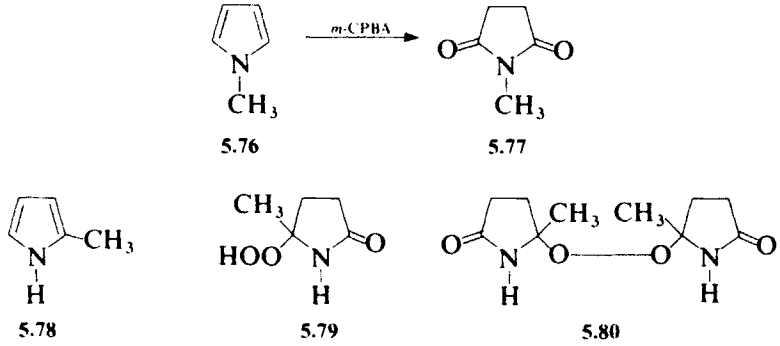
Scheme 5.7

monomeric pyrrolin-2-ones are obtained with hydrogen peroxide in pyridine.[55-58]

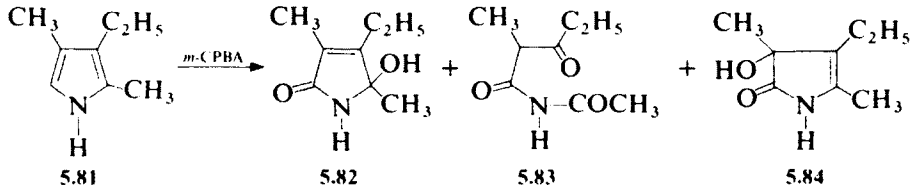
The typical reaction pathways leading to the low-molecular weight products from the oxidation of pyrroles and its alkyl derivatives **5.67** with hydrogen peroxide and peracids are summarized in Scheme 5.8. According to Scheme 5.8, the first oxidation step is the electrophilic attack of the pyrrole **5.67** by hydrogen peroxide to form the hydroxy derivative **5.68**. It should be noted, however, that convincing electron-spin resonance (ESR) evidence for an attack by hydroxyl radicals has been reported.[59,60] The pyrrolinones **5.69** are the main products when R^3 and R^4 are alkyl groups or when the pyrrole ring is unsubstituted.[59] On the other hand, the tautomeric 4-pyrrolinones **5.70** are preferred, when the substituents R^5 are alkyl groups.[60,61] If both α positions of the pyrrole ring are unsubstituted, the initially formed pyrrolinones **5.69** and **5.70** can be further oxidized under vigorous conditions to give the succinimides **5.73**. 1-Methylpyrrole (**5.76**), for instance, gives *N*-methylsuccinimide **5.77** in 92% yield on oxidation with *m*-chloroperbenzoic acid in pyridine.[168] The presence of one α-alkyl substituent prevents, on the other hand, the formation of **5.73**. In such cases, the peroxidic compounds **5.72** and **5.75** can be obtained. The oxidation of 2-methylpyrrole **5.78**, for instance, gave the hydroperoxide **5.79** and the peroxide



Scheme 5.8

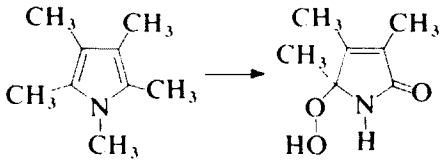


5.80.[60] The formation of the hydroxypyrrolinones **5.71** has been demonstrated in the case of kryptopyrrole (**5.81**).[62] Its oxidation with m-chloroperbenzoic acid gave the hydroxypyrrolinone **5.82** in 9.5% yield along with the amide **5.83**



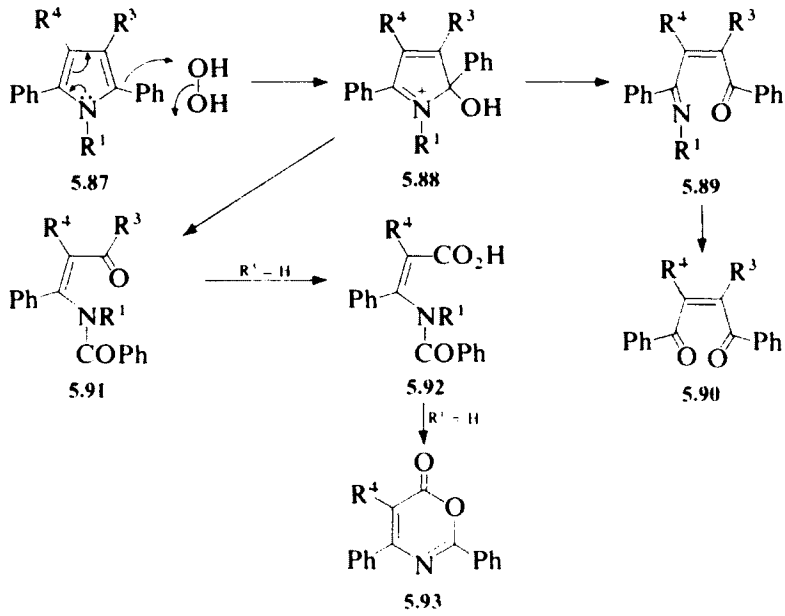
5.81 5.82 5.83 5.84

(19%) and the β-hydroxypyrrolinone **5.84** (37%). If both α-positions of the pyrrole ring are substituted with alkyl groups, the formation of hydroperoxy pyrrolinones **5.74** takes place according to the pathway shown in Scheme 5.8. For instance, pentamethylpyrrole (**5.85**) was found to give the hydroperoxypyrroline **5.86** on treatment with 70% hydrogen peroxide.[63]



5.85 5.86

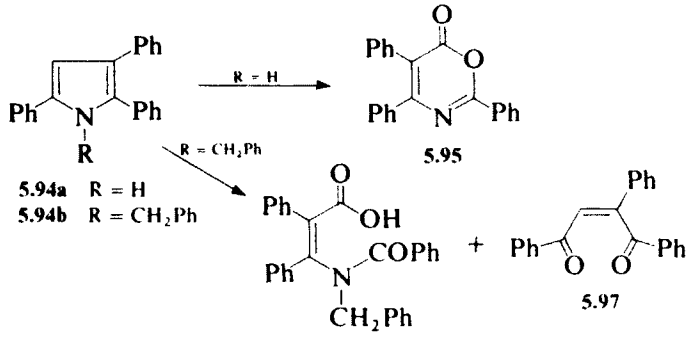
Polyarylpyrroles undergo more profound oxidation compared with alkylpyrroles. Open-chain products are frequently isolated. Substitution at the pyrrolic nitrogen does not significantly influence the oxidation pathways. According to Scheme 5.9, the initial step involves the electrophilic attack of the pyrrole **5.87** by



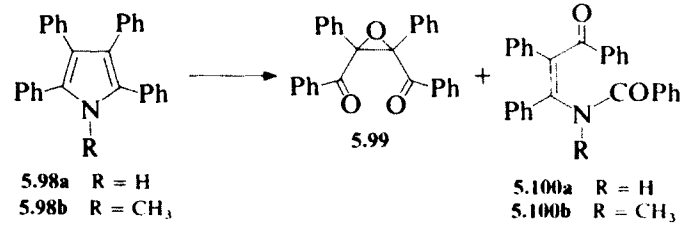
5.87 5.88 5.89 5.90 5.91 5.92 5.93

Scheme 5.9

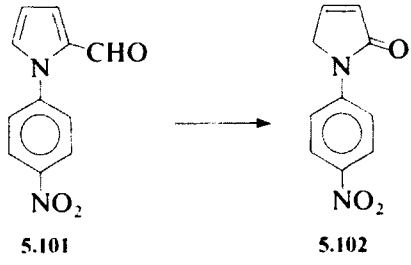
hydrogen peroxide to give the hydroxy compound **5.88**. This can hydrolyze to the diketone **5.90** through the open-chain imine **5.89**. A second possibility involves the cleavage of the 2,3-bond to give the amide **5.91**, which can be further oxidized to the carboxylic acid **5.92** (R^3 = H). Cyclization of the latter may lead to the oxazine derivative **5.93**. Hence, Scheme 5.9 explains well the formation of the oxidation products **5.95–5.97** during the oxidation of the triphenylpyrroles **5.94a,b**.[64,65] It should be pointed out, however, that the formation of products



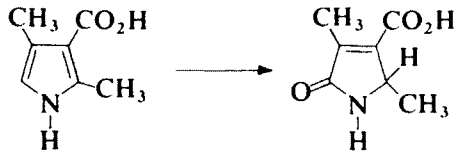
not directly explainable on the basis of Scheme 5.9 have been also reported. Thus, Lutz and Boykin have isolated the epoxide **5.99**, along with the keto-amides **5.100a, b** from the reaction mixture obtained on oxidation of the pyrroles **5.98a,b**.[66] The oxidation of pyrrole aldehydes affords generally 3-pyrrolinones,



under elimination of the formyl group.[67,68] Thus, 2-formyl-1-*p*-nitrophenyl-pyrrole (**5.101**) gives 53% yield of the pyrrolinone **5.102** on oxidation with hydrogen peroxide in formic acid.[68] Pyrrolyl ketones are normally inert against hydrogen peroxide oxidation.[69]

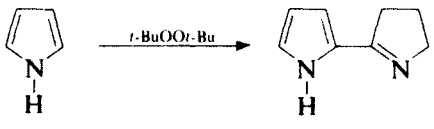


Pyrrole carboxylic acids are also quite stable to oxidation, except when the electron-withdrawing effect of the carboxyl group is compensated by additional alkyl substituents. Such compounds are oxidized to 3-pyrrolinones, as demonstrated in the case of the pyrrole derivative **5.103** and its oxidation product **5.104**.[10]

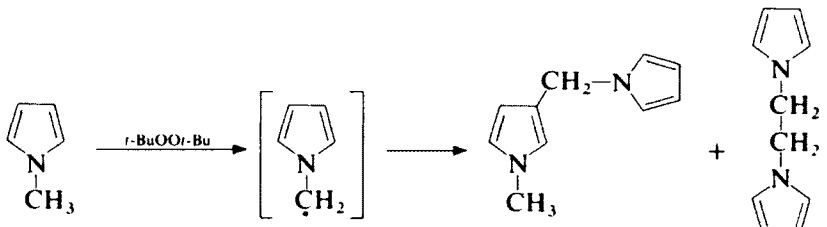


5.103 **5.104**

The oxidation of pyrroles with organic peroxides has received relatively little attention. Thus, pyrrole (**5.105**) was reported to give the pyrrolylpyrroline **5.106** on reaction with di-*t*-butylperoxide.[70] Under the same conditions, 1-methylpyrrole (**5.107**) gives the compounds **5.109** and **5.110**, presumably through the intermediacy of the free radical **5.108**.[70]



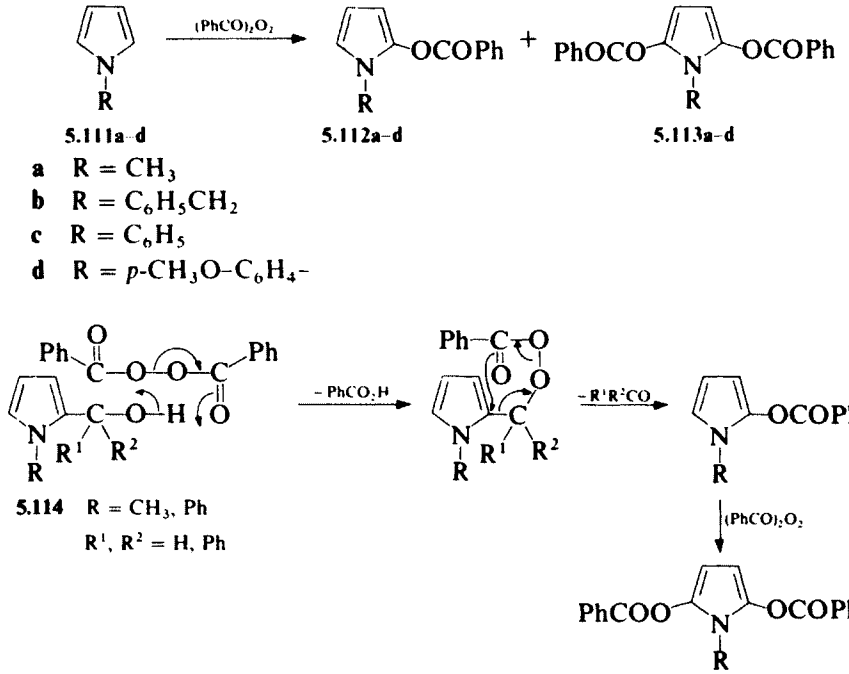
5.105 **5.106**



5.107 **5.108** **5.109** **5.110**

Nabih and Helmy[71] have reported the isolation of *N*-methylsuccinimide from the reaction of 1-methylpyrrole with dibenzoylperoxide. The reaction of this peroxide with pyrroles was reinvestigated more recently by Aiura and Kanaoka,[72,73] who found that 1-substituted pyrroles **5.111a–d** give the 2-benzoyloxypyrroles **5.112a–d**, together with the 2,5-dibenzoyloxy derivatives **5.113a–d**.

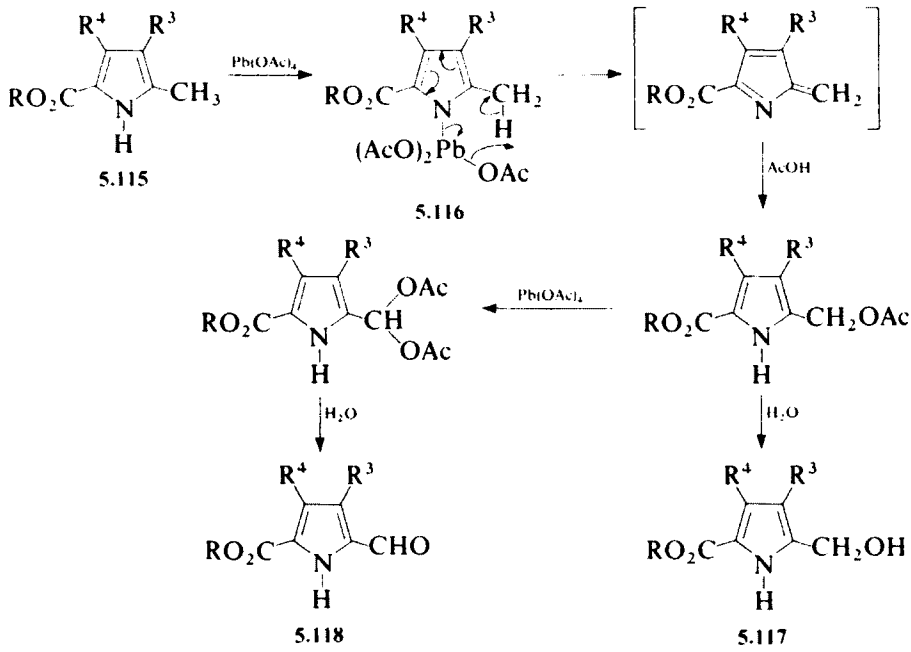
An interesting C–C bond cleavage was repoted to take place in *N*-substituted pyrrol-2-ylmethanols **5.114** on treatment with dibenzoylperoxide.[72,73] The proposed mechanism of this reaction leading to benzoates of the type **5.112**, and **5.113** is outlined in Scheme 5.10.



Scheme 5.10

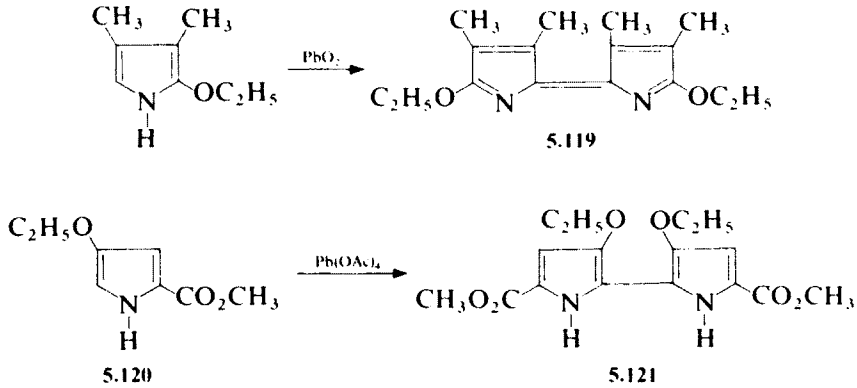
3.5.3.2. Lead Dioxide and Lead Tetraacetate

The oxidation of pyrroles with Pb(IV) compounds is interesting from the preparative point of view.[1-3] Particularly the reaction of 5-methylpyrrole-2-carboxylic esters **5.115** with lead tetraacetate in acetic acid[74] provides an useful method for the synthesis of the corresponding 5-hydroxymethyl derivatives **5.117**.[74] At higher temperatures, reaction with a second mole of the oxidizing agent occurs, thus yielding the aldehydes **5.118**.[74] A probable mechanism of this reaction involving the formation of an organolead intermediate **5.116** is outlined in Scheme 5.11.[3] Recently, Montforts and Schwartz have found that the yields of 2-formylpyrroles are improved if the lead tetraacetate oxidation of 5-methylpyrrole-2-carboxylic esters is carried out in chloroform rather than in acetic acid.[75] On treatment with Pb(IV) compounds, pyrroles with unsubstituted α positions form dimeric products. Thus, 2-ethoxy-3,4-dimethyl pyrrole gives the diazafulvalene **5.119** on reaction with lead dioxide in benzene.[76] On the other hand, methyl 4-ethoxypyrrole-2-carboxylate (**5.120**) reacts with lead tetraacetate to give the bipyrrole **5.121**.[77] The nature of products obtained from the reaction of tetraphenylpyrrole (**5.122**) with lead tetraacetate depends critically on the solvent used. In benzene, the principal compound isolated is the 2-acetoxy derivative **5.123**, together with some isomeric 3-acetoxy derivative **5.124**.[78] In acetic acid, however, the sole product isolated was the hydroxy



5.115 5.116 5.118 5.117

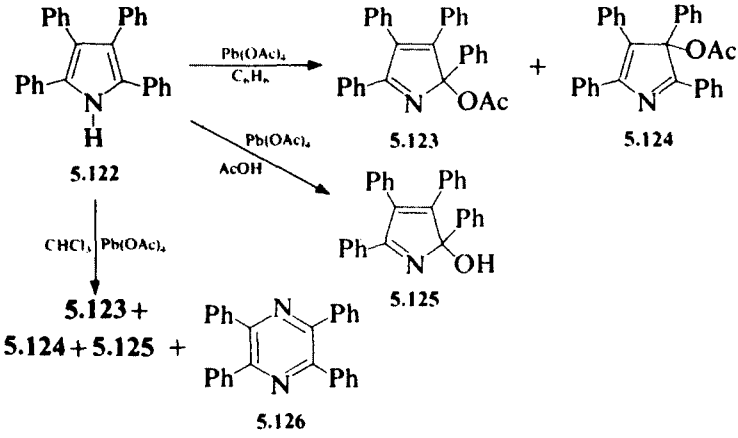
Scheme 5.11

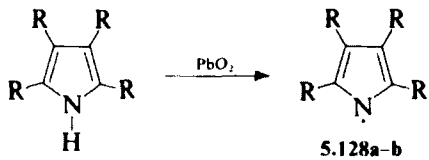


5.119 5.120 5.121

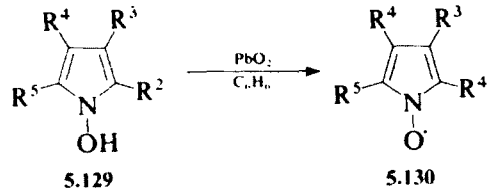
compound **5.125**.[66,78] Its formation is probably the consequence of the (hydrolytic) workup. An unexpected pyrazine **5.126** was reported to be formed in chloroform, together with the derivatives **5.123**–**5.125**.[78,79]

Lead dioxide in benzene or toluene generate stable free pyrrolyl radicals **5.128a,b**, which have been characterized in the case of tetraphenylpyrrole **5.127a**[80–82] and of tetrakis(trifluormethylthio)pyrrole **5.127b**.[83] The radicals **5.128a,b** can dimerize[80,83] or react with oxygen to give peroxides.[16] Another class of stable pyrrolyl radicals **5.130** is produced by the oxidation of 1-hydroxypyrroles **5.129** with lead dioxide in benzene.[84–87]





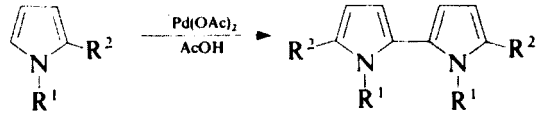
a R = Ph
b R = CF_3S



$R^2 = R^5$ = Ph, $(CH_3)_3C$, CH_3
$R^3 = R^4$ = H, CO_2Et, Ph

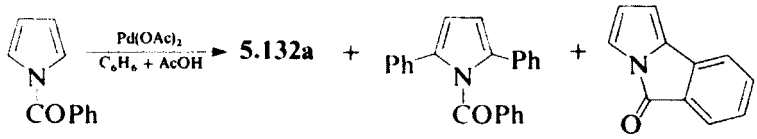
3.5.3.3. Palladium(II) Acetate

Itahara[88] has reported in 1980 that the oxidation of 1-aroylpyrroles **5.131a–c** with palladium(II) acetate in acetic acid gives the 1,1'-diaroyl-2,2'-bipyrroles **5.132a–c** in good yields. Likewise, 2-benzoyl-1-methylpyrrole (**5.131d**) affords the dimer **5.132d**. On the other hand, *N*-aroylpyrroles undergo arylation on treatment with palladium(II) acetate in acetic acid containing aromatic hydrocarbons.[89–91] Thus, 1-benzoylpyrrole (**5.133**) gave the 2,5-diphenylated compound **5.134** accompanied by a small amount of the dimer **5.132a** and the tricyclic compound **5.135**.[90] The latter compound is formed by intramolecular ring-closure reaction between the pyrrolic and benzoyl moiety of the starting pyrrole **5.133**.



5.131a–d 5.132a–d

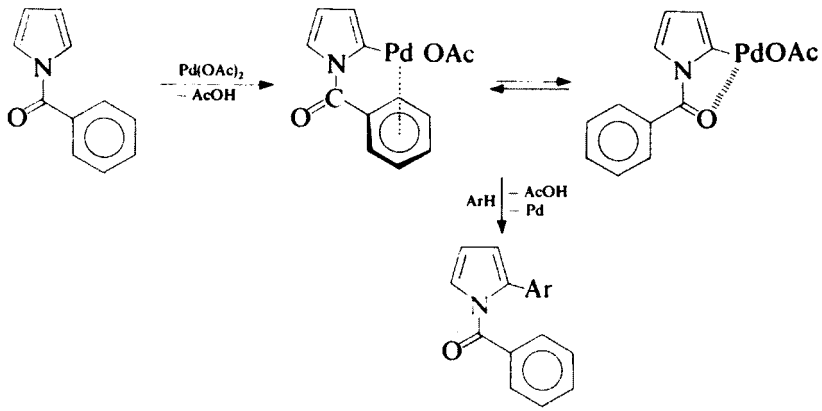
a $R^1 = PhCO$, $R^2 = H$
b $R^1 = p\text{-}MeC_6H_4CO$, $R^2 = H$
c $R^1 = \alpha$-naphthoyl, $R^2 = H$
d $R^1 = CH_3$, $R^2 = PhCO$



5.133 5.134 5.135

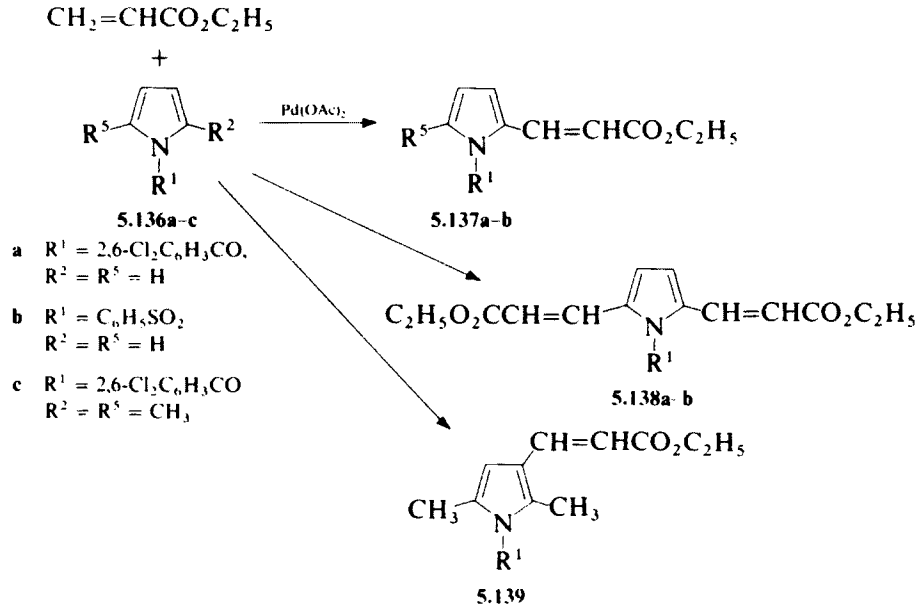
The intramolecular cyclization can be prevented by appropriate substitution on the pyrrolic nitrogen. Thus, 1-(2,6-dichlorobenzoyl)pyrrole, does not yield any tricyclic compound.

The remarkable α-regioselectivity of the pyrrole arylation compared with the preferentially β-arylation in the furan and thiophene series was explained in terms of formation of an α-pyrrolylpalladium intermediate stabilized by chelation with the benzoyl groups[90] (see Scheme 5.12).



Scheme 5.12

Palladium(II) acetate also promotes the oxidative coupling between acrylates and pyrroles **5.136a,b** to yield the corresponding pyrrolylacrylates **5.137a,b** and **5.138a,b**.[92] If both α positions are blocked, as in the case of **5.136c**, the β-substituted product **5.139** is formed.



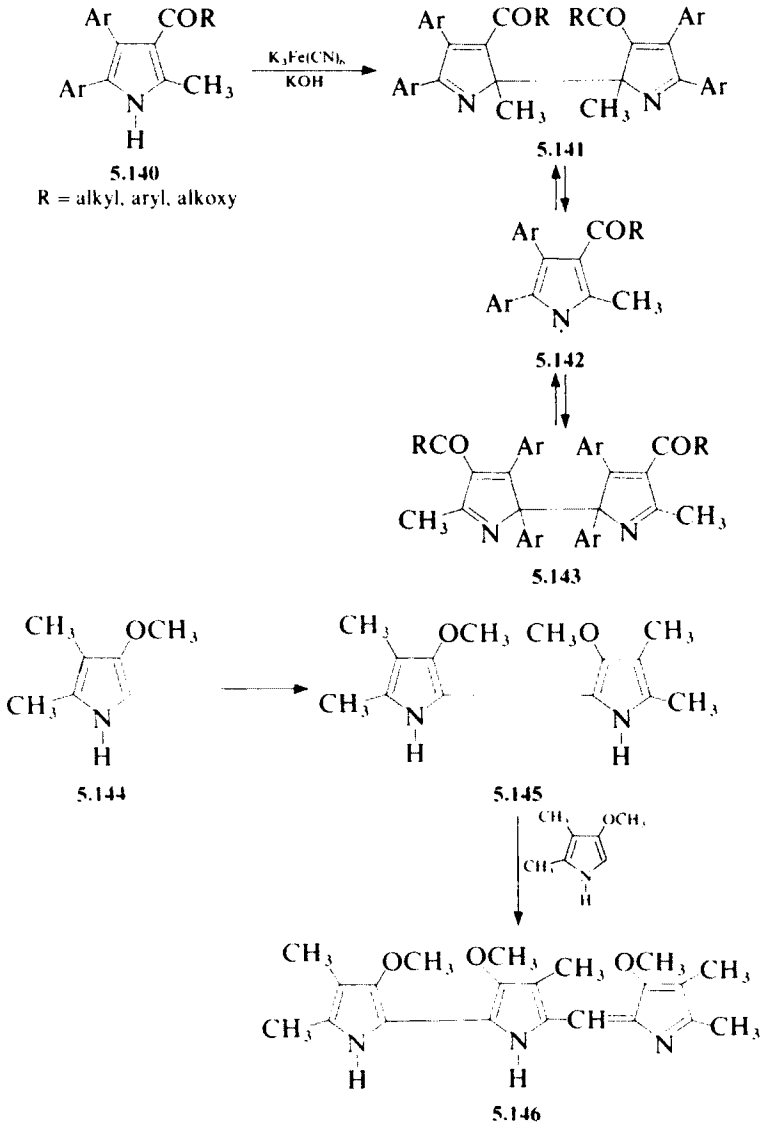
3.5.3.4. Iron(III) and Copper(II) Salts

Oxidation of α,α′-unsubstituted pyrroles by Fe(III) salts leading to a polymeric material, so-called pyrrole black, has been known for many years.[93,94] This reaction regained interest in the past decade, because pyrrole blacks display interesting properties as an electrically conducting polymer[94] (see also Section 3.5.4). The elemental composition of pyrrole black has been reported as $C_{4.0-4.5}H_{3.0-4.5}N_{1.0}O_{1-1.5}$.[96] It is believed, that the pyrrole moiety remains intact during the polymerization, which takes place at the α positions.[5,93,94]

The kinetics of oxidative polymerization of pyrrole by various Fe(III) and Cu(II) complexes, especially by iron(III) chloride, was studied recently.[95,97] The preparation of colloidal polypyrrole by $FeCl_3$ oxidation of pyrrole in aqueous methylcellulose solutions was reported by Bjorklund and Liedberg.[98] Rapi and co-workers have described the procedure[99] for the synthesis of bulk quantities of polypyrrole by oxidation with selected Fe(III) and Cu(II) salts in water.

The 3-alkoxycarbonyl- and 3-acylpyrroles **5.140** are oxidized with potassium ferricyanide to give the dimeric thermochromic compounds **5.141** and **5.143**, which are interconvertible via the radical **5.142**.[100-102]

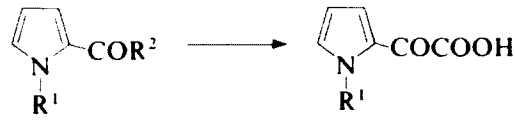
On oxidation with Fe(III) salts, 3-alkoxypyrroles afford tri- or tetrameric compounds.[77,103] The β-methoxypyrrole **5.144**, for example, yields the trimer **5.146**, presumably through the intermediacy of the initially formed dimer **5.145**.[103]



3.5.3.5. Chromium(VI) and Manganese(VII) Compounds

Acidic potassium permanganate readily oxidizes α-methyl and formyl groups on the pyrrole ring to give the corresponding carboxylic acids, which are normally stable to further oxidation.[68,104]

α-Pyrrolylketones of general structure **5.147** yield the corresponding glyoxylic acids **5.148**.[105–107] In general, 1-alkylpyrroles are resistant to the action of potassium permanganate.

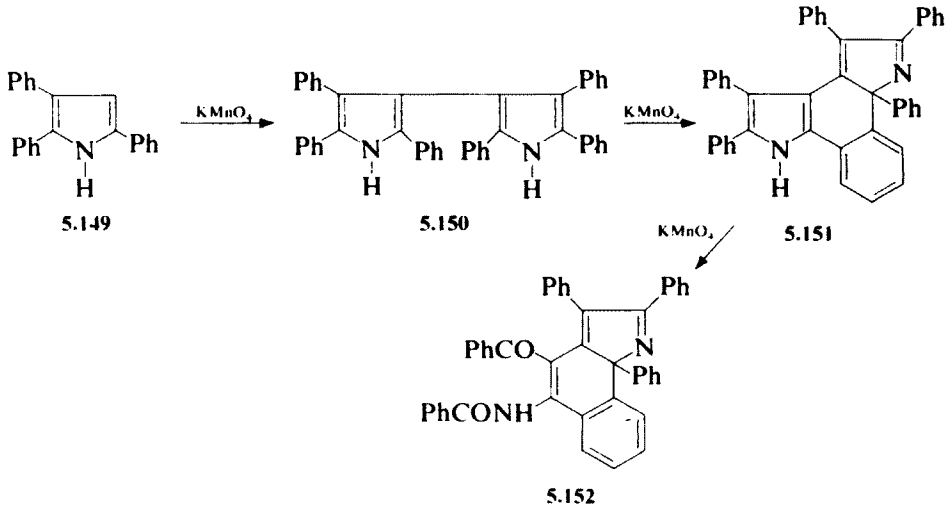


5.147 5.148

$R^1 = H, CH_3$

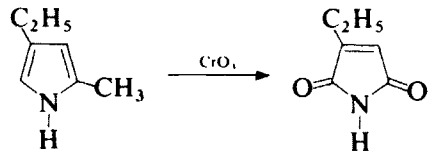
$R^2 = CH_3, C_2H_5, C_6H_5CH_2$

The sole product isolated from the permanganate oxidation of *N*-acetyl-2,3,4-triphenyl-pyrrole was reported to be benzoic acid.[108] On treatment with potassium permanganate in a mixture of water and benzene, 2,4,5-triphenylpyrrole (**5.149**) gives the dimeric compound **5.150**, together with the tetracyclic derivative **5.151**. Further oxidation of **5.151** affords the amide **5.152**.[13]



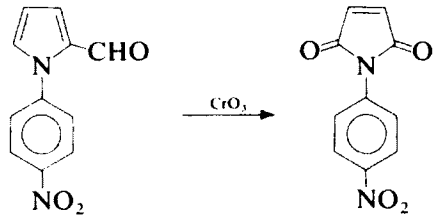
5.149 5.150 5.151 5.152

The oxidation of pyrrole and its alkyl derivatives by dichromate or chromic anhydride under acidic conditions proceeds with the loss of the α-substituents, giving the corresponding maleinimides.[109–111] Thus, 4-ethyl-2-methylpyrrole (**5.153**) yields 3-ethylmaleinimide (**5.154**).[112,113] As expected, the α-formyl group



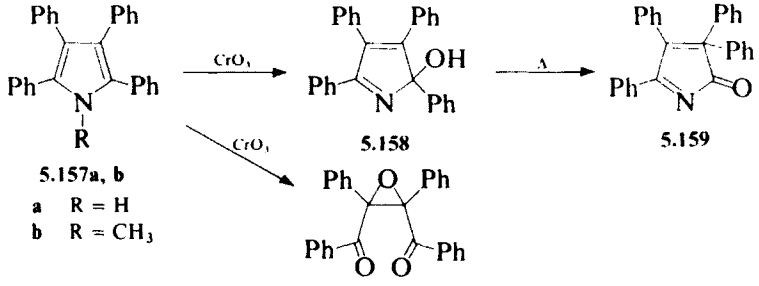
5.153 5.154

of the aldehyde **5.155** was lost on treatment with CrO_3 in acetic acid and the maleimide **5.156** was isolated in 66% yield.[68] Arylpyrroles undergo more extended oxidations when reacted with Cr(VI) compounds. Ring cleavages and



5.155 5.156

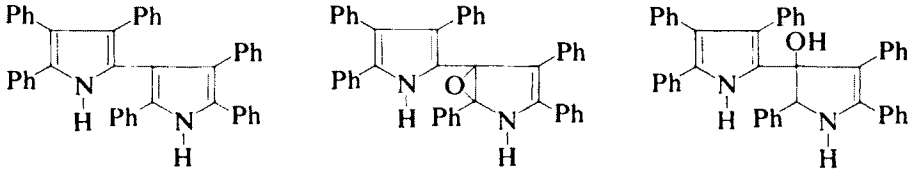
rearrangements occur frequently.[3] Thus the tetraphenylpyrrole **5.157a** gives the hydroxy tetraphenylpyrrolenine **5.158**, which rearranges in boiling acetic acid to the pyrrolinone **5.159**.[66] In contrast, with 1-methyl-2,3,4,5-tetraphenylpyrrole (**5.157b**), the ring-opened product **5.160** was obtained.[66] The oxidation of 2,4,5-



5.157a, b
a R = H
b R = CH_3

5.158 5.159 5.160

triphenylpyrrole (**5.149**) with potassium dichromate in benzene[114] leads to the same products, **5.150–5.152**, which are obtained by reaction with $KMnO_4$. However, the 2,3-dimer **5.161** and the oxygenated products **5.162** and **5.163** are also formed.



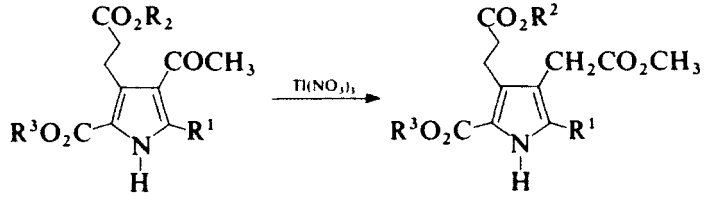
5.161 5.162 5.163

The determination of chemical oxygen demand of water-containing pyrrole by dichromate oxidation has been also reported.[115]

3.5.3.6. Miscellaneous

3.5.3.6.1. Thallium(III) Nitrate

Thallium(III) nitrate in methanol promotes the synthetically useful rearrangement of β-acetylpyrroles (e.g., **5.164a**) to the corresponding pyrrolylacetic acid



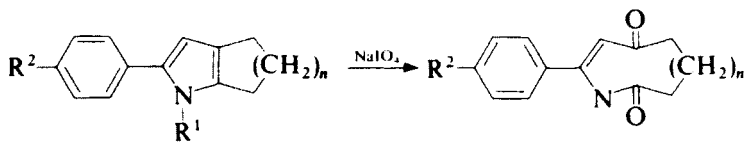
5.164a, b **5.165 a, b**

a $R^1 = CH_3$, $R^2 = R^3 = C_2H_5$ **a** $R^1 = CH_3$, $R^2 = R^3 = C_2H_5$
b $R^1 = CH_3$, $R^2 = CH_3$, $R^3 = PhCH_2$ **b** $R^1 = CHO$, $R^2 = CH_3$, $R^3 = PhCH_2$

derivatives **5.165a**.[116] The reactivity of thallium(III) nitrate is enhanced when it is supported on montmorillonite clay, so that the oxidative rearrangement of the β-acetyl group of **5.164b** is accompanied by the oxidation of the α-methyl group to give the aldehyde **5.165b**.[117]

3.5.3.6.2. Sodium Periodate

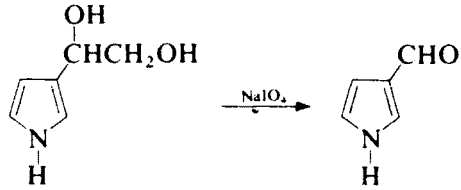
Sodum periodate has been reported to oxidize α-unsubstituted pyrroles to the corresponding 3-pyrrolin-2-ones.[118] If the α positions are occupied, the oxidations of the α-methyl group to the aldehyde function was observed.[118] On treatment with $NaIO_4$, 2,3,4,5-tetraphenylpyrrole yields 3,3,4,5-tetraphenyl-4-pyrrolin-2-one.[118] An interesting route to medium-sized ketolactams **5.167** by



5.166 **5.167**

$R^1 = H, CH_3$
$R^2 = H, CH_3, CH_3O, O, Br, Cl$
$n = 0\text{-}4$

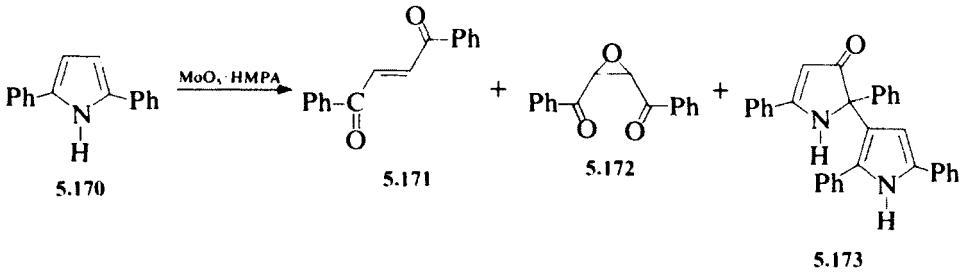
$NaIO_4$-promoted oxidative cleavage of bicyclic pyrroles **5.166** has been reported recently.[119,120] The oxidative cleavage of the diol **5.168** with $NaIO_4$ has been used for a high-yield synthesis of 3-formylpyrrole (**5.169**).[121]



5.168 **5.169**

3.5.3.6.3. $MoO_5 \cdot HMPTA$

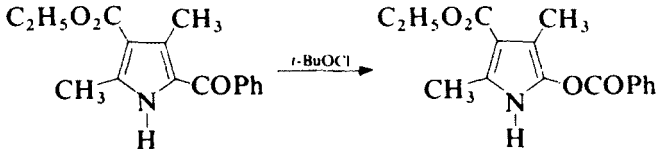
The reaction of 2,5-diphenylpyrrole (**5.170**) with (hexamethylphosphoramide)oxodiperoxomolybdenum(VI) ($MoO_5 \cdot HMPA$) for 2 weeks gave the *trans*-olefin **5.171** and the *cis*-epoxide **5.172**, as well as the dimeric product **5.173**.[122]



5.170 **5.171** **5.172** **5.173**

3.5.3.6.4. *tert*-Butyl Hypochlorite

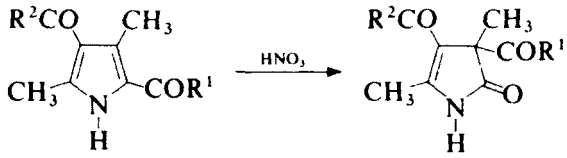
An interesting Bayer–Villiger-type oxidation of the pyrrolylketone **5.174** with *tert*-butyl hypochlorite in the presence of 2-propanol, yielding the benzoyloxypyrrole **5.175**, has been reported by McGillivray and co-workers.[123]



5.174 **5.175**

3.5.3.6.5. Nitric and Nitrous Acid

The oxidation of alkylpyrroles[124,125] and tetrahalogenpyrroles[126] with nitric acid is accompanied by loss of the α-substituents, so that the products are the corresponding maleinimides. Pyrrolylalkylketones may be oxidized by dilute nitric acid to give either the corresponding pyrrolylglyoxalic acids[127] or furoxans.[128] An oxidative rearrangement of α-acetyl-, carbalkoxy-, or dialkylcarbamoylpyrroles **5.176** with concentrated nitric acid has been reported by



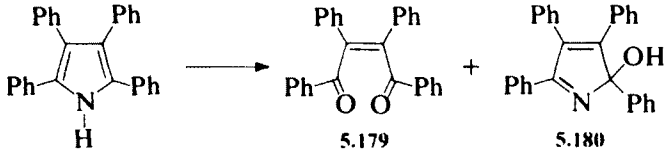
5.176 **5.177**

$R^1 = CH_3, OCH_3, OC_2H_5, N(CH_3)_2, N(C_2H_5)_2,$

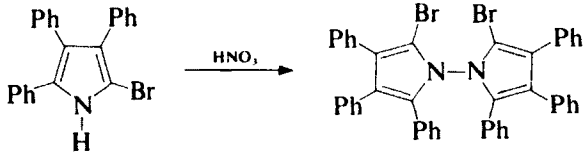
$R^2 = CH_3, OCH_3, OC_2H_5$

Moon[129] to yield the pyrrolinones **5.177**. An analogous oxidative rearrangement giving 4-pyrrolin-2-one derivatives has been observed with 1-methyl-2,3,4,5-tetraphenylpyrrole.[66]

The main oxidation product of tetraphenylpyrrole **5.178** with nitric or nitrous acid in acetic acid is *cis*-benzoylstilbene (**5.179**) with some 2-hydroxypyrrolenine **5.180**.[66,130] The dimeric structure **5.182** has been attributed to the compound



5.178 **5.179** **5.180**



5.181 **5.182**

obtained from 3-bromopyrrole **5.181** by the action of nitric acid.[131] Nitrous acid reacts with unsubstituted pyrrole to give pyrrole black.[132]

3.5.3.6.6. Ozone

There are only a few publications concerning the ozonolysis of pyrroles. Freri[133,134] obtained pyrrole black from ozonization of pyrrole and alkylpyrroles at room temperature in acidic medium. Somewhat later, Wibaut et al. isolated the expected carbonyl compounds resulting from the cleavage of the 2,3- and 4,5-bonds of the pyrrole ring by ozone at $-45°C$ in chloroform.[135–138] However, products resulting from the cleavage of the formal 3,4-single bond were also isolated.[135,136]

3.5.3.6.7. Phosphorus Pentachloride

The tetraphenylpyrrole **5.178** is converted by PCl_5 into a phosphorus complex, which can be hydrolyzed to the 2-hydroxypyrrolenine **5.180**.[66]

3.5.4. Electrooxidation

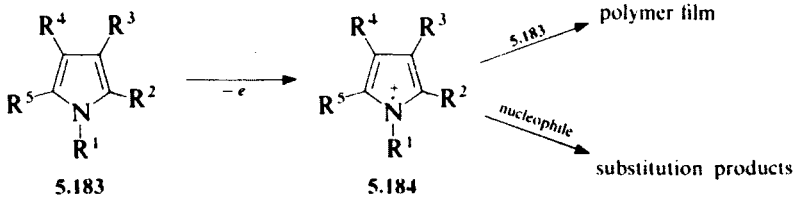
Early workers observed that pyrrole black is deposited on the anode during the electrolysis of pyrrole in acidic medium.[139,140]

In 1979 Diaz and Kanazawa[141] prepared a sample of polypyrrole by electropolymerization of pyrrole in acetonitrile containing tetramethylammonium tetrafluoroborate. The polypyrrole formed a durable electrically conducting film, which adhered strongly onto the electrode surface. Its elemental analysis

indicated that it consisted primarily of polymerized pyrrole units and BF_4^- ions in the ratio of about 4 to 1, with the formula $C_{4.00}H_{3.44}N_{0.87}(BF_4)_{0.26-0.30}$. Somewhat later, it was reported that the polypyrrole film attached to an electrode surface can be repeatedly driven electrochemically between the electrically conducting oxidized, and insulating reduced state.[142] This produces a color change in the film from yellow, when reduced, to black, when oxidized.[143] The preparation of polypyrrole films was also successful with *N*-alkylated and arylated pyrroles,[144-146] as well as with *C*-alkyl[144] and 3,4-dihalogeno pyrroles.[147,148] Pyrroles with substituted α-positions, however, form only soluble materials, which do not deposit on the electrode.[149]

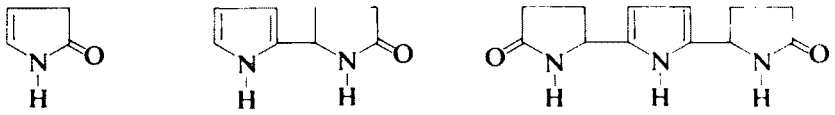
The electrochemical and physical properties of polypyrrole films were studied intensively by several research groups.[141-148,150-152] Anodic oxidation of pyrroles leading to low-molecular-weight products has received relatively little attention. Nevertheless, there are several reviews dealing with this subject.[2,3,153,154]

The first step in one-electron anodic oxidation of pyrroles **5.183** is believed to be the irreversible formation of a radical π-cation **5.184**.[149] This extremely short-lived species can react further either with pyrrole in situ to give polymers, or, with added or adventitious nucleophiles, to give substitution products.



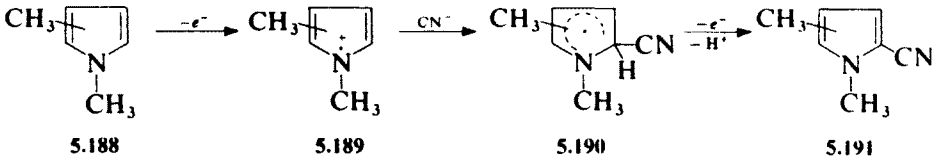
The anodic oxidation potentials for a series of 117 substituted pyrroles were recently measured with cyclic voltametry by Tabba and Smith.[155]

The electrooxidation of pyrrole in the presence of bases has been shown to produce compounds **5.185**, **5.186**, and **5.187**.[156] The anodic oxidation of a series



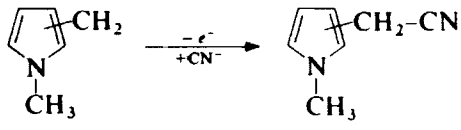
5.185 **5.186** **5.187**

of *N*-substituted methylpyrroles in methanolic sodium cyanide was studied by Yoshida, who reported the formation of two types of products.[157,158] Most of them contained a cyano group on the aromatic ring but, in some cases, side-chain cyanation occurred. The formation of the ring substitution products can be explained in terms of Scheme 5.13.[153] The radical cation **5.189**, formed by oxidation of the pyrrole **5.188**, reacts with the cyanide ion to give the radical **5.190**. The subsequent loss of a second electron and a proton leads to the substitution product **5.191**. The formation of a side-chain substitution product



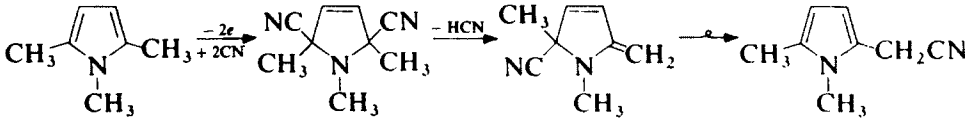
5.188 5.189 5.190 5.191

Scheme 5.13



5.192 5.193

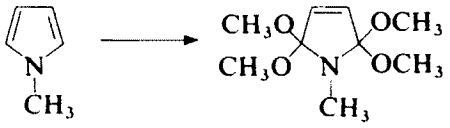
5.193 was supposed to proceed through the radical **5.192**, formed by deprotonation of **5.189**.[153,157,158] This hypothesis was, however, questioned somewhat later by Eberson,[159] who showed that the 2-cyanomethyl-1,5-dimethylpyrrole **5.197**, formed during the anodic oxidation of the trimethylpyrrole **5.194** in methanolic cyanide solution, was the result secondary reactions of the 2,5-dicyanoadduct **5.195**. In fact, the adduct **5.195** could be isolated after the



5.194 5.195 5.196 5.197

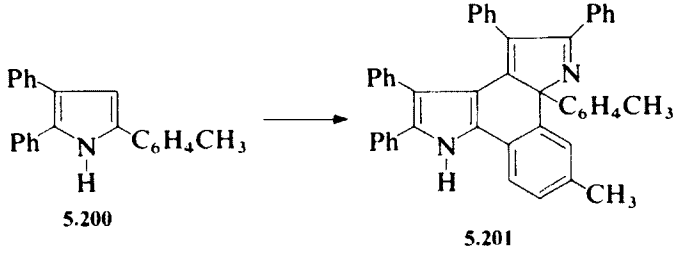
electrochemical and also chemical [with potassium hexaferrate(III)] oxidation of **5.194**. The thermal or base-induced decomposition of **5.195** was shown to give the product **5.197**, presumably through the intermediate **5.196**.

Electrolysis of 1-methylpyrrole (**5.198**) in methanol gives 2,2,5,5-tetramethoxy-1-methyl-pyrrole **5.199** in 64% yield.[160] Although a mechanism involving a dication derived from **5.198** was proposed by the authors for the formation of **5.199**, the tetramethoxylation of **5.198** can be easily explained on the basis of Scheme 5.13 using methanol as a nucleophile.



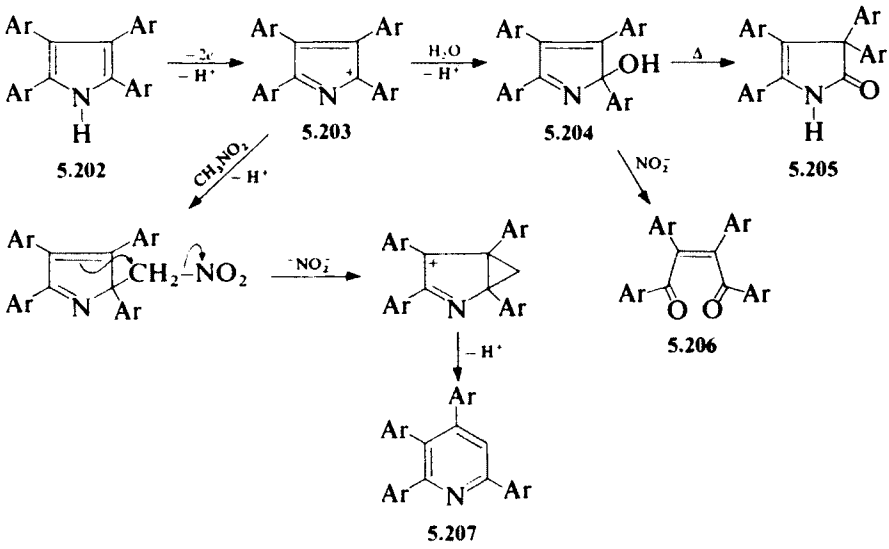
5.198 5.199

The anodic oxidation of polyarylpyrroles has been studied in more detail.[161-167] Thus, the electrooxidation of 4,5-diphenyl-2(*p*-tolyl)pyrrole (**5.200**) in acetonitrile[161] give the same product **5.201** as the oxidation with potassium dichromate[114] (cf. Cr(VI) and Mn(VII) compounds). The products obtained



5.200 5.201

from the electrolysis of 2,3,4,5-tetraphenylpyrrole[163,164] or 2,3,4,5-tetrakis(*p*-tolyl)pyrrole (**5.202**),[166] in nitromethane, are the compounds **5.204**–**5.207**. The relative yield of each product depends critically on the reaction temperature. Their mechanism of formation is summarized in Scheme 5.14. The cation **5.203** can react with traces of water to give the hydroxycompound **5.204**, which rearranges, at higher temperature, to the pyrrolinone, **5.205**. The dibenzoylstilbene **5.206** arises from the oxidation of **5.204** by the nitrite anion, which is formed during the reaction of **5.203** with the solvent, giving the pyridine **5.207**. When all five pyrrole atoms are substituted with aromatic groups, the electrooxidation gives relatively stable radical cations.[162] They were characterized spectrometrically, but no reaction products were isolated.



5.202 5.203 5.204 5.205 5.206 5.207

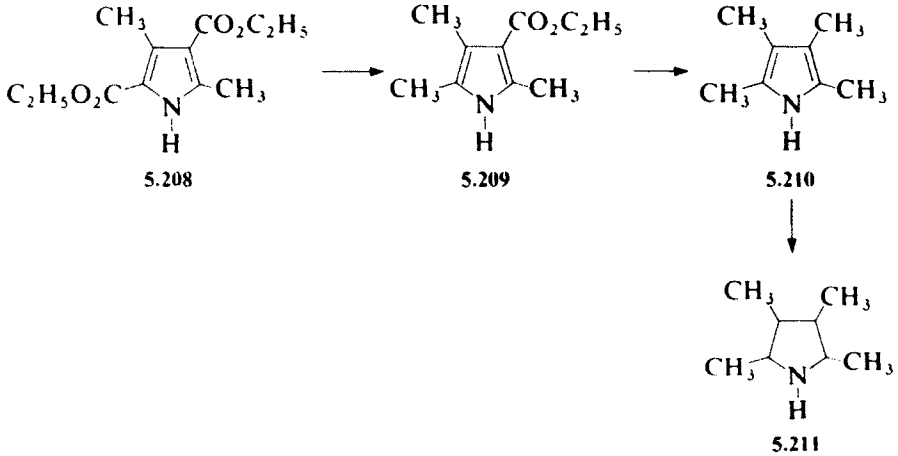
Scheme 5.14

3.5.5. Reduction of the Pyrrole Ring

The reduction of the pyrrole ring by chemical reagents, particularly by catalytic hydrogenation, has been extensively studied. Several excellent reviews dealing with this subject are available.[2–4,169,170]

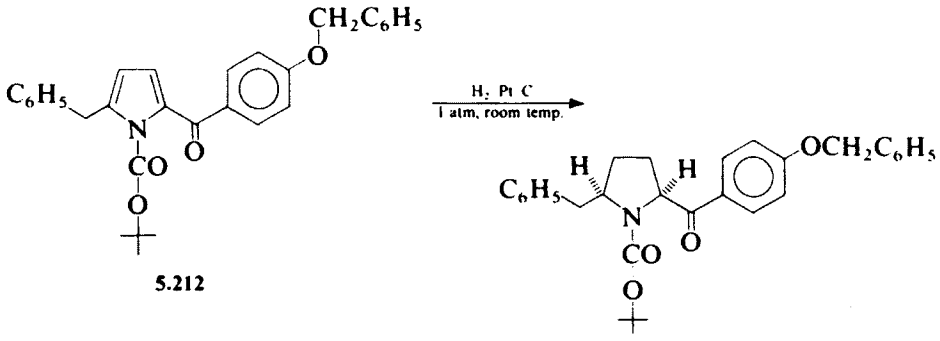
Pyrrole and its derivatives can be catalytically hydrogenated at moderate temperature and pressures using platinum,[171–180] palladium,[181–186] rhodium,[187–194] ruthenium,[195–199] or Raney-nickel[200–204] catalysts to give the corresponding pyrrolidines. The catalytic hydrogenation of pyrroles is a reversible process. The equilibrium is deplaced to the starting material at higher temperatures.[181,205–207]

The presence of electron-withdrawing substituents at the α or β positions of the pyrrole ring inhibits the hydrogenation of the pyrrole nucleus, so that side-chain reduction can take place.[171,200,208] An α-substitutent is reduced more rapidly than a β-substituent. The reduction of the diester **5.208** on $CuCr_2O_4$ at 225°C, for instance, takes place giving subsequently the compounds **5.209**–**5.211**.[200] On the other hand, the hydrogenation of the pyrrole ring is



5.208 **5.209** **5.210** **5.211**

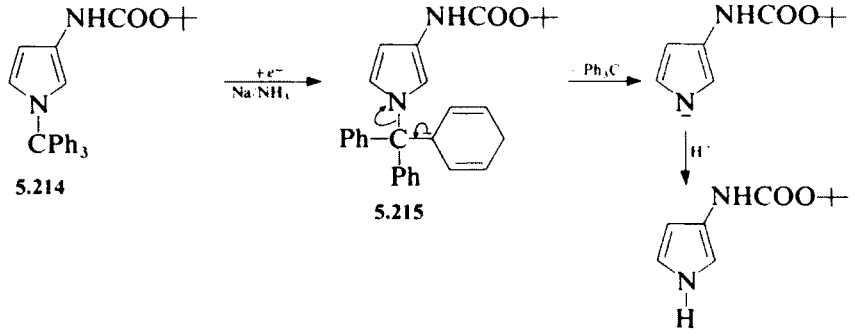
facilitated if the delocalization of the nitrogen electron pair is attenuated by an electron-withdrawing substituent on the nitrogen atom.[176,209,210] Thus, the 1-*tert*-butoxycarbonylpyrrole derivative **5.212** gave the pyrrolidine **5.213** on hydrogenation in ethanol at room temperature and atmospheric pressure over



5.212 **5.213**

platinum–charcoal catalyst.[176] No hydrogenolysis of the sensitive benzyloxy group took place.

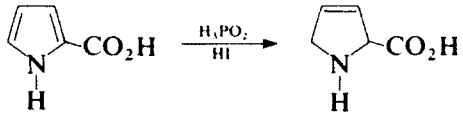
In general, the electron-rich pyrrole ring is not readily reduced by chemical reducing agents. Thus, pyrrole is inert to the action of alkali metals in both alcohols[211,212] and liquid ammonia.[213–215] The preferential reactivity of the benzene ring with sodium in ammonia, compared with the pyrrole nucleus,[215] was used for the mild reductive cleavage of the trityl *N*-protective group of the derivative **5.214** to give the pyrrole **5.216**.[216]



5.214 **5.215** **5.216**

Not surprisingly, the pyrrole nucleus is also stable in lithium aluminum hydride,[217,218,220] sodium borohydride,[219,220] and diborane.[220,221] Consequently, these reagents may be used for the reduction of side-chain groups without affecting the pyrrole ring.

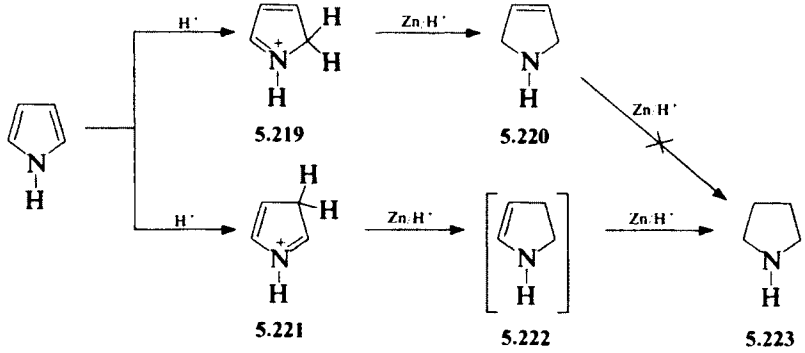
The pyrrole-2-carboxylic acid **5.217** can be effectively reduced with hypophosphorous acid and gaseous hydrogen iodide to the dehydroproline **5.218**.[222,223]



5.217 **5.218**

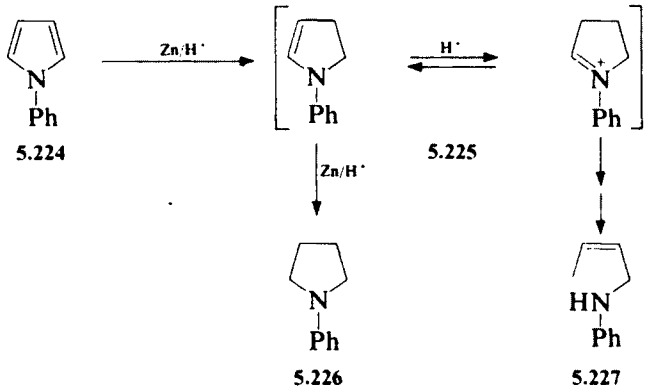
The low reactivity of the pyrrole ring toward reducing agents mentioned above contrasts sharply with the easy reduction which takes place in metal–acid systems.[2–4]

The reduction of pyrrole with zinc in acetic acid was observed for the first time by Ciamician and Dennstedt.[224,225] The major product of this reaction, the 3-pyrroline **5.220**, was shown later[226] to contain variable quantities (up to 15%) of pyrrolidine (**5.223**). The precursors for **5.220** and **5.223** are the pyrroleninium cations **5.219** and **5.221**, respectively, which are formed by the protonation of pyrrole. The zinc acid reduction of the thermodynamically preferred cation **5.219** gives rise to the major product **5.220**, which withstands further reduction. The enamine character of the intermediate 2-pyrroline **5.222** facilitates, on the other hand, its reduction to give pyrrolidine (**5.223**) as the final product.

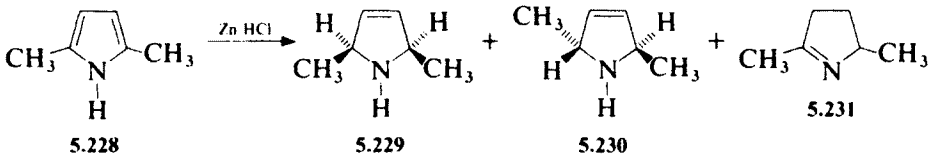


Likewise, simultaneous formation of 3-pyrroline and pyrrolidine takes place during the reduction of 1-methylpyrrole,[227,228] 2,5-diphenylpyrrole, and some pyridylpyrroles[229] with zinc in the presence of hydrochloric acid.

The reaction pathway involving the 2-pyrroline **5.225** seems to be the prevailing one in the reduction of 1-phenylpyrrole (**5.224**). The products of this reaction are *N*-phenylpyrrolidine (**5.226**) and the aniline derivative **5.227**.[230]



The zinc–hydrochloric acid reduction of *C*-methylpyrroles also leads to the corresponding 3-pyrrolines as the major products.[230–233] 2,5-Dimethylpyrrole (**5.228**), for example, gave both diastereomeric pyrrolines **5.229** and **5.230**, together with some 1-pyrroline **5.231**.[231,233]



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3.6. NUCLEOPHILIC SUBSTITUTION OF THE PYRROLE RING

Nicholas Dennis*

School of Chemical Sciences, University of East Anglia, Norwich NR4 7TJ, UK

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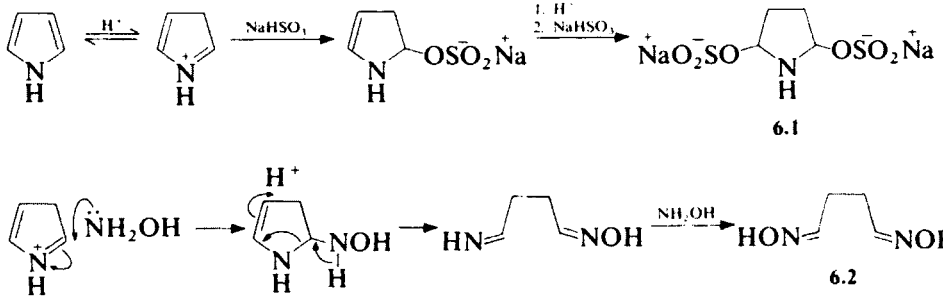
3.6.1. Acid-Catalyzed Nucleophilic Substitution Reactions

As is evident from earlier sections of this chapter, pyrrole reacts with electrophiles but is less susceptible to nucleophilic attack. In general, electrophilic reactions occur on the neutral molecule or on the pyrrolyl anion. However, when the pyrrole ring is initially protonated (see Section 3.2), the system is susceptible to reaction with nucleophiles.

Protonation of pyrroles promotes nucleophilic addition to the heterocyclic ring. Thus, pyrrole reacts with sodium hydrogen sulfite to form the adduct **6.1**[1–3] (Scheme 6.1). Similarly, nucleophilic attack by hydroxylamine[4] or phenylhydrazine on the protonated pyrrole ring results in ring opening to the dioxime

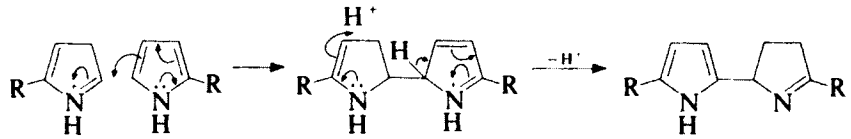


Scheme 6.1

**Present Affiliation*: School of Science and Technology, Bond University, Private Bag 10, Gold Coast Mail Centre, Queensland 4217, Australia.

of succinaldehyde **6.2**.[5] This ring cleavage by hydroxylamine has been used synthetically to regenerate, under mild conditions, primary amines, which have been protected as pyrroles.[4]

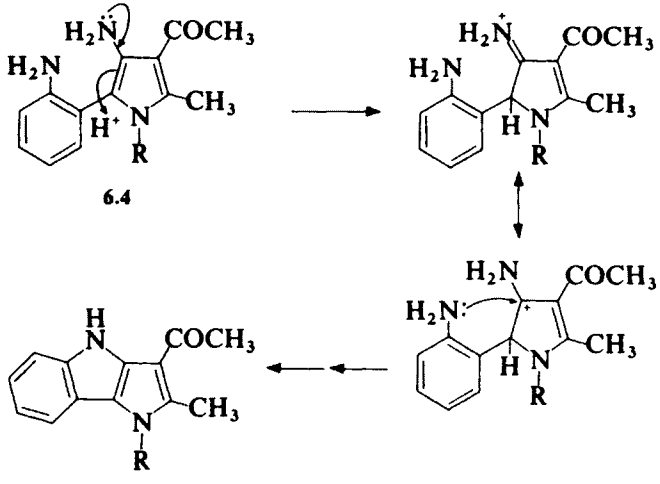
Monoalkyl- and dialkylpyrroles form dimers **6.3** on protonation with anhydrous HCl via the nucleophilic reaction between the neutral pyrrole and a low concentration of the conjugate acid[6] (Scheme 6.2) (see also Section 3.2.4). However, tri- and tetra-substituted pyrroles do not dimerize and pyrrole, under controlled conditions, is converted into a trimer (see Section 3.2.4).



6.3

Scheme 6.2

The conversion of 3-amino-2-(2-aminophenyl)pyrroles **6.4** into pyrrolo[3,2-*b*]indoles **6.5** is also acid-catalyzed[7] (Scheme 6.3). The reduction of the 3-acyl-1,2-dimethyl-4-nitro-5-(2-nitrophenyl)pyrrole with iron in acetic acid also produces the cyclized product. The intramolecular nucleophilic reaction involves expulsion of the pyrrolyl amino group, as shown by isotopic labeling, and this implies that cyclization proceeds via nucleophilic attack by the phenylamino group on the pyrrole ring. Such a reaction would be facilitated by protonation of the 5 position of the ring. Some evidence for this mechanism is provided by the observation that the corresponding 3-halo derivative produced lower yields of the pyrrolo[3,2-*b*]indole than did the 3-amino derivative, whereas the 3-nitro derivative failed to cyclize, although the nitro group would have been expected



6.4 **6.5**

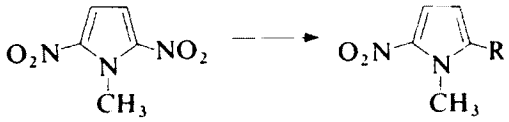
Scheme 6.3

to be a much better leaving group than the amino group. These facts are in accord with the expected basicities of the α position of the ring as a result of the electronic effect of the adjacent β-substituent. This rationalization is not precluded by the recent observation that thermodynamic protonation of 3-aminopyrroles occurs on the amino group.[8]

3.6.2. Direct Nucleophilic Substitution of the Pyrrole Ring

A nitro group on the pyrrole nucleus activates the ring to nucleophilic attack. When good leaving groups, including the nitro group itself, are attached to the ring, either normal aromatic nucleophilic substitution (S_NAr) takes place or, with certain arrangements of the nitro and the leaving groups, cine-substitution or ring-opening reactions may occur.

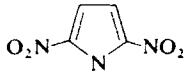
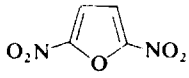
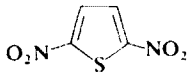
ipso-Substitution of the 2-nitro group of 1-methyl-2,5-dinitropyrrole by methoxide ions in MeOH,[9-11] thiophenoxide ions in MeOH,[12] and piperidine in acetonitrile[11,13] has been reported (Scheme 6.4). The rates of the nucleophilic substitution of the pyrrole ring are less than those observed with 2,5-dinitrofuran and 2,5-dinitrothiophene (Table 3.6.1).



R	m.p. (°C)
OMe	120–121
p-MeC_6H_4S	84.5–85.5
NC_6H_{10}	79–80

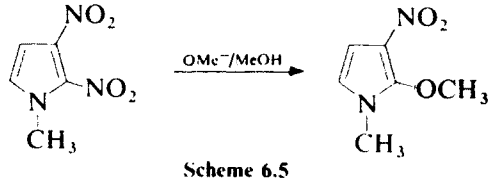
Scheme 6.4

TABLE 3.6.1. RELATIVE RATES OF NUCLEOPHILIC SUBSTITUTION

Compound	*p*-Thiophenol (25°C)[a]	Piperidine (25°C)[b]
	1	1
	1.7×10^3	2.4×10^6
	1.6×10^2	4.4×10^3

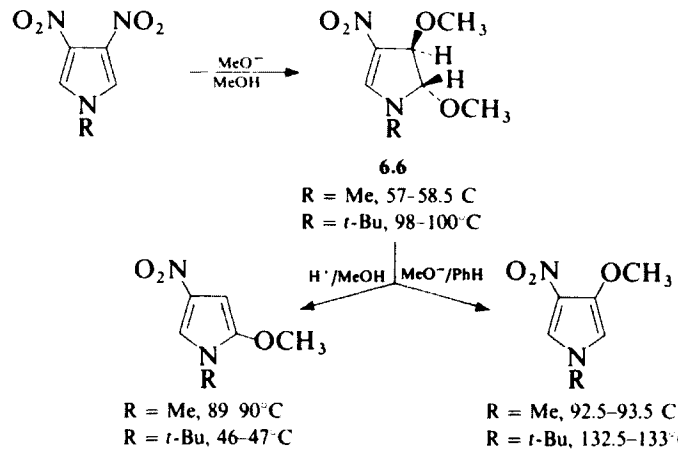
[a] In MeOH.
[b] In CH_3CN.

The denitration of 2-nitro group of 2,3-dinitropyrrole by methoxide ion has recently been reported[9] (Scheme 6.5) to be lower than the reactivity of 2,5-dinitropyrrole by a factor of 3.4.



Scheme 6.5

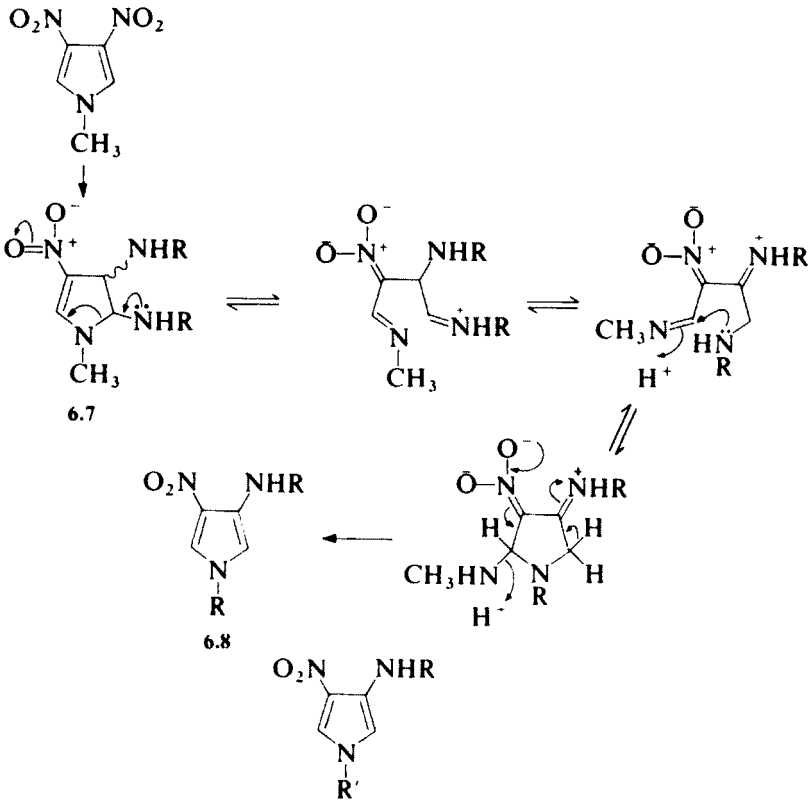
Both ipso- and cine-nucleophilic substitutions of 1-alkyl-3,4-dinitropyrroles occur with sodium methoxide[14,15] (Scheme 6.6). The reaction proceeds via the initially formed *trans*-2,3-dimethoxy-4-nitro-Δ^4-pyrroline (**6.6**), which, under acidic conditions (CF_3COOH, MeOH), yields 2-methoxy-4-nitropyrrole, while prolonged reaction with base produces 3-methoxy-4-nitropyrrole. The acid-promoted elimination of MeOH is thought to involve an E1-like reaction pathway via protonation, extrusion of methanol, and subsequent loss of a proton. The cationic intermediate, produced by extrusion of methanol from the β position is relatively more stable than the analogous cation, which results from extrusion of methanol from the α position of **6.6.** Under basic conditions, elimination of methanol is expected to occur by a stepwise E1cB mechanism. The initial abstraction of a proton from the β position is favored by the proximity of the adjacent nitro group, which increases its acidity.



Scheme 6.6

An apparently analogous cine- and ipso-substitution of the 3-nitro group of 1-methyl-3,4-dinitropyrrole by secondary and primary amines has been reported. The reaction with primary amines yields 1-substituted 3-alkylamino-4-nitropyrroles **6.8** in which the pyrrolyl *N*-substituent corresponds to that of the

primary amine. A ring-opening–ring-closure reaction mechanism is envisioned in which a diaminopyrroline intermediate **6.7**, analogous to **6.6**, is initially formed[17] (Scheme 6.7). In this case, however, the pyrroline intermediate **6.7** cannot be isolated, although, in the related case of 2,5-dimethyl-3,4-dinitrothiophene, good yields of the dimorpholino and dipiperidino addition products were isolated.[18]

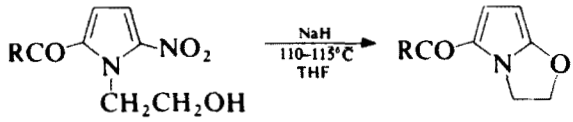


R	R'	m.p. (°C)
t-Bu	*t*-Bu	137.5–139
t-Bu	Me	91–92

Scheme 6.7

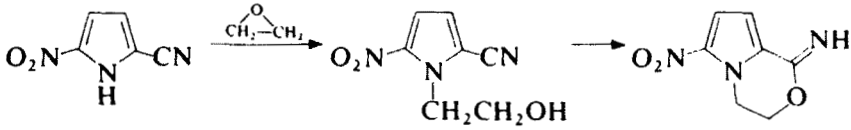
An intramolecular ipso-substitution of a nitro group activated by an acyl substituent, as shown in Scheme 6.8, has been recorded.[16] In the case of the unactivated 1-(2-hydroxyethyl)-2-nitropyrrole, no cyclization takes place. The related reaction of 2-cyano-5-nitropyrrole with ethylene oxide leads[16] to the formation of the pyrrolo[2,1-*c*]oxazine derivative **6.9** (Scheme 6.9).

The congugate addition of alkyl Grignard reagents to 1-alkyl-2-nitropyrroles proceeds smoothly to give both the 1,4- and the 1,6-addition products, for example, **6.10** and **6.11**, which, on oxidation with DDQ in a one-pot reaction



R	m.p. (°C)
CH_3	93–94
C_3H_7	48–50
C_6H_5	112–113
$C_{17}H_{35}$	80–81

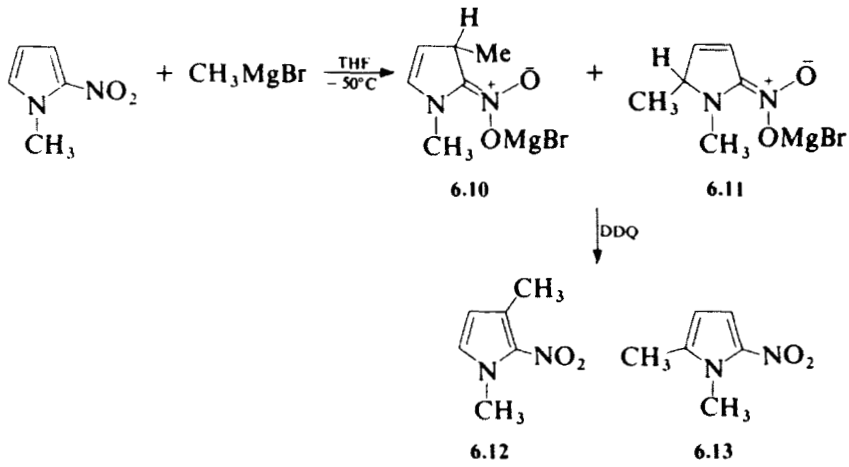
Scheme 6.8



6.9

Scheme 6.9

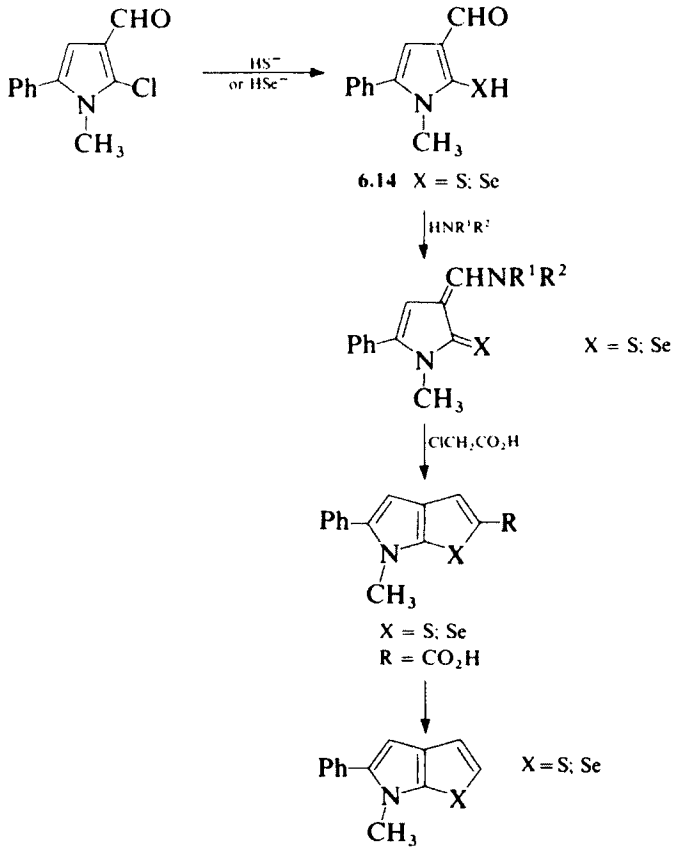
yield the corresponding 1,3-dialkyl-2-nitropyrrole **6.12** and 1,5-dialkyl-2-nitropyrrole **6.13**, with prevalence of the former isomer[19] (Scheme 6.10). This reaction pathway is analogous to that observed with 2-nitrothiophene, whereas the corresponding reaction with 2-nitrofuran leads to only ring-opened products. In spite of the steric hindrance presented by the 1-substituent the reactions of alkyl Grignard reagents with 1-(triisopropylsilyl)-3-nitropyrrole leads exclusively to the 2-alkylated isomers.[19]



6.10 6.11 6.12 6.13

Scheme 6.10

The nucleophilic displacement of the 2-chloro group of 2-chloro-3-formyl-1-methyl-5-phenylpyrrole by both potassium hydrogen selenide and sulfide to yield the corresponding pyrroles **6.14**, has been utilized[20] in the synthesis of thieno- and selenopheno[2,3-*b*]pyrroles (Scheme 6.11). The 3-formyl group activates the 2 position to electrophilic attack in the same way that the nitro group of 3-bromo-2-nitrothiophene activates the nucleophilic displacement of the 2-bromo group by a variety of nucleophiles.[21]

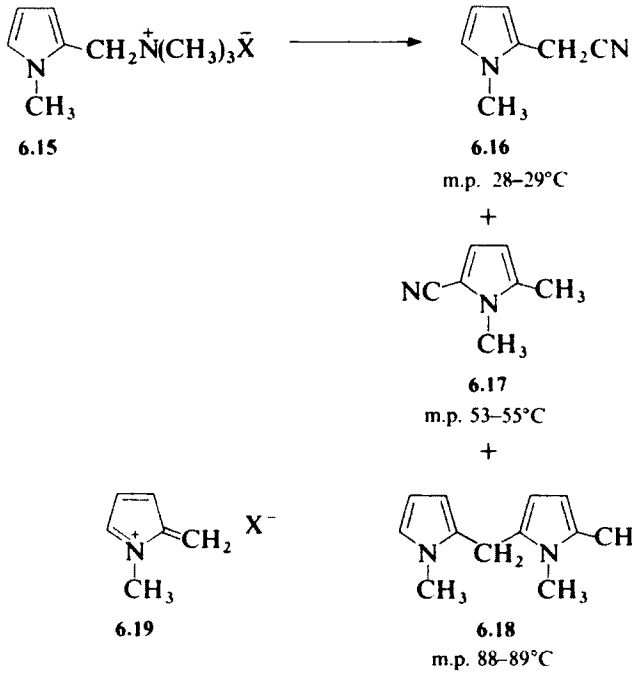


Scheme 6.11

3.6.3. "Abnormal" Nucleophilic Substitution Reactions and Rearrangement Reactions

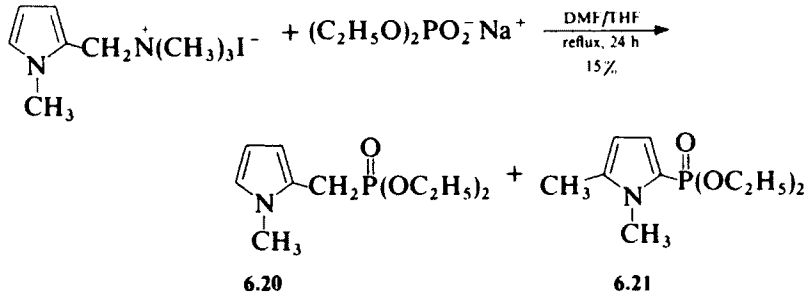
The reaction of pyrrol-2-ylmethylammonium salts **6.15** with cyanide ion led to the "abnormal" 2-cyano-1,5-dimethylpyrrole (**6.17**), in addition to the expected "normal" product **6.16** (Scheme 6.12).[22] This type of "abnormal" substitution has also been observed[23] with 2-chloromethylfuran. Formally, the

"abnormal" displacement of trimethylamine probably occurs via an S_N2' mechanism. However, since the relative yields of **6.17**, compared with the "normal" nucleophilic substitution product **6.16**, depends on the solvent and the counter-anion, it is possible that the mechanism proceeds by an S_N1-type mechanism and involves the initial formation of the pyrrolylmethyl cation **6.19**. The highest yield of **6.17** was obtained from the chloride salt in dimethyl sulfoxide, and, in most reactions, minor amounts of dipyrrolylmethanes **6.18** were also formed.[22]



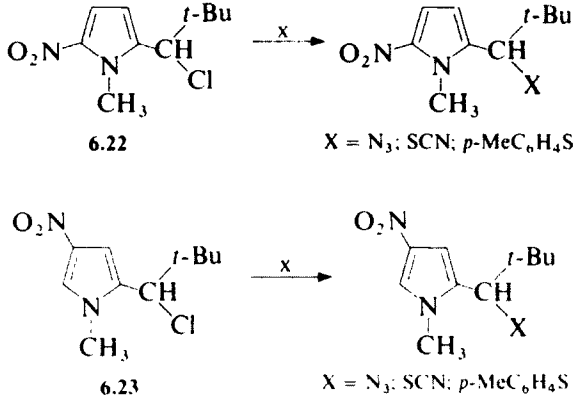
Scheme 6.12

Recently, the related reaction of pyrrol-2-ylmethylammonium iodide **6.15** (X = I) with the anion of diethyl phosphite was reported to yield the expected "normal" phosphonate **6.20**, together with the "abnormal" phosphonate **6.21**



Scheme 6.13

(Scheme 6.13) as an approximately 2:1 mixture of isomers, which could not be readily separated.[24,25] Again, the cine-substitution product is believed to originate from an S_N2' process. In contrast, the 4- and 5-nitropyrrol-2-yl methyl chlorides **6.23** and **6.22** react with azide, thiocyanate, and *p*-toluenethiolate ions in dimethylformamide via the cationic species in an S_N1-type process. This contrasts with the $S_{RN}1$ and S_N(AEAE) processes, by which their analogs in the benzene, furan, or thiophene systems react[26] (Scheme 6.14). Also, the methyl chlorides are readily solvated in methanol to high yields of the corresponding methyl ethers.

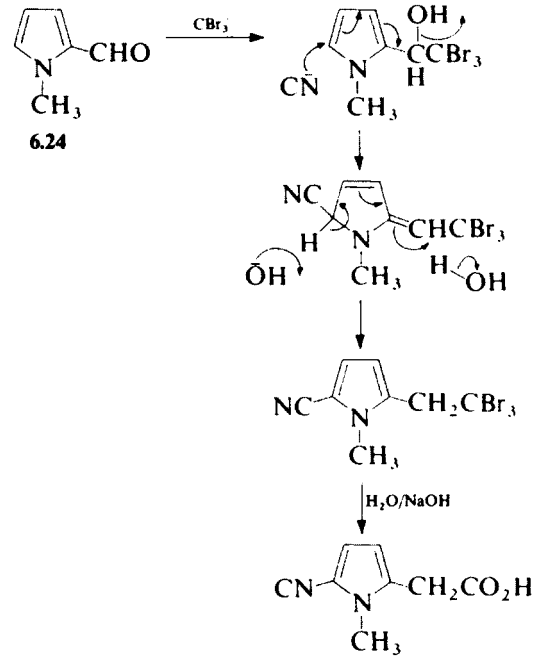


Scheme 6.14

A Japanese patent infers[27] a related "abnormal" substitution in the base-catalyzed conversion of 2-formyl-1-methylpyrrole (**6.24**) into 5-cyanopyrrol-2-ylacetic acid (**6.25**) by cyanide ion in bromoform. The mechanism probably involves an initial nucleophilic attack on the aldehyde group by the tribromomethyl anion, followed by a nucleophilic addition of the cyanide ion at the 5 position of the pyrrole ring. Subsequent rearomatization of the 5-membered ring and base-catalyzed hydrolysis of the tribromomethyl group yields the carboxylic acid (Scheme 6.15).

The Sommelet rearrangement of the trimethyl (2-pyrrolylmethyl)ammonium ion (**6.15**) (X = Cl) to yield 2-methyl-3-dimethylaminopyrrole (**6.26**) involves an intramolecular nucleophilic attack on the pyrrole ring, with concurrent cleavage of the carbon–nitrogen bond[28] (Scheme 6.16). Under similar conditions, the 3-isomer **6.27** undergoes nucleophilic displacement mainly on the side chain (87%), with only 13% of the rearranged product **6.28**.

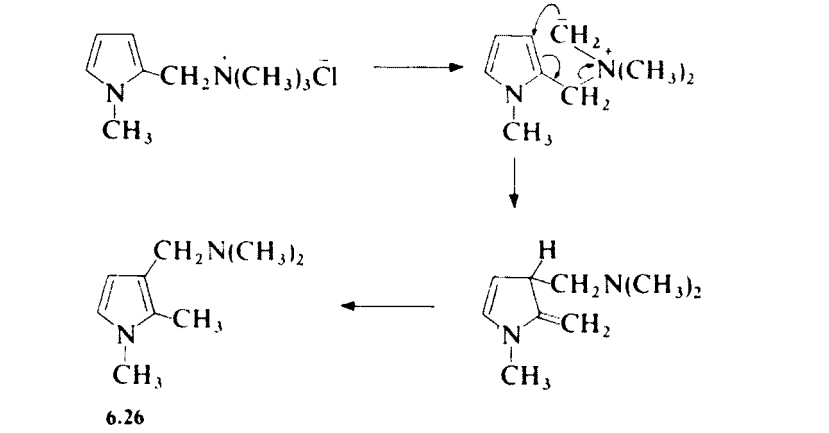
A novel Pummerer-like chlorination of pyrrol-3-yl sulfoxides **6.29** with thionyl chloride to give 2,3-disubstituted pyrroles **6.32** has been reported recently.[29] Although the yields of the 2-chloropyrroles are generally low, the chlorine atom is introduced regiospecifically into the 2 position of the pyrrole. The mechanism is thought to involve a Pummerer-like reaction of the sulfoxide **6.29** with the thionyl chloride to form the sulfoxonium chloride **6.30**, which can



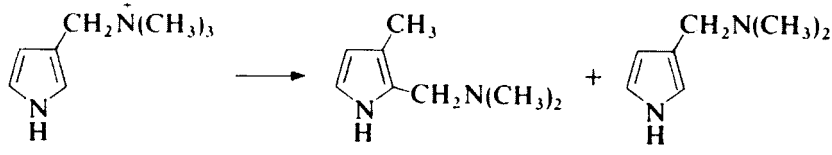
6.24

6.25

Scheme 6.15

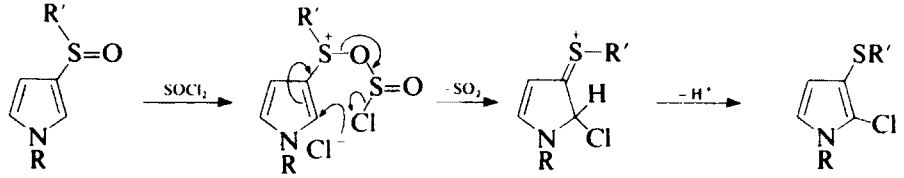


6.26



6.27 6.28

Scheme 6.16



6.29 **6.30** **6.31** **6.32**

Scheme 6.17

eliminate SO_2 concurrently with a nucleophilic attack by the chloride ion at the 2 position. Subsequent loss of a proton from the sulfonium salt **6.31** leads to the aromatic compound **6.32** (Scheme 6.17). The analogous reaction of indol-3-yl sulfoxides yields the chloroindoles in high yields.

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CHAPTER 4

Physical and Theoretical Aspects, Synthesis, and Chemical Reactivity of 2*H*- and 3*H*-Pyrroles

Michael P. Sammes

Department of Organic Chemistry
University of Hong Kong
Pokfulam Road, Hong Kong

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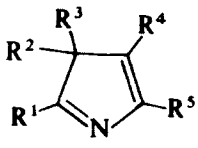
4.1. INTRODUCTION

Two classes of 2*H*- and 3*H*-pyrroles may be recognized. These are, respectively, systems having a tetrahedral carbon atom in the ring (structures **1** and **2**), which were known in the early literature as *pyrrolenines* or *isopyrroles*, and systems having an exocyclic double bond. The latter class may further be conveniently subdivided into systems with an exocyclic C=C bond (the 1-azafulvenes **3** and the 2-azafulvenes **4**), and those having an exocyclic heteroatom X (structures **5** and **6**), which include pyrrolones, pyrrolimines, and diazopyrroles.

1



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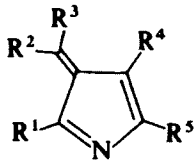

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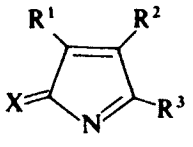

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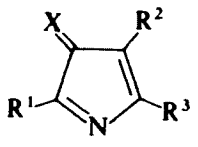


6

Although 2*H*- and 3*H*-pyrroles have been discussed in general works on heterocyclic chemistry[1,2] as well as specific texts on pyrroles,[3,4] they have received considerably less attention than their 1*H*-counterparts. Some new methods of synthesis are included in a review on pyrroles covering the period 1966–1974,[5] and systems having a tetrahedral carbon atom have been the subject of a recent comprehensive review.[6]

In their chemistry, the 2*H*- and 3*H*-pyrroles behave very differently from the 1*H*-compounds. With the possible exception of azafulvenes **3** and **4** having strong electron-donating groups on the exocyclic double bond, they lack the aromatic sextet. Further, they are more basic because of the presence of the pyridine-like nitrogen atom, which also causes the rings to be electrophilic rather than nucleophilic in character.

This chapter includes discussion of physical and theoretical aspects, synthesis, and chemical reactivity of structure types **1** to **6**, as well as their *N*-oxides, and those salts that can be isolated or characterized in solution and in which the positive charge resides predominantly in the ring. Specifically excluded are the numerous transient tetrahedral intermediates in the electrophilic substitution of 1*H*-pyrroles, the many dipyrromethenes and their salts, and benz-fused systems. Since most published work concerns structure types **1** and **2**, for convenience these will be referred to simply as 2*H*- and 3*H*-*pyrroles*. Structure types **3** and **4**

will be named as 1- and 2-*azafulvenes*, respectively, while types **5** and **6** will be described as 2*H*- and 3*H*-*pyrroles with an exocyclic C=X bond.*

The literature has been covered comprehensively up to the end of 1987, and some references from 1988 are included.

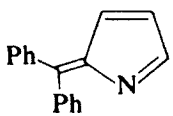
4.2. PHYSICAL PROPERTIES

Physical and theoretical data for individual compounds contained in specific papers are indicated in Tables 4.34–4.55 in Section 4.6.

4.2.1. Ultraviolet and Visible Spectra

Ultraviolet absorption data for representative 2*H*- and 3*H*-pyrroles are given in Tables 4.1 and 4.2, respectively, in which the effect of substituents may be seen. In general, for similarly substituted compounds, 3*H*-pyrroles absorb approximately 20 nm to longer wavelength than their 2*H*-isomers, but log ε values are little different. Changing the solvent from methanol to cyclohexane has no significant effect in the case of alkyl substituted 2*H*-pyrroles.[21] Spectra of both classes show a bathochromic shift of about 20 nm when solutions are acidified.[8,11,13,26] Whereas for 2*H*-pyrroles this is accompanied by a significant increase in log ε, in the case of 3*H*-pyrroles log ε shows little change. Ultraviolet spectroscopy has been used to determine the site of protonation of 1*H*-pyrroles in strongly acidic media.[32,33] Those protonated at C_3 to give 3*H*-pyrrolium salts absorb approximately 40 nm to longer wavelengths than do products from protonation at C_2 (Table 4.3). Data for some stable 2*H*-pyrrole salts are presented in Table 4.4, while Table 4.5 lists those for 2*H*-pyrrole *N*-oxides. For similarly substituted compounds, the introduction of the *N*-oxide function causes a large bathochromic shift in $\lambda_{max.}$.

For 1- and 2-azafulvenes, the effect of substituents can be seen in Tables 4.6 and 4.7, respectively. In many instances absorption extends into the visible region, and the compounds are colored. The spectrum of the 2-azafulvene **7** may be compared with that of the diphenylfulvene **8**, also measured in hexane, [$\lambda_{max.}$ 322 nm (log ε 4.29)].[41] A number of papers also include data for the corresponding protonated forms,[41–43,47,51] but it is difficult to detect any trends since in some cases the cations are essentially substituted 1*H*-pyrroles.[43] The effect of substituents on $\lambda_{max.}$ for some colored azafulenium salts has been studied,[53] and



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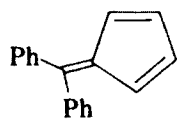

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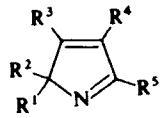
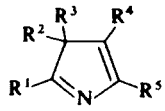
TABLE 4.1. UV SPECTROSCOPIC DATA FOR SELECTED 2*H*-PYRROLES



Substituent							
R^1	R^2	R^3	R^4	R^5	λ_{max} (nm) (log ε)	Solvent	Ref.
Me	$CH_2CH{=}CH_2$	H	H	Me	207(3.57)	MeOH	7
Me	$CHMeCH{=}CH_2$	H	H	Me	211(3.57)	MeOH	7
Et	$CHMeCH{=}CH_2$	H	H	Me	217(3.68)	MeOH	7
Me	Me	H	Me	Me	236(3.42)	EtOH	8
					255(3.48)	EtOH/HCl	8
Me	Me	Me	H	Me	233(3.38)	EtOH	8
					250(3.47)	EtOH/HCl	8
Me	Et	Me	Me	H	248(3.49)	EtOH	8
					271(3.58)	EtOH/HCl	8
Me	Me	Me	Me	Me	243(3.40)	EtOH	8
					266(3.45)	EtOH/HCl	8
Me	Me	H	H	Ph	212.5(4.08), 217.5(4.08), 249(4.00)	MeOH	9
Me	Me	H	Ph	H	224(4.18), 268(3.70), 287sh, 296sh	MeOH	9
Me	Me	Me	H	Ph	244(4.19), 277sh(3.5), 285sh(3.3)	EtOH	10
					216(3.83), 279(4.35)	EtOH/HCl	11
Me	Me	Ph	Me	Et	252.5(3.78)	EtOH	12
Me	Ph	Me	H	Ph	215(4.37), 245(4.21)	EtOH	13
Me	Me	Ph	H	Ph	248(4.25)	EtOH	12
Me	Me	Ph	Me	Ph	240(4.17)	EtOH	12
Me	$CHCl_2$	H	H	Me	233(3.38)	EtOH	14
Me	$CHCl_2$	Me	Me	Me	247(3.45)	EtOH	14
Me	Me	H	H	CO_2Et	242(3.41)	EtOH	15
Me	Me	CN	H	Ph	237(4.17), 276sh(3.76)	EtOH	16
Me	Me	Ph	CO_2Me	H	230sh(3.55), 251(3.60), 280sh(3.59)	MeOH	17
Me	Me	Ph	CO_2Me	CO_2Me	227(3.58), 293(3.57)	MeOH	17
Me	Me	CO_2Me	CO_2Me	Ph	230.5(3.87), 248sh(3.74), 283sh(3.19)	EtOH	18
Me	Me	Ph	CO_2Et	Ph	222(4.19), 245sh(4.10), 287sh (3.68)	EtOH	19
H	H	Me	Me	OMe	200(3.82)	*t*-BuOH	20
t-Bu	OOH	H	H	*t*-Bu	205(3.60), 235(3.08), 275sh(2.51)	MeOH	21
t-Bu	OOH	*t*-Bu	H	*t*-Bu	< 204(3.53), 249(3.44), 285sh(2.92)	MeOH	21
Me	Me	OMe	H	Me	255(3.65)	—	22
Me	Me	NMe_2	H	Me	333(4.04)	—	22
H	H	OH	Ph	NMe_2	222(4.08), 287(4.30)	MeOH	23
H	Me	OH	Me	NEt_2	228(4.00), 289(4.29)	MeOH	23
Me	Me	OH	Me	NEt_2	226(4.00), 287(4.35)	EtOH	24
Cl	Cl	Cl	Cl	Cl	220(3.48), 282(3.00)	—	25

TABLE 4.2. UV SPECTROSCOPIC DATA FOR SELECTED 3*H*-PYRROLES

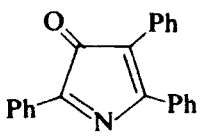


Substituent							
R^1	R^2	R^3	R^4	R^5	$\lambda_{max.}$ (nm) (log ε)	Solvent	Ref.
Me	Me	Me	H	Me	253(3.08)	EtOH	11
					271(3.07)	EtOH/HCl	11
Me	Me	Et	Me	H	254(3.49)	EtOH	26
					272(3.50)	EtOH/HCl	26
Me	Me	Me	Me	Me	262(3.41)	EtOH	26
					283(3.42)	EtOH/HCl	26
Me	Me	Et	Me	Me	264(3.33)	EtOH	26
					286(3.35)	EtOH/HCl	26
Ph	Me	Me	H	Me	215(3.97), 250sh(3.51), 303(3.94)	EtOH	11
					214sh(3.65), 260(3.61), 330(3.96)	EtOH/HCl	11
Me	Me	Me	H	Ph	218(4.28), 222(4.28), 270(3.85)	EtOH	13
					235(4.27), 272sh(3.54)	EtOH/HCl	13
Me	Me	Ph	H	Ph	217(4.37), 268sh(3.89), 279sh(3.73)	EtOH	13
					240(4.29), 280(3.91)	EtOH/HCl	13
Ar[a]	Ph	Ph	H	Ph	220(4.97), 264(4.68)	EtOH	27
t-Bu	Me	CO_2Et	H	Me	210sh(3.23), 257(3.38)	EtOH	28
Ph	Me	CO_2Et	H	Me	215sh(3.82), 300(3.83)	EtOH	28
Me	Me	CO_2Et	Me	Ph	225(4.11), 273(3.69)	EtOH	28
Ph	Me	CO_2Et	H	Ph	217(4.18), 255(4.56), 322(3.78)	EtOH	28
Bu_2N	H	H	H	Bu_2N	269(—)	EtOH	29
NH_2	$PhCH_2$	$PhCH_2$	CO_2Et	$NHCH_2Ph$	240(4.41), 330(3.99)	EtOH	30
Me	Ph		NH_2	CN	250(3.96), 336(3.62)	EtOH	31

[a] Ar = 1-isoquinolinyl.

UV-visible spectra have been published for complexes between azafulvenium cations and the tetracyano-*p*-quinodimethane (TCNQ) radical anion.[54]

Only a few data have been reported for 2*H*- and 3*H*-pyrroles with an exocyclic C=X bond. Representative examples are given in Tables 4.8 and 4.9, respectively. The spectrum of the triphenylpyrrolone **9** is similar to that for



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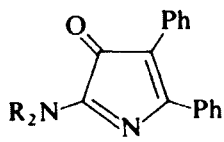

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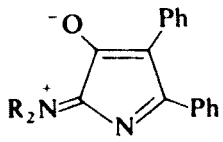

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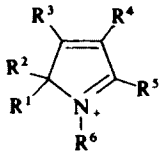
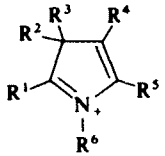
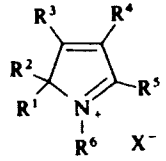
TABLE 4.3. UV SPECTROSCOPIC DATA FOR 2*H*- AND 3*H*-PYRROLIUM IONS GENERATED IN AQUEOUS SULFURIC ACID

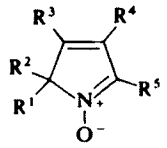
Substituent						
R^1	R^3	R^4	R^5	R^6	$\lambda_{max.}$ (nm) (log ε)	Ref.
			2H-Pyrrolium Ions			
H	H	H	H	H	241(3.59)	32
H	Me	H	H	H	258(3.68)	32
H	H	H	Me	H	233(3.65)	32
H	H	H	H	Me	247(3.61)	32
Me	H	H	Me	H	237(3.61)	33
H	Me	Me	H	H	271(3.76)	32
H	Me	H	Me	H	249(3.72)	32
Me	H	H	Me	Me	243(3.69)	33
Me	Me	H	Me	H	252(3.76)	32
Me	Me	Me	Me	H	265(3.70)	32
Me	Me	Me	Me	Me	269(3.74)	32
			3H-Pyrrolium Ions			
Me	H	H	Me	H	275(3.40)	33
Me	H	H	Me	Me	280(3.41)	33

TABLE 4.4. UV SPECTROSCOPIC DATA FOR SELECTED 2*H*-PYRROLE SALTS



Substituent									
R^1	R^2	R^3	R^4	R^5	R^6	X	$\lambda_{max.}$ (nm) (log ε)	Solvent	Ref.
Me	Me	Me	Me	Me	Me	I	218(4.18), 270(3.75)	EtOH	8
Me	Me	Me	Me	Me	Me	ClO_4	205(3.50), 272(3.70)	EtOH	34
$(CH_2)_5$		Me	$(CH_2)_4$		Me	ClO_4	282(3.85)	EtOH	35
$(CH_2)_5$		Ph	$(CH_2)_4$		Me	ClO_4	285(3.81)	EtOH	35
Me	CH_2CO_2Et	Me	CO_2Et	Me	Me	I	225(3.89), 260sh(3.32)	MeOH	36
H	H	OH	Ph	NMe_2	H	Cl	241(4.21)	MeOH	23

TABLE 4.5. UV SPECTROSCOPIC DATA FOR 2*H*-PYRROLE *N*-OXIDES



Substituent							
R^1	R^2	R^3	R^4	R^5	$\lambda_{max.}$ (nm) (log ε)	Solvent	Ref.
Me	Me	H	Me	*t*-Bu	300(3.71)	EtOH	37
Me	Me	H	*t*-Bu	*t*-Bu	299(3.65)	EtOH	37
Me	Me	H	Me	Ph	241(4.24), 316(3.67)	EtOH	38
Me	Me	Ph	H	*t*-Bu	237(4.03), 348(4.04)	EtOH	38
Me	Me	Ph	H	Ph	273(4.47), 357(3.95)	EtOH	38
Me	Me	H	H	CN	213(3.83), 322(3.73)	EtOH	39
Me	Me	Me	H	CN	217(3.97), 332(3.76)	EtOH	39
Me	Me	Ph	H	CN	211(3.93), 256(4.07), 362(3.95)	EtOH	39
Me	Me	Br	H	*t*-Bu	318(3.76)	EtOH	38
Me	Me	Br	Br	Ph	251(4.28), 332(3.69)	EtOH	38
Me	Me	Br	Ph	Ph	236(3.20), 257(4.28), 337(3.60)	EtOH	40

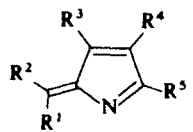
tetraphenylcyclopentadienone [$\lambda_{max.}$ 497 nm (log ε 3.05)].[57] The colors of the aminopyrrolones **10** have been explained in terms of a significant contribution from the cyclomerocyanine structure **11**.[57,60] This is supported by the sensitivity of $\lambda_{max.}$ to the dielectric constant of the solvent,[60], as well as by an X-ray-crystallographic study[61] and by MO calculations (see Section 4.3.1).[62]

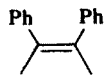
4.2.2. Infrared Spectra

Since many of the compounds covered in this chapter carry aryl substituents, it is often difficult to identify the pyrrole ring C=C and C=N absorptions with certainty. Assignments are thus made in the following tables only where there is no ambiguity.

For 2*H*- and 3*H*-pyrroles, IR data are given in Tables 4.10 and 4.11, respectively. A peak, generally assigned to $\nu_{C=N}$, falls in the ranges 1600–1665 and 1610–1675 cm^{-1} for 2*H*- and 3*H*-pyrroles, respectively, and that for the $\nu_{C=C}$ vibration is within the ranges 1515–1575 and 1545–1590 cm^{-1}. In at least two papers, four peaks have been reported between 1550 and 1665 cm^{-1} in simple 2*H*-pyrroles without aryl substituents.[34,72] The generalization has been made[70] that $\Delta\nu(\nu_{C=N} - \nu_{C=C})$ for 2*H*- and 3*H*-pyrroles lies in the ranges 90–125 and 25–70 cm^{-1}, respectively, thus supporting the 2*H*-structure (**12**) for pentachloropyrrole, rather than the isomeric 3*H*-form (**13**). Examination of the data in Tables 4.10 and 4.11 shows that this is generally true, although there are

TABLE 4.6. UV SPECTROSCOPIC DATA FOR SELECTED 1-AZAFULVENES



Substituent							
R^1	R^2	R^3	R^4	R^5	$\lambda_{max.}$ (nm) (log ε)	Solvent	Ref.
Ph	Ph	H	H	H	242(4.04), 337(4.29)	Hexane	41
Ph	Ph	Ph	H	Ph	380(4.20)	MeCN	42
		Ph	H	Ph	384(4.63)	MeCN	42
Ph	NMe_2	H	H	H	237.5(3.85), 353(4.35)	Hexane	43
4-MeC_6H_4	NMe_2	H	H	H	249(3.95), 352(4.31)	Hexane	43
4-ClC_6H_4	NMe_2	H	H	H	247.5(3.97), 354(4.24)	Hexane	43
4-$MeOC_6H_4$	NMe_2	H	H	H	264(4.00), 353.5(4.17)	Hexane	43
OH	Et	CO_2Me	H	Ph	248(3.88), 340(4.06)	MeOH	44
Ph	H	Me	Me	OH	323(4.42)	MeOH	45
Ph	H	Me	Me	OEt	323(4.52)	EtOH	45
4-MeC_6H_4	H	Me	Me	OMe	237(4.03), 245(4.00), 332(4.55)	EtOH	46
4-$Me_2NC_6H_4$	H	Me	Me	NMe_2	250(4.00), 397(4.37)	EtOH	46

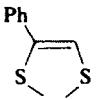
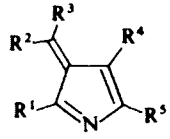
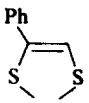
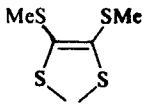
		H	H	H	320sh(2.74), 400sh(3.93), 421(4.19), 441(4.19)	CCl_4	47
		Me	H	Me	416(4.55)	MeCN	42
	H	H	Br	H	200(4.07), 250(3.53), 297(3.92), 345(4.24)	EtOH	48
	H	Br	Br	Br	200(4.20), 348(4.36)	EtOH	48
Ph	H	OH	H	OMe	240, 309sh, 374	MeOH	49
Ph	H	OMe	H	OMe	235, 323sh	MeOH	49
Ph	H	OMe	H		237, 337sh, 350	MeOH	49
Ph	H	OH	CO_2Me	OMe	242, 308sh, 350	MeOH	49
Ph	H	OMe	CO_2Me	OMe	235, 339sh	MeOH	49
Ph	H		CO_2Me	OMe	274, 335sh, 345	MeOH	49
CN	CO_2Me	NMe_2	Cl	NMe_2	268(3.57), 398(4.37)	CH_2Cl_2	50

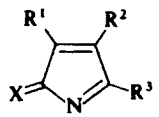
TABLE 4.7. UV SPECTROSCOPIC DATA FOR SELECTED 2-AZAFULVENES



Substituent							
R^1	R^2	R^3	R^4	R^5	$\lambda_{max.}$ (nm) (log ε)	Solvent	Ref.
Ph	Ph	Ph	H	Ph	347(4.12), 466(3.60)	MeCN	42
Me			H	Me	380(ca.3.6), 393(ca.3.7)[a]	CCl_4	47
Me			H	Me	412(4.38)	MeCN	42
Me			H	Me	409(4.08)	MeCN	51
	Ph	4-$Et_2NC_6H_4$	CN	Ph	265(4.31), 318(4.29), 455(4.28), 580(4.11)	$CHCl_3$	52
Cl	Ph	4-$Et_2NC_6H_4$	CN	Ph	285(—), 362(—), 538(—)	Hexane	52
					305(4.17), 383(3.99), 506sh, 588(4.58)	$CHCl_3$	52
					300(4.19), 372(3.98), 486(3.97), 603(4.66)	MeOH	52

[a] Unstable in solution.

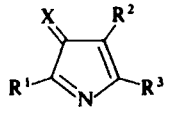
TABLE 4.8. UV SPECTROSCOPIC DATA FOR 2*H*-PYRROLES BEARING AN EXOCYCLIC C=X BOND



Substituent						
X	R^1	R^2	R^3	$\lambda_{max.}$ (nm) (log ε)	Solvent	Ref.
O	H	H	OAd[a]	276(2.44), 3.10(2.83)	$(CH_2Cl)_2$	55
N_2	Ph	H	Ph	345(4.00)	EtOH	56
N_2	Ph	COMe	Me	351(3.76)	EtOH	56

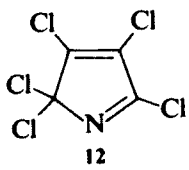
[a] Ad = 1-adamantyl.

TABLE 4.9. UV SPECTROSCOPIC DATA FOR SELECTED 3*H*-PYRROLES BEARING AN EXOCYCLIC C=X BOND

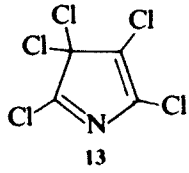


Substituent						
X	R^1	R^2	R^3	$\lambda_{max.}$ (nm) (log ε)	Solvent	Ref.
O	Ph	Ph	Ph	485(3.04)	CH_2Cl_2	57
O	NMe_2	Ph	Ph	261(4.19), 333(4.18), 596(3.45)	MeCN	57
O		Ph	Ph	262(4.19), 334(4.20), 587(3.37)	MeCN	57
O		Ph	Ph	263(4.20), 337(4.20), 605(3.36)	MeCN	57
O	NMe_2	Cl	NMe_2	307(3.88), 482(3.14)	CH_2Cl_2	50
S	NMe_2	NMe_2	NMe_2	347(4.21), 563(3.65)	PhH	50
N_2	Ph	H	Me	360(4.00)	EtOH	58
N_2	Ph	H	Ph	387(3.70)	EtOH	58
N_2	Ph	Ph	Ph	405(4.11)	EtOH	58
N_2	Me	Me	CO_2Et	333(3.56)	EtOH	58
N_2	Ph	COMe	Me	244(4.08)	EtOH	59
N_2	Ph	COMe	Ph	250(4.18)	EtOH	59
N_2	Ph	NO_2	Ph	339(3.90), 399(4.00)	EtOH	58

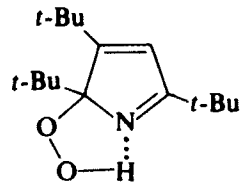
exceptions. An absorption in the range 1310–1335 cm^{-1} has been assigned to ν_{C-N} of 2*H*-pyrroles;[13] its range may be extended at least to 1350 cm^{-1}.[66] For the hydroperoxy compound **14**, ν_{OH} at 3100 and 2820 cm^{-1} is shifted to 2280 and 2125 cm^{-1} on deuterium exchange. In the case of 2*H*-pyrrole *N*-oxides (Table 4.12), both $\nu_{C=N}$ and $\nu_{C=C}$ are shifted to lower frequency relative to values for the free bases, and the latter peak varies over approximately 100 cm^{-1}. Intense absorption between 1200 and 1300 cm^{-1} may arise from the N–O group.



12



13



14

Tables 4.13–4.15 list IR data respectively for azafulvenes and for 2*H*- and 3*H*-pyrroles with exocyclic C=X bonds. In these cases it is not possible to assign bands specifically as $\nu_{C=N}$ or $\nu_{C=C}$ with any certainty. Absorptions due to

TABLE 4.10. IR SPECTROSCOPIC DATA FOR SELECTED 2*H*-PYRROLES

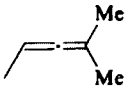
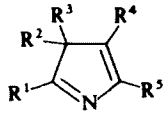
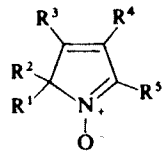
Substituent					$\nu_{max.}$ (cm^{-1})				
R^1	R^2	R^3	R^4	R^5	C=N	C=C	Others	Medium	Ref.
Me	n-C_3H_7	H	H	Me	1615	1525		Film	63
Me	Me	Me	H	Me	1640	1552	1320(C–N), 805(C–H)	Film	13
Me		Me	Me	H	1660	1575	1970(C=C=C)	Film	64
Me	Me	Me	Me	Me	1665	1570		CCl_4	26
Me	Me	H	H	Ph	1610			CCl_4	10
Me	Ph	Me	H	Me	1636	1557	1334(C–N), 836(C–H)	Film	13
Me	Me	Me	H	Ph	1626	1534	1310(C–N)	Film	13
Me	$CHCl_2$	H	H	Me	1610	1520		CCl_4	65
					1622	1532	1349(C–N)	Film	66
Me	$CHCl_2$	Me	Me	Me	1661	1573	1330(C–N)	Nujol	66
Ph	$CHCl_2$	Me	Me	Ph	1654	1545	1351(C–N)	Nujol	66
CF_3	CF_3	H	H	t-Bu	1610			Film	67
CF_3	CF_3	H	H	Ph	1610			KBr	67
CF_3	CF_3	H	Ph	t-Bu	1632			Film	67
CF_3	CF_3	Ph	H	t-Bu	1620			Film	67
Me	Me	H	H	CO_2Me	1597	1516	1712(C=O)	$CHCl_3$	15
Me	CO_2Et	Me	H	Me	1635	1555	1735(C=O)	Film	28
Me	CO_2Et	Me	Me	Me	1655	1565	1725(C=O)	Film	28
Me	CO_2Et	Me	H	Ph	1630	1530	1735(C=O)	Film	28
CF_3	CF_3	H	CO_2Me	H	1635		1735(C=O)	Film	68
CF_3	CF_3	CO_2Me	CO_2Me	H	1645		1740(C=O)	Film	68
t-Bu	OOH	H	H	t-Bu	1625	1550	3100(OH)	Nujol	21
t-Bu	OOH	t-Bu	H	t-Bu	1630	1560	3100, 2820(OH)	Nujol	21
Ph	OMe	Ph	Ph	Ph	1630		2830(OMe)	$CHCl_3$	69
Me	Me	OMe	H	Me	1660	1550		—	22
Me	Me	NEt_2	H	Me	1610	1540		—	22
Me	Me	Cl	H	Ph	1612			CCl_4	10
H	H	OH	Ph	NMe_2	1603	1563	3205(OH)	KBr	23
H	Me	OH	Me	NEt_2	1613	1553	3155(OH)	KBr	23
Me	Me	OH	Me	NEt_2	1613	1538	3130(OH)	KBr	24
Cl	Cl	Cl	Cl	Cl	1610	1520	1240(C–N)	CCl_4	70

TABLE 4.11. IR SPECTROSCOPIC DATA FOR SELECTED 3*H*-PYRROLES



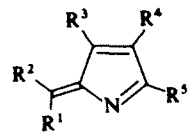
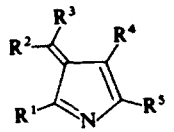
Substituent					$\nu_{max.}$ (nm)				
R^1	R^2	R^3	R^4	R^5	C=N	C=C	Other	Medium	Ref.
Me	Me	Me	H	Me	1630	1580		Film	13
Me	Me	Et	Me	H	1615	1575		CCl_4	26
Me	Me	Me	Me	Me	1650	1580		CCl_4	26
Me	Me	Et	Me	Me	1650	1580		CCl_4	26
Me	Me	Me	$(CH_2)_4$		1641	1555		Film	13
H	Me	Me	H	Ph	1612	1550		Film	13
Ph	Me	Me	H	H	1675			Film	71
Me	Me	Me	H	Ph	1640			Film	13
t-Bu	Me	CO_2Et	H	Me	1635	1555	1735(C=O)	Film	28
Me	Me	CO_2Et	Me	Me	1650	1590	1730(C=O)	Film	28
Me	Me	CO_2Et	$(CH_2)_4$		1650	1580	1730(C=O)	Film	28
Ph	Me	CO_2Et	H	Me	1620	1545	1735(C=O)	Film	28

TABLE 4.12. IR SPECTROSCOPIC DATA FOR SELECTED 2*H*-PYRROLE *N*-OXIDES



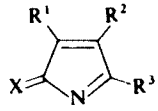
Substituent					$\nu_{max.}$ (nm)				
R^1	R^2	R^3	R^4	R^5	C=N	C=C	Other	Medium	Ref.
Me	Me	H	Me	*t*-Bu	1604	1490	1283, 1237	Nujol	37
Me	Me	H	*t*-Bu	*t*-Bu	1570	1434	1300, 1234	Nujol	37
Me	Me	Ph	H	*t*-Bu		1403	1265, 1232	Nujol	38
Me	Me	H	H	CN	1565	1402	2225, 1257	Nujol	39
Me	Me	Me	H	CN	1602	1490	2223, 1250, 1204	Nujol	39
Me	Me	Ph	H	CN		1492	2201, 1257, 1205	Nujol	39
Me	Me	Br	H	*t*-Bu	1573	1400	1249, 1218	Film	38

TABLE 4.13. IR SPECTROSCOPIC DATA FOR SELECTED 1- AND 2-AZAFULVENES

Substituent							
R^1	R^2	R^3	R^4	R^5	$\nu_{max.}$ (cm^{-1})	Medium	Ref.
			1-Azafulvenes				
–O–		H	H	H	2110	Film, – 196°C	73
		H	H	H	1538, 1500	KBr	47
	H	H	Br	H	1618	$CHCl_3$	48
	H	H	Br	Br	1620	$CHCl_3$	48
	H	Br	Br	Br	1625	$CHCl_3$	48
NMe_2	H	Et	Me	Br	1630	KBr	74
NMe_2	H	$(CH_2)_2CO_2Me$	Me	Br	1730, 1625	KBr	74
NMe_2	H	Me	$(CH_2)_2CO_2Me$	Br	1740, 1635	KBr	74
CN	CO_2Me	NMe_2	Cl	NMe_2	2200, 1721, 1622, 1537	KBr	50
			2-Azafulvenes				
Me			H	Me	1535, 1475	KBr	47

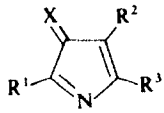
TABLE 4.14. IR SPECTROSCOPIC DATA FOR SELECTED 2*H*-PYRROLES BEARING AN EXOCYCLIC C=X BOND



Substituent						
X	R^1	R^2	R^3	$\nu_{max.}$ (cm^{-1})	Medium	Ref.
O	H	H	OAd[a]	1745, 1732, 1600, 1530	KBr	55
O	OH	Cl	SCF_3	3500, 3210, 1744, 1584	KBr	75
N_2	Ph	H	Ph	2138	KBr	56
N_2	Ph	COMe	Me	2146	KBr	56
N_2	Ph	NO_2	Ph	2172	KBr	56

[a] Ad = 1-adamantyl.

TABLE 4.15. IR SPECTROSCOPIC DATA FOR SELECTED 3*H*-PYRROLES BEARING AN EXOCYCLIC C=X BOND



Substituent						
X	R^1	R^2	R^3	$\nu_{max.}$ (cm^{-1})	Medium	Ref.
O	Ph	Ph	Ph	1720	CH_2Cl_2	57
O	NMe_2	Ph	Ph	1670	KBr	57
O	NMe_2	Cl	NMe_2	1665, 1638, 1571	KBr	50
S	NMe_2	NMe_2	NMe_2	1579	KBr	50
N_2	Ph	H	Me	2062	KBr	58
N_2	Ph	H	Ph	2095	KBr	58
N_2	Ph	Ph	Ph	2088	KBr	58
N_2	Me	Me	CO_2Et	2155	KBr	58
N_2	Ph	COMe	Me	2120, 1620	Nujol	59
N_2	Ph	COMe	Ph	2130, 1640	Nujol	59
N_2	Ph	CO_2Et	Ph	2130, 1670	Nujol	76
N_2	Ph	CN	Ph	2210, 2120	Nujol	76

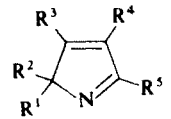
functional groups have also been included where appropriate. Limited IR data for azafulvenium salts have also been published.[47,51,77]

4.2.3. Nuclear Magnetic Resonance Spectra

4.2.3.1. ^1H *NMR*

Most papers published since the mid-1960s describing compounds that are the subject of this chapter include ^1H NMR data. Data listed in Tables 4.16 to

TABLE 4.16. ^{1}H CHEMICAL SHIFTS (δ) FOR SELECTED 2*H*-PYRROLES

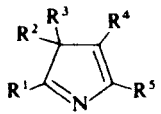


Substituent					Chemical Shift						
R^1	R^2	R^3	R^4	R^5	R^1	R^2	R^3	R^4	R^5	Solvent	Ref.
$PhCH_2$	$PhCH_2$	H	H	H	3.12 7.12	3.12 7.12	7.25[a]	6.02[a]	7.76[b]	$CDCl_3$	78
Me	$PhCH_2$	H	H	Me	1.18	2.80 7.02	7.02	5.90	2.05	CCl_4	79
Me	Me	Me	H	Me	1.19	1.19	1.95[c]	5.85[c]	2.16	$CDCl_3$	13
$PhCH_2$	$PhCH_2$	Me	Me	H	2.92[d], 3.32[d] 7.0–7.2	3.32 7.0–7.2	2.02[e]	1.46[e]	7.54	$CDCl_3$	78
Me	Me	Me	Me	Me	1.17	1.17	1.82	1.82	2.18	$CDCl_3$	26
Me	Me	H	H	Ph	1.36	1.36	7.30[a]	6.70[a]	7.3–7.5 7.8–8.0	$CDCl_3$	10
Me	Ph	Me	H	Me	1.60	7.1–7.2	1.86[c]	5.95[c]	2.26	$CDCl_3$	13
Me	Me	Me	H	Ph	1.32	1.32	2.06	6.45	7.3–7.5 7.8–8.0	$CDCl_3$	13
Me	CH_2=$CHCH_2$	Ph	Et	H	1.30	1.4–2.9	7.1–7.7	1.03 2.20	8.03	CCl_4	80
Me	Ph	Me	H	Ph	1.73	7.24	1.93	6.54	7.3–7.5 7.9–8.1	$CDCl_3$	13
Me	Me	Ph	H	Ph	1.51	1.51	7.2–7.9	7.08	7.2–7.9 7.9–8.2	$CDCl_3$	81

Me	$CHCl_2$	H	H	Me	1.47	6.01	7.33[f]	6.43[f]	2.19	CCl_4	66
Me	$CHCl_2$	Me	Me	Me	1.39	5.86	1.71[g]	1.39[g]	2.19	CCl_4	66
CF_3	CF_3	H	H	*t*-Bu	—	—	7.23[a]	6.92[a]	1.28	CCl_4	67
CF_3	CF_3	H	CO_2Me	H	—	—	7.92[b]	3.99	8.66[b]	$CDCl_3$	68
Me	Me	H	H	CO_2Et	1.35	1.35	7.33	6.59	1.35 4.37	$CHCl_3$	15
Me	CO_2Et	Me	H	Me	1.50	1.22 4.14	2.04	6.03	2.24	$CDCl_3$	28
Me	CO_2Et	Me	Me	Me	1.45	1.22 4.12	1.89	1.85	2.21	$CDCl_3$	28
Me	Me	H	CO_2Me	Ph	1.40	1.40	7.90	3.72	7.2–7.5 7.5–7.6	CCl_4	19
Me	Me	CO_2Me	H	Ph	1.32	1.32	3.80	7.29	7.2–7.5 7.7–8.1	CCl_4	19
Me	Me	Ph	CO_2Me	H	1.32	1.32	7.0–7.5	3.60	8.15	CCl_4	17
H	H	Me	Me	OMe	3.27	3.27	1.96	1.70	3.90	$CDCl_3$	46
t-Bu	OOH	H	H	*t*-Bu	0.99	11.70	7.08[h]	6.35[h]	1.18	CCl_4	21
t-Bu	OOH	*t*-Bu	H	*t*-Bu	1.00	12.65	1.17	6.10	1.33	CCl_4	21
t-Bu	OH	*t*-Bu	H	*t*-Bu	1.00	4.80	1.12	6.00	1.26	CCl_4	21
Me	Me	OH	Me	NEt_2	1.18	1.18	7.71	1.97	1.23 3.54	CCl_4	24

[a] $^3J_{HH}$ 5 Hz.
[b] No evidence of coupling.
[c] $^4J_{HH}$ 1.3 Hz.
[d] $^2J_{HH}$ 13.2 Hz.
[e] $^5J_{HH}$ 1.1 Hz.
[f] $^3J_{HH}$ 5.4 Hz.
[g] $^5J_{HH}$ 1.2 Hz.
[h] $^3J_{HH}$ 5.6 Hz.

TABLE 4.17. ^{1}H CHEMICAL SHIFTS (δ) FOR SELECTED 3*H*-PYRROLES



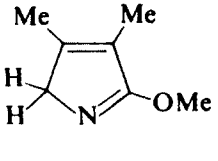
Substituent					Chemical Shift						
R^1	R^2	R^3	R^4	R^5	R^1	R^2	R^3	R^4	R^5	Solvent	Ref.
Me	Me	Me	H	Me	2.09	1.11	1.11	5.63[c]	2.07[c]	$CDCl_3$	13
Me	Me	Et	Me	H	2.08	1.02	0.38, 1.58	1.75[d]	6.64[d]	$CDCl_3$	26
Me	Me	Me	Me	Me	2.12	0.99	0.99	1.71	2.01	$CDCl_3$	26
Me	Me	Et	Me	Me	2.07	0.98	0.37, 1.55	1.65[e]	2.06[e]	$CDCl_3$	26
H	Me	Me	H	Ph	7.90[a]	1.26	1.26	6.39[a]	7.3–7.5 7.8–7.9	$CDCl_3$	13
Ph	Me	Me	H	H	7.4–7.5 8.0–8.1	1.39	1.39	6.30[b]	7.00[b]	$(CD_3)_2CO$	71
Ph	Me	Me	H	Me	7.3–7.5 7.9–8.0	1.38	1.38	5.76[c]	2.19[c]	$CDCl_3$	13
Me	Me	Me	H	Ph	2.02	1.22	1.22	6.34	7.2–7.5 7.8–7.9	$CDCl_3$	13
Me	Me	Ph	H	Ph	2.07	1.60	7.1–7.4	6.54	7.2–7.4 7.8–7.9	$CDCl_3$	13
Me	Me	CO_2Et	H	Me	2.20	1.40	1.20, 4.12	5.74	2.12	$CDCl_3$	28
t-Bu	Me	CO_2Et	H	Me	1.29	1.51	1.19, 4.08	5.52	2.14	$CDCl_3$	28
Me	Me	CO_2Et	H	*t*-Bu	2.22	1.39	1.20, 4.10	5.67	1.21	$CDCl_3$	28

Me	Me	CO_2Et	Me	Me	2.18	1.31	1.19, 4.10	1.75	2.05	$CDCl_3$	28
Ph	Me	CO_2Et	H	Me	7.3–7.4 7.7–7.9	1.52	1.08 4.08, 4.16	5.84	2.23	$CDCl_3$	28
Ph	Me	CO_2Et	H	*t*-Bu	7.3–7.5 7.8–7.9	1.50	1.07 4.08	5.77	1.29	$CDCl_3$	28
Ph	Me	CO_2Et	H	Ph	7.2–7.5 7.9–8.1	1.65	1.06 4.07, 4.13	6.48	7.2–7.5 7.9–8.1	$CDCl_3$	28
Me	Me	CO_2Et	H	Ph	2.32	1.51	1.21 4.12, 4.14	6.41	7.3–7.4 7.8–7.9	$CDCl_3$	28
Me	Me	CO_2Et	Me	Ph	2.26	1.43	1.20, 4.13	2.04	7.2–7.5 7.7–7.8	$CDCl_3$	28
Ph	Me	CN	H	Me	7.4–7.6 8.0–8.2	1.64	—	5.95	2.26	$CDCl_3$	28
Ph	Me	CN	H	*t*-Bu	7.4–7.6 8.0–8.2	1.63	—	5.88	1.29	$CDCl_3$	28
Ph	Me	CN	H	Ph	7.4–7.6 8.2–8.3	1.74	—	6.52	7.4–7.6 7.9–8.0	$CDCl_3$	28
NH_2	Ph	Ph	CO_2Me	H	4.3	7.23	7.23	3.55	7.62	$CDCl_3$	82

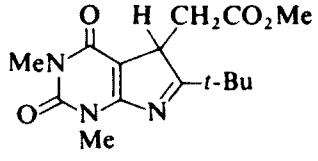
[a] $^5J_{HH}$ 1.34 Hz.
[b] $^3J_{HH}$ 3.2 Hz.
[c] $^4J_{HH}$ 1.3 Hz.
[d] $^4J_{HH}$ 1.5 Hz.
[e] $^5J_{HH}$ 1.2 Hz.

4.23 have been selected to be as representative as possible, and to show the influence of substituents.

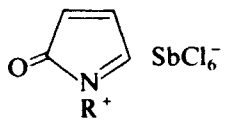
Tables 4.16 and 4.17 list ^{1}H chemical shifts for 2*H*- and 3*H*-pyrroles. For 2*H*-pyrroles, data have been reported for only one example unsubstituted at C_2 (**15**; δ 3.27).[46] Protons at C_3 (δ 7.0–7.9) give signals to lower field than those at C_4 (δ 5.8–7.1), consistent with the direction of polarization of the C=C bond. When both positions are unsubstituted, ^3J coupling (4.8–5.6 Hz) is observed. The few known examples having a proton at C_5 have a signal in the range δ 7.5–8.7; no coupling has been reported between this signal and those for H_4 or H_3. A methyl group at C_3 may couple with a proton or a methyl group at C_4 ($^4J_{HH}$ = 1.3–2.0 Hz; $^5J_{HH}$ = 1.1–1.2 Hz), while methylene groups at C_2 are diastereotopic, showing geminal coupling ($^2J_{HH}$ = 13–16 Hz).[34,36,78,79,83]



15



16



17 R = H
18 R = Me

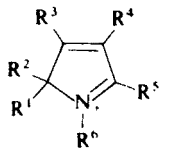
Proton chemical-shift data have been reported for only one 3*H*-pyrrole having a proton at C_3 (**16**; δ 3.39).[84] Signals for H_4 lie in the range δ 5.5–6.5 and show coupling with H_1 ($^5J_{HH}$ = 1.34 Hz), H_5 ($^3J_{HH}$ = 3.2 Hz), or a 5-Me group ($^4J_{HH}$ = 1.3 Hz). Only one example is known with a proton at C_1 (δ 7.90),[13] and the three examples with a proton at C_5 have a signal in the range δ 6.6–7.6. One of the latter has shown coupling of H_5 with a 4-Me group ($^4J_{HH}$ = 1.5 Hz).

Most published data for 2*H*-pyrrole salts are for solutions of 1*H*-pyrroles in strong acid, protonated at C_2. The third entry in Table 4.18, however, is for one of a series of isolated fluoroborate salts,[85] and the last three are stable crystalline salts full substituted at C_2. Where comparisons can be made, ring protons and methyl groups show a downfield shift relative to the free bases, as expected. ^{1}H Chemical shifts for 2*H*-pyrrole *N*-oxides are given in Table 4.19.

In general, signals for H_3 and H_5 are shifted upfield by approximately 1 ppm, relative to the free bases, while those for H_4 are little changed. Coupling between H_4 and H_5 is now observable ($^3J_{HH}$ = 1 Hz), while that between H_3 and H_4 in the one reported example[90] is larger by about 1.5 Hz ($^3J_{HH}$ = 6.6 Hz). Data for 1- and 2-azafulvenes are given in Tables 4.20 and 4.21.

Chemical shifts for R" = H respond to the electronic influence of the other substituents in a predictable manner. 6-Dialkylamino groups have shown evidence of restricted rotation in the 1-aza-compounds.[43,92,94] For a series of such compounds, bearing, in addition, a substituted aryl group at C_6, $\Delta G^{\ddagger}$ for rotation from VTNMR falls in the range 58.6–64.4 kJ mol^{-1},[43] and it was concluded that the aryl group is twisted out of the plane of the azafulvene system. For the corresponding salts (Table 4.22), data are very limited. Where

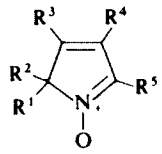
TABLE 4.18. ^{1}H CHEMICAL SHIFTS (δ) FOR SELECTED 2*H*-PYRROLE SALTS



Substituent						Chemical Shift							
R^1	R^2	R^3	R^4	R^5	R^6	R^1	R^2	R^3	R^4	R^5	R^6	Solvent	Ref.
H	H	H	H	H	H	5.23	5.23	8.40	7.35	9.20	10.83	H_2SO_4	32
H	H	H	H	H	Me	5.07	5.07	8.02	7.02	8.88	4.07	H_2SO_4	32
H	H	H	H	H	*t*-Bu	5.55	5.55	8.85	8.00	9.65	—	CD_3CN	85
H	Me	H	H	Me	H	5.16[a]	1.75[a]	8.10[b]	7.03[b]	2.88	—	H_2SO_4	32
H	Me	H	H	Me	Me	5.03	1.64	7.83	6.87	2.70	3.70	H_2SO_4	32
H	Me	H	Me	Me	Me	4.80	1.67	2.35	6.62	2.65	3.67	H_2SO_4	32
H	Me	Me	Me	Me	Me	4.65	1.57	2.20	2.07	2.53	3.63	H_2SO_4	32
H	CO_2Et	Me	H	Me	Me	5.50	1.36	2.37	6.70	2.64	3.67	H_2SO_4	86
H	CO_2Et	Me	Me	Me	Me	5.50	1.38	2.24	2.01	2.58	3.64	H_2SO_4	86
							4.37						
H	Me	Me	CN	NH_2	H	4.85	1.60	2.50	—	7.85	8.9	CF_3CO_2H	87
Me	CH_2CO_2Et	Me	CO_2Et	Me	Me	1.88	3.25, 3.73	2.60	1.42	3.02	3.91	$CDCl_3$	36
							1.16, 4.05		4.44				
Me	Me	Ph	H	Ph	Me	1.78	1.78	7.4–8.2	7.27	7.4–8.2	3.7	$CDCl_3$	88
CO_2Et	CO_2Et	Ph	H	Ph	Me	1.22	1.22	7.5–8.0	8.10	7.5–8.0	4.40	CD_3CN	89
						4.40	4.40						

[a] $^3J_{HH}$ 7.5 Hz.
[b] $^3J_{HH}$ 6 Hz.

TABLE 4.19. ^{1}H CHEMICAL SHIFTS (δ) FOR SELECTED 2*H*-PYRROLE *N*-OXIDES



Substituent					Chemical Shift						
R^1	R^2	R^3	R^4	R^5	R^1	R^2	R^3	R^4	R^5	Solvent	Ref.
Me	Me	H	H	H	1.39	1.39	6.35[a]	6.49[a,b]	7.24[b]	$CDCl_3$	90
Me	Me	H	Me	*t*-Bu	1.30	1.30	6.11[d]	2.11[d]	1.43	$CDCl_3$	37
Me	Me	Ph	H	H	1.60	1.60	7.35	6.70[b]	—[c]	$CDCl_3$	90
Me	Me	H	Me	Ph	1.45	1.45	6.28[d]	2.12[d]	7.4–7.6 7.8–8.0	$CDCl_3$	37
Me	Me	Me	H	Ph	1.41	1.41	2.03[e]	6.58[e]	7.45 8.42	$CDCl_3$	90
Me	Me	H	H	CN	1.44	1.44	6.47	6.47	—	$CDCl_3$	39
Me	Me	Me	H	CN	1.40	1.40	2.01[d]	6.13[d]	—	$CDCl_3$	39
Me	Me	Ph	H	CN	1.67	1.67	7.3–7.7	6.78	—	$CDCl_3$	39
Me	Me	CHO	H	Ph	1.60	1.60	9.70	7.80	7.50 8.31	$CDCl_3$	90
Me	Me	Br	H	*t*-Bu	1.30	1.30	—	6.47	1.30	$CDCl_3$	38

[a] $^3J_{HH}$ 6.6 Hz.
[b] $^3J_{HH}$ 1 Hz.
[c] Under aryl signal.
[d] $^4J_{HH}$ 2 Hz.
[e] $^4J_{HH}$ 1.4 Hz.

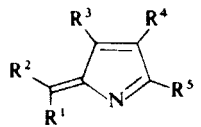
the two exocyclic substituents form part of a 1,3-dithiole system, chemical shifts suggest that the positive charge resides predominantly outside the pyrrole ring. Several ^{1}H NMR studies have demonstrated that protonation of 2- and 3-acetyl- and 2- and 3-formyl-1*H*-pyrroles occurs at the carbonyl group in strongly acidic media to give 6-hydroxyazafulvenium salts.[96]

Very few ^{1}H chemical shifts have been published for systems with an exocyclic C=X bond. Selected examples are presented in Table 4.23. Restricted rotation of dialkylamino groups has been observed in a number of cases.[50,57,60] A complete analysis of the ^{1}H NMR spectra of the 2*H*-pyrrolone salts **17** and **18** has been carried out.[99]

4.2.3.2. ^{13}C NMR

Carbon-13 chemical shifts for the ring carbon atoms in selected 2*H*- and 3*H*-pyrroles are given in Tables 4.24 and 4.25, respectively. Signals for the tetrahedral carbon atom in the 2*H*-compounds (δ 73–98) are generally ca. 20 ppm to lower field than in similarly substituted 3*H*-compounds (δ 49–70), whereas the

TABLE 4.20. ^{1}H NMR DATA FOR SELECTED 1-AZAFULVENES



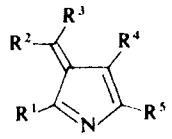
Substituent					Chemical Shift (δ)						
R^1	R^2	R^3	R^4	R^5	R^1	R^2	R^3	R^4	R^5	Solvent	Ref.
Ph	Ph	H	H	H	7.14–7.77		6.62[a]	6.99[a, b]	8.11[b]	CCl_4	41
CH_2CO_2Me	CO_2Me	Me	Me	OEt	3.69	3.77	1.85	1.98	1.40	CCl_4	91
					3.89				4.44		
OH	Et	CO_2Me	H	Ph	12.75	1.21	3.93	6.72	7.1–8.0	$CDCl_3$	44
						2.85					
Ph	H	Me	Me	OH	7.40	6.12	2.11	1.20	—	$CDCl_3$	45
Ph	H	Me	Me	OEt	7.20	6.32	2.03	1.83	1.41	CCl_4	45
									4.50		
4-MeC_6H_4	H	Me	Me	OMe	2.41	6.60	2.10	1.90	4.19	$CDCl_3$	46
					7.28						
4-$Me_2NC_6H_4$	H	Me	Me	OMe	3.04	6.49	2.10	1.90	4.13	$CDCl_3$	46
					7.45						
		H	H	H	6.78	6.78	6.94[c]	6.40[c, d]	7.52[d]	CCl_4	47
					7.23	7.23	7.16[c]	6.54[c, d]	7.58[d]	MeCN	

TABLE 4.20. (*Contd.*)

Substituent					Chemical Shift (δ)						
R^1	R^2	R^3	R^4	R^5	R^1	R^2	R^3	R^4	R^5	Solvent	Ref.
NMe_2	H	$(CH_2)_2CO_2Me$	Me	Br	3.66	6.98	2.62 3.29	2.15	—	$CDCl_3$	74
NMe_2	H	CO_2Me	CH_2CO_2Me	OEt	3.66 3.70	7.98	3.58	3.29 3.58	1.32 4.31	$(CD_3)_2SO$	92
NMe_2	H	CO_2Me	CH_2CO_2Me	Cl	3.71 3.78	8.45	3.81	3.39 3.81	—	$(CD_3)_2SO$	92
Ph	H	OMe	H	OMe	7.2–7.5 8.1–8.3	6.67	3.70	5.20	4.03	$CDCl_3$	49
Ph	H	OMe	CO_2Me	OMe	7.2–7.5 8.1–8.3	6.83	3.84	4.13	4.17	$CDCl_3$	49
OEt	Ph	$NHCH{=}CH_2$	H	H	1.48 4.08	7.49 7.73	4.69[f]	5.52[g]	7.95[g]	$CDCl_3$	93[e]
Ph	OEt	$NHCH{=}CH_2$	H	H	7.4–7.6	1.39 3.95	8.59[f]	5.73[g]	7.90[g]	$CDCl_3$	93[e]

[a] $^3J_{HH}$ 4.74 Hz.
[b] $^3J_{HH}$ 0.86 Hz.
[c] $^3J_{HH}$ 4 Hz.
[d] $^3J_{HH}$ 0 Hz.
[e] Data for N → $W(CO)_5$ complex.
[f] Signal for NH.
[g] $^3J_{HH}$ 1.9 Hz.

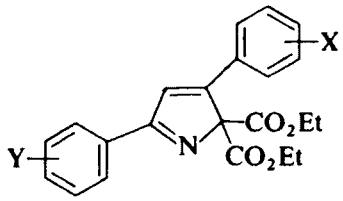
TABLE 4.21. ^{1}H NMR DATA FOR SELECTED 2-AZAFULVENES



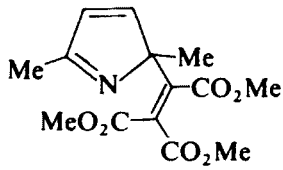
Substituent					Chemical Shift (δ)						
R^1	R^2	R^3	R^4	R^5	R^1	R^2	R^3	R^4	R^5	Solvent	Ref.
Me			H	Me	2.32	6.73	6.73	5.86	2.15	$CDCl_3$	47
					[a]	7.10	7.10	6.05	[a]	CD_3CN	47
					[a]	7.23	7.23	5.95	[a]	$(CD_3)_2CO$	47
Me			H	Me	2.40	7.1–7.6		5.95	2.17	$CDCl_3$	47

[a] Chemical shift not reported.

C=N carbon signal is to higher field in the 2*H*- (δ 161–185) relative to the 3*H*-compounds (δ 174–191). The influence of the substituents X and Y on ^{13}C chemical shifts in the 2,2-diesters **19** has been investigated; good correlations with Hammett constants are found at a number of sites.[102] The structure of pentachloropyrrole was confirmed as **12** rather than **13** by observation of changes in δ_C on incremental addition of the shift reagents Eu(*fod*)$_3$ and Yb(*fod*)$_3$.[70] Few coupling constants have been reported for 2*H*- and 3*H*-pyrroles. In addition to those included in Tables 4.24 and 4.25, values for longer-range couplings have been published for two 2*H*-pyrroles;[10,100] the spectrum of the second compound, **20**, has been analyzed in detail.



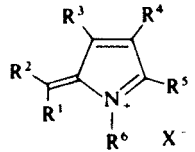
19

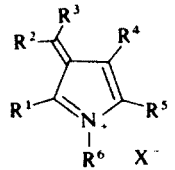


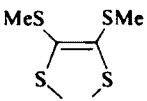
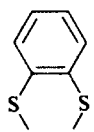
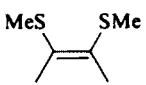
20

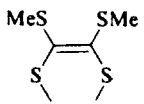
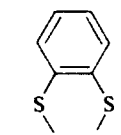
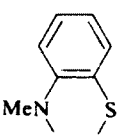
There have been no reports of ^{13}C NMR data for 2*H*-pyrrole *N*-oxides. The few data available for 2*H*-pyrrole salts are listed in Table 4.26, together with some one bond coupling constants. Table 4.27 lists the only ^{13}C chemical shifts published to date for 1-azafulvenes. Differences between the spectra of the base

TABLE 4.22. ^{1}H NMR DATA FOR 1- AND 2-AZAFULVENIUM SALTS



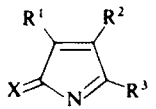


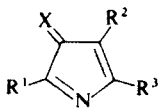
Substituent							Chemical Shift (δ)							
R^1	R^2	R^3	R^4	R^5	R^6	X	R^1	R^2	R^3	R^4	R^5	R^6	Solvent	Ref.
1-Azafulvenium Salts														
Ph	Ph	H	H	H	H	BF_4	7.6–8.0		—[a]	7.44	9.07	—[b]	$(CD_3)_2CO$	41
		H	H	H	H	I	8.56	8.56	7.69[c,d]	6.6[c,e]	7.88[d,e]	—[b]	$(CD_3)_2SO$	47
		H	H	H	H	BF_4	2.77	2.77	7.65[f,g]	6.65[f,h]	7.93[g,h]	—[b]	$(CD_3)_2NCDO$	51
		H	H	H	H	ClO_4	7.7–8.0 8.3–8.6		—[a]	6.80[c,e]	8.10[d,e]	—[b]	$(CD_3)_2SO$	47
2-Azafulvenium Salts														
Me			H	Me	H	BF_4	2.48	2.79	2.79	6.10	2.20	—[b]	$CDCl_3$	51

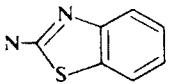
Me		H	Me	H	I	2.55	8.49	8.49	6.48	2.23	—[b]	$(CD_3)_2SO$	47
Me		H	Me	H	BF_4	2.48	2.66	2.66	6.38	2.15	—[b]	$(CD_3)_2SO$	51
Me		H	Me	H	ClO_4	2.62	7.7–8.5		6.55	2.22	—[b]	$(CD_3)_2SO$	47
SMe		H	H	H	Br	2.53	—[b]		6.88[i]	7.24[i]	—[b]	CF_3CO_2H	95

[a] Buried under aryl signal.
[b] Not reported.
[c] $^3J_{HH}$ = 5 Hz.
[d] $^4J_{HH}$ = 1 Hz.
[e] $^3J_{HH}$ = 3 Hz.
[f] $^3J_{HH}$ = 4.5 Hz.
[g] $^4J_{HH}$ = 1.1 Hz.
[h] $^3J_{HH}$ = 2.2 Hz.
[i] $^3J_{HH}$ = 3.0 Hz.

TABLE 4.23. ^{1}H NMR SPECTROSCOPIC DATA FOR SELECTED 2*H*- AND 3*H*-PYRROLES BEARING AN EXOCYCLIC C=X GROUP

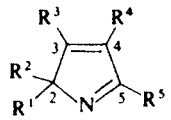




Substitutent				Chemical Shift (δ)					
X	R^1	R^2	R^3	X	R^1	R^2	R^3	Solvent	Ref.
				2H-Pyrroles					
O	H	H	OAd[a]	—	6.41[b]	6.79[b]	1.71, 2.17 2.33	$CDCl_3$	55
		Cl	NMe_2	7.2–8.1	2.91	—	3.44	$CDCl_3$	50
				3H-Pyrroles					
O	NMe_2	Ph	Ph		3.42 3.57		7.0–7.5 7.7–8.1	$CDCl_3$	57
S	NMe_2	NMe_2	NMe_2	—	3.76 4.17	2.91	3.37	$CDCl_3$	50
NPh	NHMe	NO_2	NHMe	6.7–7.3	3.30 9.62	—	3.15 9.23	$CDCl_3/(CD_3)_2SO$	96
N_2	Ph	H	Ph		7.0–8.1	6.80	7.0–8.1	$CDCl_3$	97
N_2	Ph	COMe	Me		7.4–7.7	2.62	2.49	$CDCl_3$	59

[a] Ad = 1-adamantyl.
[b] $^3J_{HH}$ = 5.2 Hz.

TABLE 4.24. ^{13}C CHEMICAL SHIFTS (δ) FOR SELECTED 2*H*-PYRROLES



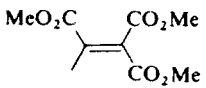
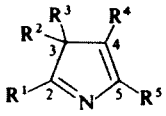
Substituent					Chemical Shift					
R^1	R^2	R^3	R^4	R^5	C_2	C_3	C_4	C_5	Solvent	Ref.
$PhCH_2$	$PhCH_2$	H	H	H	86.0	157.7	136.8	163.4	$CDCl_3$	78
Me		H	H	Me	82.1	156.3[a]	128.5[b]	173.3	$CDCl_3$	100
Me	Me	Me	H	Me	78.1	170.1	123.0	172.0	$CDCl_3$	13
Me	Et	Me	H	Me	81.2	170.4	124.4	170.9	$CDCl_3$	13
$(CH_2)_4$		Me	H	Me	89.1	168.6	123.8	169.6	$CDCl_3$	13
$PhCH_2$	$PhCH_2$	Me	Me	H	86.2	158.8	133.3	167.1	$CDCl_3$	78
Me	Me	H	H	Ph	79.5	162.6	123.1	169.6	$CDCl_3$	9
Me	Me	H	Ph	H	80.3	153.6	138.1	161.3	$CDCl_3$	9
Me	Ph	Me	H	Me	83.3	172.5	124.1	172.1	$CDCl_3$	13
Me	Me	Me	H	Ph	77.9	168.5	118.8	171.8	$CDCl_3$	13
Me	Ph	Me	H	Ph	83.8	171.2	120.4	173.3	$CDCl_3$	12
Me	Me	Ph	H	Ph	79.1	168.2	120.0	172.0	$CDCl_3$	12
Me	Ph	Me	$(CH_2)_2CH=CH_2$	Ph	81.9	166.5	132.9	174.3	$CDCl_3$	101
Me	CO_2Et	Me	H	Me	85.1	166.9	126.4	175.1	$CDCl_3$	28
Me	CO_2Et	Me	H	*t*-Bu	84.6	165.8	123.7	185.4	$CDCl_3$	28

TABLE 4.24. (*Contd.*)

Substituent					Chemical Shift					
R^1	R^2	R^3	R^4	R^5	C_2	C_3	C_4	C_5	Solvent	Ref.
Me	CO_2Et	Me	Me	Me	83.6	157.4	132.4	176.4	$CDCl_3$	28
Me	CO_2Et	Me	H	Ph	85.8	167.4	123.4	173.8	$CDCl_3$	28
Me	Me	CN	H	Ph	82.0	143.8	133.7	167.5	CCl_4	16
CO_2Et	CO_2Et	Ph	H	Ph	92.3	163.0	125.7	176.7	$CDCl_3$	102
CO_2Et	CN	$3,4\text{-}Me_2C_6H_3$	H	$4\text{-}MeOC_6H_4$	79.1	160.8	124.4	178.4	$CDCl_3$	103
CH=CHCOCH=CH		Ph	H	OEt	75.0	164.1	123.0	175.5	$CDCl_3$	104
CH=CHCOCH=CH		Ph	H		76.3	162.2	122.0	168.7	$CDCl_3$	104
Me	Me	Ph	Ph	NH_2	73.5	163.0	130.8	166.3	$CDCl_3$	12
Me	OH	NH_2	COMe	Me	94.6	182.0	105.5	168.9	$(CD_3)_2SO$	105
Me	OH	NH_2	CO_2Et	Me	93.5	180.5	95.7	169.0	$(CD_3)_2SO$	105
Ph	OH	NH_2	CO_2Et	Me	94.4	181.0	98.0	172.1	$(CD_3)_2SO$	105
CONHCONHCNH		NMe_2	H	NMe_2	78.8	166.4	91.3[c]	172.6	$CDCl_3$	106
Cl	Cl	Cl	Cl	Cl	98.3	151.1	125.3	164.0	$CDCl_3$	70

[a] $^1J_{CH}$ 176.1 Hz.
[b] $^1J_{CH}$ 171.3 Hz.
[c] $^1J_{CH}$ 170.6 Hz.

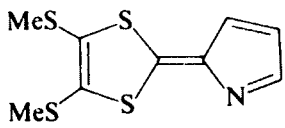
TABLE 4.25. ^{13}C CHEMICAL SHIFTS (δ) FOR SELECTED 3*H*-PYRROLES



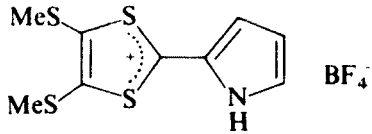
Substituent					Chemical Shift					
R^1	R^2	R^3	R^4	R^5	C_2	C_3	C_4	C_5	Solvent	Ref.
Me	Me	Me	H	Me	188.3	56.5	128.6	149.4	$CDCl_3$	13
Me	Me	Me	$(CH_2)_3$		191.4	57.3	146.7	157.2	$CDCl_3$	13
H	Me	Me	H	Ph	181.0	57.6	128.0	152.1	$CDCl_3$	13
Ph	Me	Me	H	Me	188.6	57.2	129.7	151.4	$CDCl_3$	13
Ph	$(CH_2)_5$		H	Me	183.9	62.6	127.4	150.4	$CDCl_3$	13
Me	Me	Me	H	Ph	188.1	56.9	127.2	151.2	$CDCl_3$	13
Me	Me	Ph	H	Ph	187.3	63.9	127.3	151.9	$CDCl_3$	13
Me	Me	CO_2Et	H	Me	182.3	66.8	122.9	153.7	$CDCl_3$	28
Me	Me	CO_2Et	H	*t*-Bu	181.4	66.1	118.9	167.2	$CDCl_3$	28
t-Bu	Me	CO_2Et	H	Me	191.3	66.5	123.6	153.4	$CDCl_3$	28
Me	Me	CO_2Et	Me	Me	179.2	68.1	129.9	147.1	$CDCl_3$	28
Me	Me	CO_2Et	$(CH_2)_4$		179.7	66.6	133.3	150.6	$CDCl_3$	28
Ph	Me	CO_2Et	H	Me	179.3	64.9	124.8	154.5	$CDCl_3$	28
Ph	Me	CO_2Et	H	*t*-Bu	178.4	64.4	120.8	167.9	$CDCl_3$	28
Me	Me	CO_2Et	H	Ph	182.4	67.4	121.3	155.2	$CDCl_3$	28
$(CH_2)_4$)		CO_2Et	H	Ph	185.2	68.7	120.3	156.3	$CDCl_3$	28
CO_2Et	Me	CO_2Et	H	Ph	173.0	67.1	125.7	155.7	$CDCl_3$	28
Me	Me	CO_2Et	Me	Ph	179.0	69.8	127.5	149.2	$CDCl_3$	28
Ph	Me	CO_2Et	H	Ph	179.1	65.6	122.7	155.8	$CDCl_3$	28
Ph	Me	CN	H	Me	175.3	49.5	121.4	155.7	$CDCl_3$	28
Ph	Me	CN	H	*t*-Bu	174.5	49.1	118.1	168.9	$CDCl_3$	28
Ph	Me	CN	H	Ph	175.1	50.1	119.3	156.4	$CDCl_3$	28
NH_2	Ph	Ph	CO_2Me	H	183.5[a]	67.6	124.9[b]	154.6[c]	$CDCl_3$	107
Me	Ph		NH_2	CN	165.1	83.8	162.8	93.5	$(CD_3)_2SO$	31

[a] $^3J_{CH}$ 13 Hz.
[b] $^2J_{CH}$ 6 Hz.
[c] $^1J_{CH}$ 183 Hz.

21 and its fluoroborate salt **22** suggest that the charge in the latter lies predominantly outside the pyrrole ring, consistent with ^1H NMR data.[51] No ^{13}C NMR spectra appear to have been reported for either 2-azafulvenes or 2*H*- and 3*H*-pyrroles having exocyclic C=X bonds; data for one 2-azafulvenium salt have been published .[51]

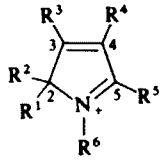


21



22

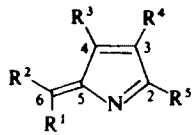
TABLE 4.26. ^{13}C CHEMICAL SHIFTS (δ) FOR 2*H*-PYRROLE SALTS

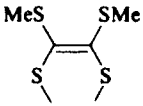


Substitutent						Chemical Shift[a]					
R^1	R^2	R^3	R^4	R^5	R^6	C_2	C_3	C_4	C_5	Solvent	Ref.
H	H	*t*-Bu	H	H	*t*-Bu	63.3 (144)	187.7	121.8 (170)	169.8 (185)	CD_3CN	85
H	H	*t*-Bu	H	*t*-Bu	H	60.9 (143)	187.6	120.4 (180)	195.5	CD_3CN	85
H	*t*-Bu	H	H	*t*-Bu	H	83.9 (152)	162.3 (181)	128.2 (180)	196.9	CD_3CN	85
H	*t*-Bu	*t*-Bu	H	*t*-Bu	H	81.7 (152)	188.9	124.2 (178)	192.4	CD_3CN	85
H	Me	Me	CO_2Et	Me	H	71.6 (146)	165.7	126.5	184.8	$H_2SO_{4(aq.)}$	86
H	Et	Me	CO_2Et	Me	H	76.3 (141)	164.4	127.3	185.0	$H_2SO_{4(aq.)}$	86
H	CO_2Et	Me	Me	Me	H	74.5 (146)	162.0	135.5	164.5	$H_2SO_{4(aq.)}$	86
H	CO_2Et	Me	Me	Me	Me	81.1	160.1	137.2	165.3	$H_2SO_{4(aq.)}$	86
CO_2Et	CO_2Et	Ph	H	Ph	H	86.2	166.0	124.1	180.6	CD_3CN	89
CO_2Et	CO_2Et	Ph	H	Ph	Me	90.9	163.9	127.1	181.6	CD_3CN	89

[a] Numbers in parentheses are $^1J_{CH}$ values (Hz).

TABLE 4.27. ^{13}C NMR SPECTROSCOPIC DATA FOR 1-AZAFULVENES



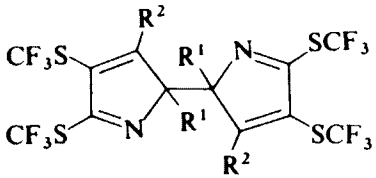
Substituent					Chemical Shift (δ)						
R^1	R^2	R^3	R^4	R^5	C_2	C_3	C_4	C_5	C_6	Solvent	Ref.
		H	H	H	153.4	124.1	124.4	141.4	161.3	$CDCl_3$	51
OH	Et	CO_2Me	H	Ph	143.6	103.5[a]	134.4	139.5	165.2	$CDCl_3$	44
OH	Ph	CO_2Me	H	Ph	142.7	103.6	134.8	145.9	164.3	$CDCl_3$	44
OEt	Ph	$NHCH=CH_2$	H	H	167.0	98.1	153.4	132.0	162.0	$CDCl_3$	93[b]

[a] $^1J_{CH}$ 170 Hz.

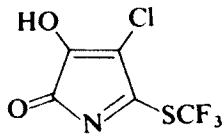
[b] Data for N → $W(CO)_5$ complex.

4.2.3.3. ^{19}F NMR

Burger and co-workers have reported ^{19}F chemical shifts for a number of 2,2-bistrifluoromethyl 2*H*-pyrroles (Table 4.28), and ratios of regioisomers have been determined from ^{19}F integrals.[67,111] Data have also been reported for the 2,2′-dimers **23**–**25**,[112,113] and for the 2*H*-pyrrol-2-one **26**.[75]



23 $R^1 = R^2 = SCF_3$
24 $R^1 = Cl$, $R^2 = SCF_3$
25 $R^1 = SCF_3$, $R^2 = Cl$

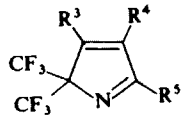


26

4.2.3.4. ^{15}N NMR

For ^{15}N-labeled pentachloro-2*H*-pyrrole **12**, $^1J_{C-N}$ and $^1J_{C=N}$ have been reported as 6.8 and approximately 5 Hz, respectively. However, δ_N was not apparently recorded.[114]

TABLE 4.28. ^{19}F NMR SPECTROSCOPIC DATA FOR SELECTED 2*H*-PYRROLES



Substituent				
R^3	R^4	R^5	$\delta_{CF_3}(CDCl_3)^a$	Ref.
H	H	*t*-Bu	− 69.7	67
H	H	Ph	− 69.1	67
Ph	H	*t*-Bu	− 67.6	67
H	Ph	*t*-Bu	− 69.7	67
Ph	H	Ph	− 66.9	67
H	Ph	Ph	− 69.0	67
Ph	Ph	*t*-Bu	− 67.5	67
Ph	Ph	Ph	− 66.7	67
H	CO_2Me	H	− 68.7	68
CO_2Me	CO_2Me	H	− 67.7	68
CO_2Me	CO_2Me	4-MeC_6H_4	− 67.4	108
CN	CN	Ph	− 67.9	109, 110
Me	NEt_2	*t*-Bu	− 68.25	111
NEt_2	Me	*t*-Bu	− 69.30	111

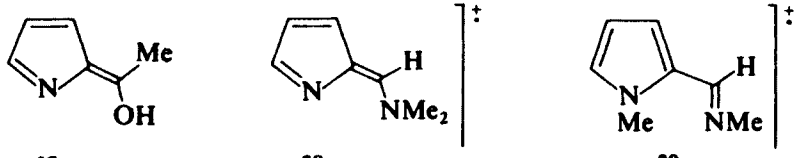
[a] Converted to δ scale, with $CFCl_3$ as reference, from external CF_3CO_2H (δ − 78.5) in original papers.

4.2.4. Mass Spectrometry

Although the mass spectra of a large number of 2*H*-pyrroles have been reported very fully, only rarely has any attempt been made to deduce fragmentation patterns.[36,115] However, a number of conclusions may be drawn from an examination of the published data. With very few exceptions, the molecular ion is observed, and often as the base peak. A prominent *M*-1 ion is frequently present, which may also be the base peak, and Wong and Ritchie have reported that relative to the molecular ion this is usually twice as intense for 2*H*-pyrroles as for similarly substituted 3*H*-pyrroles.[26] The major initial fragmentation step appears to be the loss of a C_2 substituent. If the two substituents at this site are different, either may be lost, giving rise to two peaks, the relative intensities of which are related to the stabilities of the radical lost and the cation formed. In a few instances, there is evidence of the loss of the C_3 and C_4 atoms together with their substituents in a reverse 1,3-dipolar cycloaddition reaction.[16,19,115]

All 2*H*-pyrrole *N*-oxides for which there are mass spectral data have two methyl groups at C_2. The parent ion, which may be the base peak, has always been observed, as has a prominent *M*-15 peak due to loss of a C_2 methyl. Bender and Döpp report intense *M*-15, *M*-16, and *M*-17 peaks for a number of *N*-oxides,[90] but while the *M*-17 has been recorded by other authors,[37,39] the *M*-16 has not. Compounds containing a *t*-butyl group show a *M*-57 peak due to loss of this fragment, and often one at *M*-42 also, perhaps due to extrusion of CMe_2 from the ring.[37,38]

Data have been reported for only two stable 1-azafulvenes, both of which show parent ions.[46] The pentafluoro derivatives of 1- and 2-azafulvene have been identified as transient intermediates from the flash photolysis of pentafluoropyridine, using time-resolved mass spectroscopy (MS).[116] Loss of the fragment **27** from *N*-alkyl-2-acetylpyrroles has been deduced from a common *M*-109 peak,[117] and evidence has been produced for the rearrangement of **28** to **29** via a [1,7]-Me shift prior to fragmentation.[118]

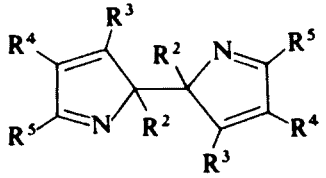


27 **28** **29**

3*H*-Pyrroles having an exocyclic C=X bond also show a parent ion.[60,119,120] Structures of type **10** show a base peak at *m/z* 178, apparently due to Ph–C=C–Ph.[60]

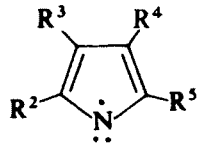
4.2.5. Electron-Spin Resonance

2*H*-Pyrroles of general structure **30** (e.g., 23–25) dissociate in solution into radicals **31**, which have been detected by ESR spectroscopy.[112,121] A variable-temperature ESR study on compound **23** in toluene gave the following data for



30

K 2



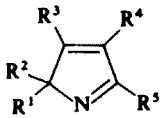
31

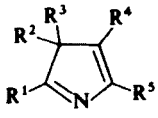
the equilibrium: $K = 6.8 \pm 2.5 \times 10^{-7}$ mol dm^{-3} (at 300 K), $\Delta G^0 = 35 \pm 1$ kJ mol^{-1}, $\Delta H^0 = 79 \pm 1$ kJ mol^{-1}, and $\Delta S^0 = 150 \pm 10$ J mol^{-1} K^{-1}.[112]

4.2.6. pK_a Measurements

Recent measurements from UV spectra have shown that 2*H*-pyrroles are more basic by about two pK units relative to similarly substituted 3*H*-pyrroles (Table 4.29), due in part, no doubt, to the more effective delocalization of the positive charge in the ring.[11]

TABLE 4.29. pK_a VALUES FOR 2*H*- AND 3*H*-PYRROLES DETERMINED PHOTOMETRICALLY IN WATER[a]



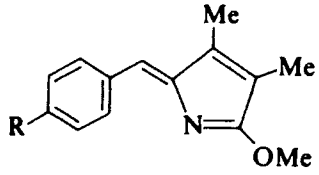


R^1	R^2	R^3	R^4	R^5	pK_a[$\lambda_{max.}$ (nm)]
			2H-Pyrroles		
Me	Me	Me	H	Me	8.39 ± 0.04 (254)
					8.41 ± 0.03 (235)
Me	Me	Me	H	Ph	7.43 ± 0.05 (280)
					7.41 ± 0.06 (244)
			3H-Pyrroles		
Me	Me	Me	H	Me	6.42 ± 0.16 (255)
Ph	Me	Me	H	Me	5.08 ± 0.06 (330)

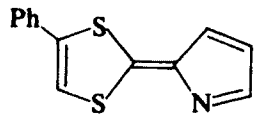
[a] From Ref. 11.

Two independent measurements on the 2*H*-pyrrole **15** by electromeric titration gave pK_a values of 10[45] and 10.2 ± 0.2[46] for protonation, while a value of pK_a 16.6 for deprotonation at C_2 was determined photometrically.[20]

For the 1-azafulvene **32**, photometric determination gave pK_a 4.24 ± 0.05, while for **33**, which contains two basic sites, values of 4.7 ± 0.1 and 3.6 ± 0.1 were found.[46]



32 R = Me
33 R = NMe_2



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4.2.7. Other Physical Properties

4.2.7.1. Dipole Moments

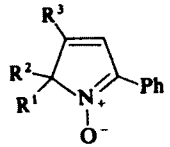
A comparison between the dipole moments of the 1-azafulvene **7** (μ 2.06D) and the fulvene **8** (μ 1.34D) indicates a larger degree of charge separation in the former.[41]

Semiempirical MO methods (MINDO/3 and MNDO) have been used to calculate dipole moments of a number of simple 2*H*- and 3*H*-pyrroles, 1-azafulvenes, and 2*H*-pyrrol-2-ones.[122,123]

4.2.7.2. Ionization Energies

Ionization energies have been measured for three 2*H*-pyrrole *N*-oxides from charge-transfer spectra of their complexes with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) and tetracyanoethylene (TCNE) in dichloromethane (Table 4.30).[124]

TABLE 4.30. IONIZATION ENERGIES OF 2*H*-PYRROLE *N*-OXIDES FROM VISIBLE SPECTRA OF CHARGE-TRANSFER COMPLEXES



R^1	R^2	R^3	Electron Acceptor	$\lambda_{max.}$(nm)	Transition Energy (kJ mol^{-1})	Ionization Energy (eV)
Me	Me	Me	DDQ	719	166.4	7.87
				582	205.6	8.37
Me	Me	Ph	DDQ	744	160.8	7.80
				580	206.3	8.38
MeO	Ph	Ph	DDQ	700	170.9	7.93
Me	Me	Me	TCNE	622	192.3	7.86
Me	Me	Ph	TCNE	640	186.9	7.79
MeO	Ph	Ph	TCNE	612	195.5	7.91

Semiempirical MINDO/3 calculations have yielded ionization energies for a series of simple 2*H*-pyrroles.[122]

4.2.7.3. Oxidation Potentials

Electrochemical oxidations of the 1-azafulvenes **21** and **34** in acetonitrile were found to be irreversible and gave oxidation potentials of 0.90 and 1.00 V, respectively, against standard calomel electrode (SCE).[54] They are thus more difficult to oxidize than are tetrathiafulvalene (0.33 V).

4.3. THEORETICAL AND STRUCTURAL ASPECTS

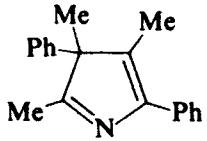
4.3.1. Molecular Orbital Calculations

Simple HMO theory has been used to calculate the resonance energy for 1-azafulvene, 2-azafulvene, and fulvene; the former has the largest resonance energy.[125,126]

Calculations of heats of formation and dipole moments for 2*H*-pyrrole[122] and for a range of simple methyl-, hydroxy-, and methoxy-substituted 2*H*- and 3*H*-pyrroles, together with their 1*H*-tautomers, have been carried out using the semiempirical MINDO/3 method.[122,123] MNDO calculations for some of these compounds give smaller values for both ΔH_f^0 and μ.[123] Data are also available for hydroxy-1-azafulvenes[122,123] and for a 2*H*-pyrrol-2-one.[123] Protonation at N raises the potential energy of 2*H*-pyrroles;[46,122] in one paper the calculated enthalpy changes are in line with observed pK_a values.[46]

Both MINDO/3 and MNDO heats of formation indicate that structure **15** is thermodynamically less stable than its 1*H*-tautomer. In practice, however, **15** is stable in solution and may be distilled.[46]

The 3*H*-pyrrole **36** is found to be more stable than either **35** or **37** by MINDO/3.[101] Optimized geometries show that the phenyl substituents at C_2 and C_5 are all rotated out of the plane of the pyrrole ring by 75–89°, with the exception of that at C_2 in compound **36** (only 5°) and it is the increased conjugation in the latter compound that accounts for its lower potential energy.



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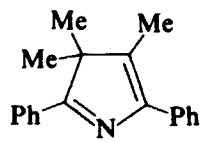

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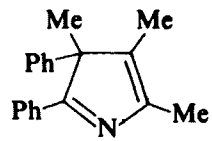
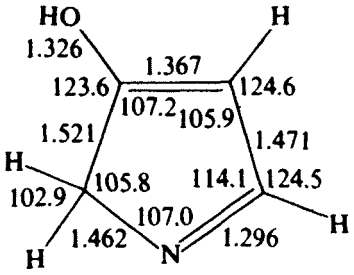


37

Optimized geometries by MINDO/3 have been published[122] for a large number of 1*H*- and 2*H*-pyrroles and their tautomers, including **38**. These may be compared with data for **39** and its 5-methoxy derivative.[46] Conversion of **38** into

4-hydroxy-1-azafulvene has little effect on geometry, in parallel with calculations for cyclopentadiene and fulvene.[122] The calculated bond lengths[62] for the 3*H*-pyrrol-3-one **40** (values in parentheses by QCFF/pi) compare well with *X*-ray-crystallographic data for **10** (R = Et)[61] (see Section 4.3.2), supporting a significant contribution from the cyclomerocyanine structure **11**. Further support comes from calculated π-bond orders and electron densities for **40**.[62]



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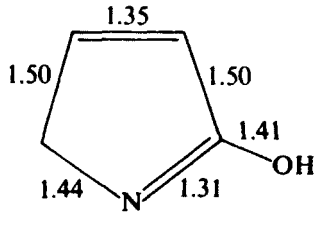

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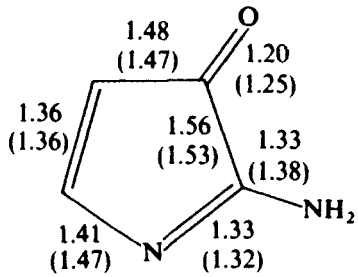
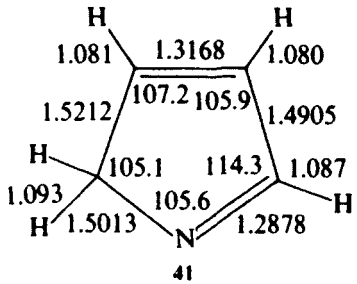


40

Semiempirical methods have also been used to calculate ionization energies (MINDO/3),[122] frontier orbital energies (MINDO/3[101,127] and MNDO[127]), and electronic spectra by PPP and QCFF/pi[62] and other methods.[128,129]

More sophisticated ab initio methods (STO-3G basis set) have yielded optimized geometries for 1*H*-, 2*H*-, and 3*H*-pyrroles.[101] Data for 1*H*-pyrrole were identical with those published earlier;[130] those for 2*H*- and 3*H*-pyrrole are illustrated (**41** and **42** respectively), and may be compared with data from X-ray



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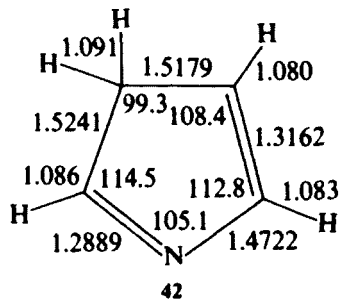
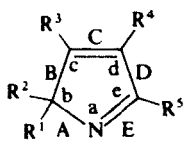
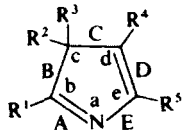
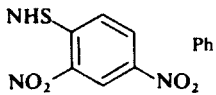
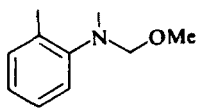
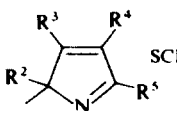


42

TABLE 4.31. BOND PARAMETERS FOR 2*H*- AND 3*H*-PYRROLES FROM *X*-RAY CRYSTALLOGRAPHIC STUDIES





Substituent					Bond Length (Å)					Bond Angle (°)					Ref.
R^1	R^2	R^3	R^4	R^5	A	B	C	D	E	a	b	c	d	e	
							2H-Pyrroles								
Me	CCl_2HgPh	H	H	*t*-Bu	1.46(2)	1.50(2)	1.35(2)	1.49(2)	1.29(2)	107(1)	106(1)	107(1)	106(1)	113(1)	133
CO_2Et	CO_2Et	4-ClC_6H_4	H	Ph	1.471(3)	1.533(4)	1.336(4)	1.462(4)	1.293(4)	106.4(2)	106.3(2)	105.2(2)	109.0(2)	113.0(2)	134
Ph		Ph	Ph	Ph	1.56(2)	1.55(3)	1.31(2)	1.51(3)	1.27(2)	108(2)	100(2)	111(2)	106(2)	114(2)	135
$CH_2CH{=}CH_2$	CO_2Me	H			1.477(4)	1.523(4)	1.336(5)	1.462(5)	1.280(4)	103.6(3)	106.4(3)	107.6(3)	104.8(3)	117.7(3)	136
Me	OH	NH_2	CO_2Et	Me	1.467(3)	1.526(4)	1.377(3)	1.459(3)	1.294(3)	108.1(2)	104.2(2)	107.5(2)	105.9(2)	113.8(2)	105
CONMeCONMeCONH		NMe_2	H	NMe_2	1.48(2)	1.51(3)	1.39(3)	1.48(3)	1.36(3)	105(2)	108(1)	107(2)	107(2)	113(2)	106
		SCF_3	SCF_3	SCF_3	1.46(1)	1.55(1)	1.32(1)	1.45(1)	1.29(1)	106.4(8)	105.5(7)	105.4(8)	108.6(9)	114.0(8)	137
							3H-Pyrroles								
Ph	Me	CN	H	Ph	1.289(2)	1.536(3)	1.499(2)	1.340(3)	1.435(2)	107.6(1)	112.0(1)	100.0(2)	108.2(1)	112.0(1)	28
NMe_2	Et	Ph	CO_2Me	CO_2Me	1.322(5)	1.530(5)	1.532(5)	1.353(5)	1.387(5)	105.7(3)	113.9(3)	98.4(3)	106.8(2)	115.1(3)	138

diffraction in Table 4.31. The same calculations, assuming that $\Delta\Delta E = \Delta\Delta H$, gave the relative stabilities ($\Delta\Delta H_f^0$) of 1*H*-, 2*H*-, and 3*H*-pyrroles, respectively, as 0.0, 44.8, and 34.3 kJ mol^{-1}.[101] The second figure, which is higher than that for 3*H*-pyrrole, in conflict with experimental evidence,[13,28,131,132] may be compared with 78.3 kJ mol^{-1} obtained from MINDO/3 calculations.[122]

4.3.2. Molecular Structure

Bond parameters for seven 2*H*-pyrroles and two 3*H*-pyrroles from *X*-ray diffraction are listed in Table 4.31. Many of the structures are perturbed by strong electron-donating groups. However, there is relatively little perturbation in the second and eighth entries, and bond parameters may be compared with those from ab initio calculations in structures **41** and **42**. The agreement between the 3*H*-pyrroles is particularly good. In all cases the 5-membered ring is essentially planar.

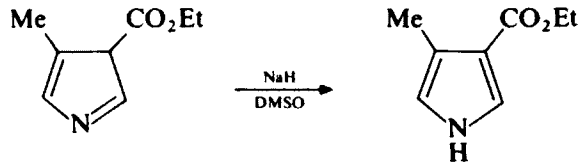
Structures have also been published for a 3*H*-pyrrol-3-one and a 3*H*-pyrrol-3-imine (Table 4.32). The pyrrolone crystallizes with two different molecules per unit cell, having significantly different bond parameters due to packing forces. Evidence for the cyclomerocyanine structure **11** (R = Et) was considered to be inconclusive.[61] However, a comparison with the data in **40** from MO calculations suggests a significant contribution from the charge separated form. The structure of the pyrrolimine was determined to establish which tautomeric form was present.[97]

Crystal structures of two 2,3-dihydropyrrol-3-ones indicate some contribution from the 2*H*-pyrrole charge separated forms.[139,140]

4.3.3. Tautomerism

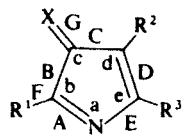
4.3.3.1. Tautomerism Not Involving Functional Groups

Although MO calculations show 2*H*- and 3*H*-pyrroles to be thermodynamically unstable relative to the 1*H*-forms,[101,122] examples carrying one or more hydrogen atoms at the tetrahedral carbon atom have been reported. Structures **15**[20,46] and **16**,[84] which have already been mentioned, appear to be stable, the latter probably for steric reasons. The 3*H*-pyrrole **43** has also been detected in



43 **44**

TABLE 4.32. BOND PARAMETERS FOR 3*H*-PYRROLES HAVING AN EXOCYCLIC C=X BOND FROM *X*-RAY CRYSTALLOGRAPHIC STUDIES



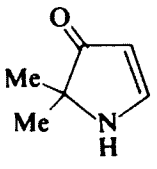
Substituent				Bond Length (A)							Bond Angle (°)					
X	R^1	R^2	R^3	A	B	C	D	E	F	G	a	b	c	d	e	Ref.
O	NEt_2	Ph	Ph	1.357	1.505	1.423	1.385	1.426	1.328	1.236	—	110.4	105.4	105.5	114.4	61[a]
O	NEt_2	Ph	Ph	1.322	1.539	1.439	1.378	1.398	1.321	1.226		110.9	103.4	105.0	115.7	61[a]
NPh	NHMe	NO_2	NHMe	1.335	1.504	1.438	1.431	1.372	1.309	1.281	104.6	114.2	101.4	106.4	113.4	97

[a]Two different molecules per unit cell.

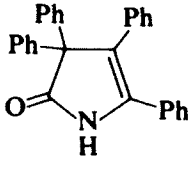
solution by ^{1}H NMR but is converted into the 1*H*-isomer **44** on treatment with base.[141] 2,5-Bis-dialkylamino-3*H*-pyrroles unsubstituted at C_3 have been described.[29] Other reports of such compounds are possibly in error.[142,143]

4.3.3.2. Compounds with Potential Hydroxy Groups

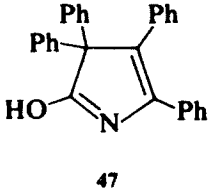
Hydroxy 2*H*- and 3*H*-pyrroles are thermodynamically unstable relative to both the oxo and the hydroxy 1*H*-pyrrole forms, according to MO calculations.[46,122,123] In practice, however, stability is considerably dependent on structure. Thus, while the pyrrolone **45** shows no evidence of the enol form in solution,[144] the lactam **46** is reported to exist as such in the solid, but in equilibrium with its tautomer **47** in acetonitrile solution.[145] The presence of a dialkylamino group at C_5 shifts the equilibrium **48** and **49** strongly to the right in both the solid state and solution,[23,24] even when R^1 and $R^2 = H$. 3-Hydroxypyrrole dimers, initially reported as having structure **50**,[146] were later shown to be the isomers **51**, and, as with the pyrrolone **45**, there was no evidence of the enolic form.[147]



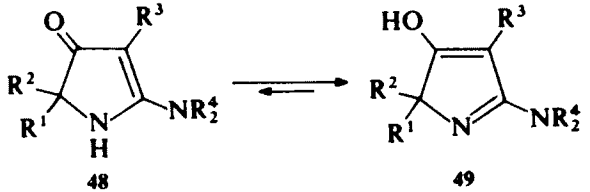
45



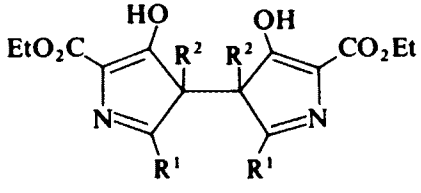
46



47



48 **49**



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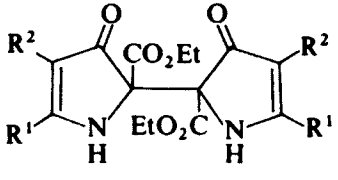
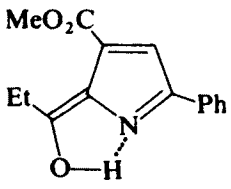


51

Although MO calculations again indicate hydroxy 1-azafulvenes to be less stable than the oxo forms,[122] a number of these compounds have nevertheless been isolated. The 6-hydroxy compounds (e.g., **52**) are stabilized by an intramolecular hydrogen bond,[44,49] while the presence of a 2-alkoxy (but not an

alkylamino) group appears to stabilize the 4-hydroxy derivatives (e.g., **53**).[49] The lactam **54**, while existing in the solid state, is reportedly converted into the enol **55** in solution in both methanol and chloroform.[45]



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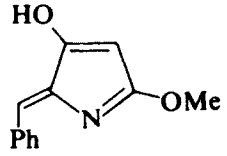

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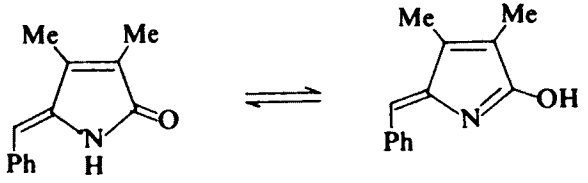
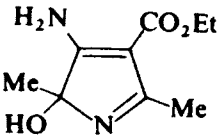


54 **55**

4.3.3.3. Compounds with Potential Amino Groups

3-Amino-2*H*-pyrroles (e.g., **56**) have recently been reported to exist as such both in the solid state and in solution.[105] Many 3*H*-pyrroles of general structure **57**⇄**58** have been described, where X is a hetero-linked substituent, and Y = CN or CO_2Et.[30,148–152] Although one group favored structure **58** as being more extensively conjugated,[150] it has never been clear which was the more stable tautomer. Recently, a comparison between the ^{13}C NMR spectra of **59**



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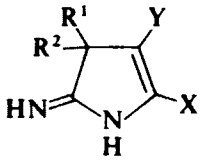

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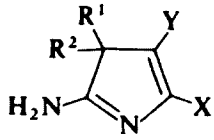

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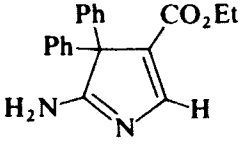

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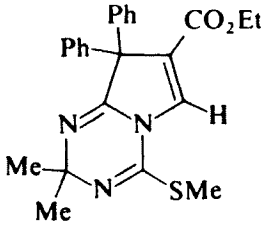

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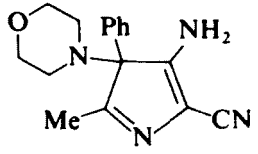

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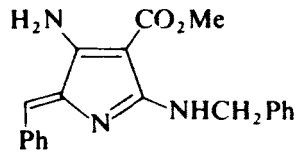
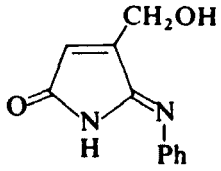


62

(Table 4.25)[107] and **60**[82] has shown that **59** exists as such in solution. 4-Amino-5-cyano-3*H*-pyrroles (e.g., **61**) also exist in the amino rather than the imino form,[31] as do 2,4-diamino-1-azafulvenes, which carry a 3-ester group (e.g., **62**).[49]

X-Ray crystallography has established structure **63** as correct rather than the 2*H*-pyrrol-2-one form,[153] and also the 3*H*-pyrrol-3-imine **64**, which is extensively hydrogen-bonded in the solid state.[97] The 3*H*-pyrrol-3-one hydrazone structure **65** is stabilized by intramolecular *H*-bonding.[120]



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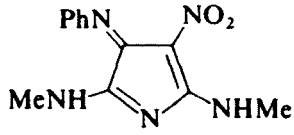

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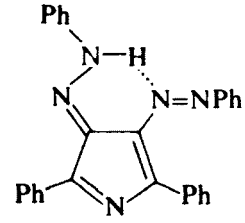
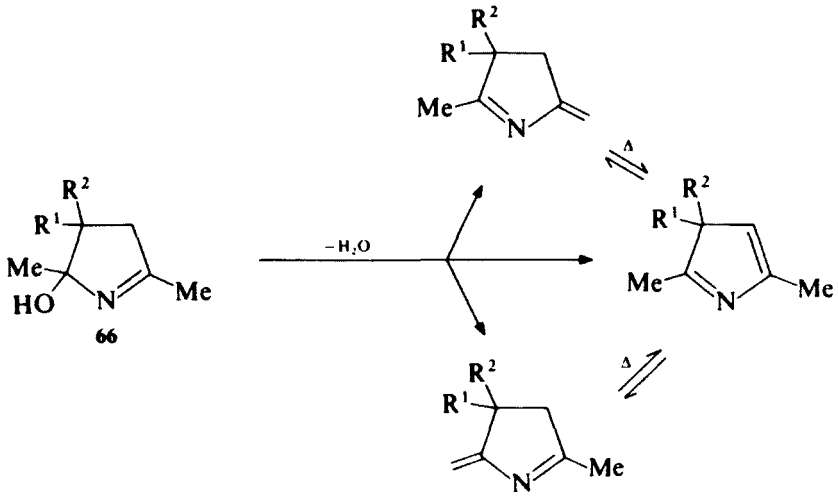


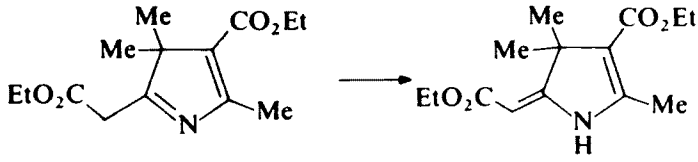
65

4.3.3.4. *Compounds with Potential Alkyl Groups*

3,3-Disubstituted 2-hydroxy-3,4-dihydro-2*H*-pyrroles having a methyl group at C_2 and/or C_5 (e.g., **66**) may be dehydrated to an equilibrium mixture of a 3*H*-pyrrole and methylene pyrroline(s).[13,28,132,154] Generally, the equilibrium fa-

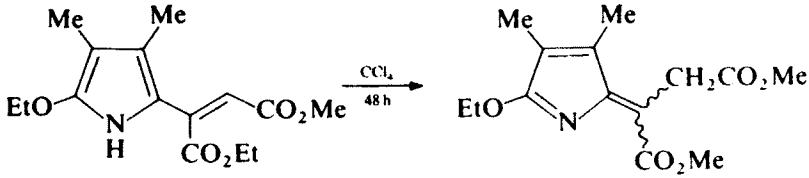


vors the 3*H*-pyrrole, with the 5-methylene isomer being present to the smallest extent. If, however, the C_2 and/or C_5 substituents are longer-chain alkyl groups, the exocyclic isomers now predominate, and if potential conjugating groups are present, the product may exist entirely in the exocyclic form (e.g., **67**).[36]



67

The 1*H*-pyrrole DMAD adduct **68**, although stable at $-30°C$, is converted into the 1-azafulvene tautomer **69** at room temperature.[91]



68 **69**

4.4. SYNTHESIS

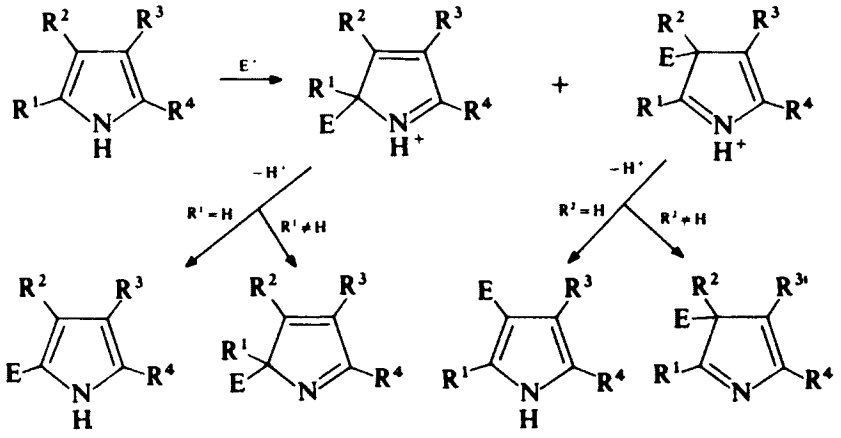
Preparative methods for the compounds described in this chapter are conveniently classified according to the nature of the fragments employed and the number of bonds formed in assembling the product. Many methods simply involve the modification of existing pyrroles, particularly by reaction with electrophiles. Historically, this was the earliest and most generally used approach, and it will be discussed first. Other important methods involve assembly of the ring from smaller fragments by formation of one, two, or three bonds; 1,3-dipolar cycloaddition is particularly useful, as is transformation of other heterocycles, especially azirines.

Under each heading, compounds will be discussed in the order: 2*H*- and 3*H*-pyrroles; 1- and 2-azafulvenes; 2*H*- and 3*H*-pyrroles with an exocyclic C=X bond. All known compounds, together with preparative methods and references to physical data are given in Tables 4.34–4.55 (Section 4.6).

4.4.1. By Modification of Other Pyrroles

4.4.1.1. From 1H-Pyrroles by Electrophilic Attack at Ring Carbon

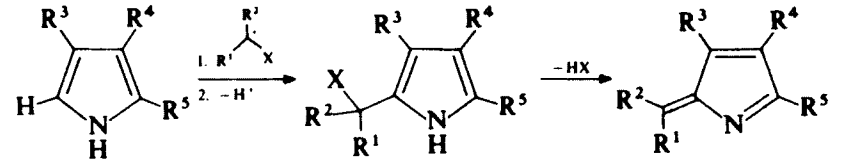
During the normal electrophilic substitution of 1*H*-pyrroles, an electrophile adds at C_2 or C_3 to form a tetrahedral intermediate cation (Scheme 1). If the site



Scheme 1

of attack by the electrophile is initially unsubstituted, subsequent proton loss gives a 1*H*-pyrrole as the product; if the site is substituted, however, a 2*H*- or 3*H*-pyrrole will be formed. Electrophiles commonly used in the preparation of 2*H*- and 3*H*-pyrroles by this method have been alkyl halides, carbenes, halogenating, and other oxidizing agents.

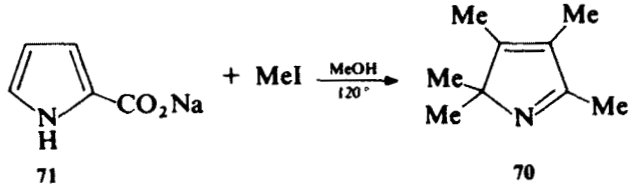
If the electrophile carries a potential leaving group X, however, and the 1*H*-pyrrole has at least one unsubstituted site, subsequent loss of HX may lead to a 1- or 2-azafulvene (Scheme 2). Electrophiles in this category are carbonyl compounds with acid, amide–acid halide complexes, and cyclic onium salts.



Scheme 2

4.4.1.1.1. Alkyl Halides and Sulfonates

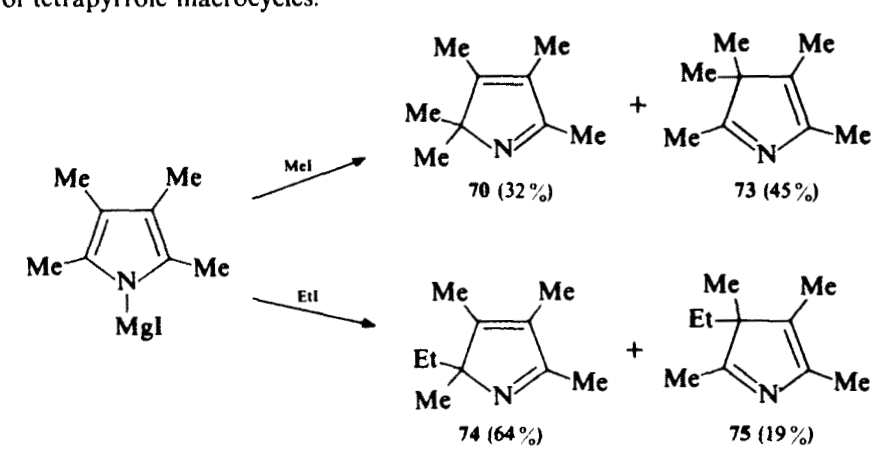
In 1888 Ciamician and Anderlini obtained what must have been 2,2,3,4,5-pentamethyl-2*H*-pyrrole **70** by heating sodium 1*H*-pyrrole-2-carboxylate **71** with methyl iodide and methanol in a sealed tube.[155] They initially identified the products from this and related reactions as 1,2-dihydropyridines,[156,157] but later corrected them to 2*H*- or 3*H*-pyrroles.[158] Reactions between 1*H*-pyrroles, containing varying numbers of methyl groups, and methyl iodide in sealed tubes in the presence of potassium carbonate also gave 2*H*- and possibly 3*H*-pyrroles, often as complex mixtures with methylene–pyrrolines.[156,159,160] An improved procedure involved the treatment of a preformed pyrrolylmagnesium halide



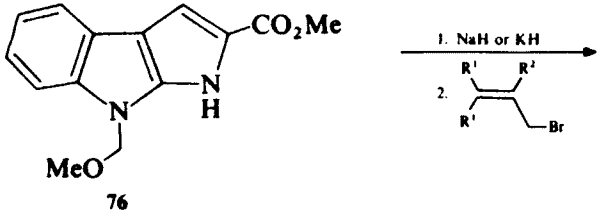
71 70

with an alkyl halide in ether to give mixed regioisomers of 2*H*- and/or 3*H*-pyrroles, together with alkylated 1*H*-pyrroles.[160–163] The mixtures were freed from 1*H*-pyrroles by extraction into acid and further separated by fractional distillation and conversion into picrates.

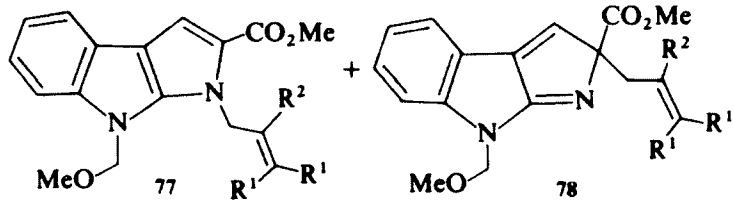
Early workers were unsure whether products were 2*H*- or 3*H*-pyrroles or mixtures. One group provided strong evidence for the 3*H*-isomers,[163] but these were later shown to be the 2*H*-compounds by a group who were unable to find any evidence of 3*H*-pyrroles.[8] The method has since been used to prepare a number of useful 2*H*-pyrroles of known regiochemistry in moderate to good yields,[7,34,63,79] including compounds such as **72** of potential use in the synthesis of tetrapyrrole macrocycles.[72]



Wong and Ritchie, however, in a classical paper[26] have shown that both the 2*H*- and the 3*H*-pyrroles are formed, the latter sometimes in the greatest yield (compare **70** and **73** with **74** and **75**). 3*H*-Pyrroles are now known to be unstable in the presence of acid, either rearranging to the 2*H*-isomers[13,28,131] or hydrolyzing to 1,4-diketones.[13,28,154] Early workers isolated products by extraction with aqueous acid, sometimes heating under reflux,[155,163] which probably explains their failure to isolate the 3*H*-compounds. The 2*H*- and 3*H*-isomers are reported to have respectively amine-like and camphor-like smells;[26] both odors were mentioned in early publications.

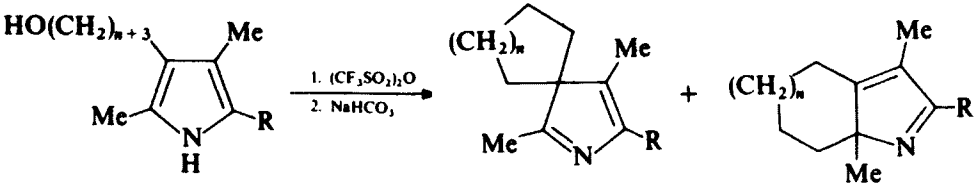


76



77 **78**

Reaction of the sodium or potassium salt of the pyrroloindole **76** with allylic bromides (R^1, R^2 = H or Me) gave mixtures of the *N*- and *C*-alkylated products **77** and **78**, with the *C*-isomer predominating when R^1 = Me.[164] Magnesium(II) complexes of pyrrocorphins undergo regioselective *C*-alkylation with methyl iodide on the 1*H*-pyrrole moiety, converting them to corphins by the generation of a 3*H*-pyrrole ring.[165]

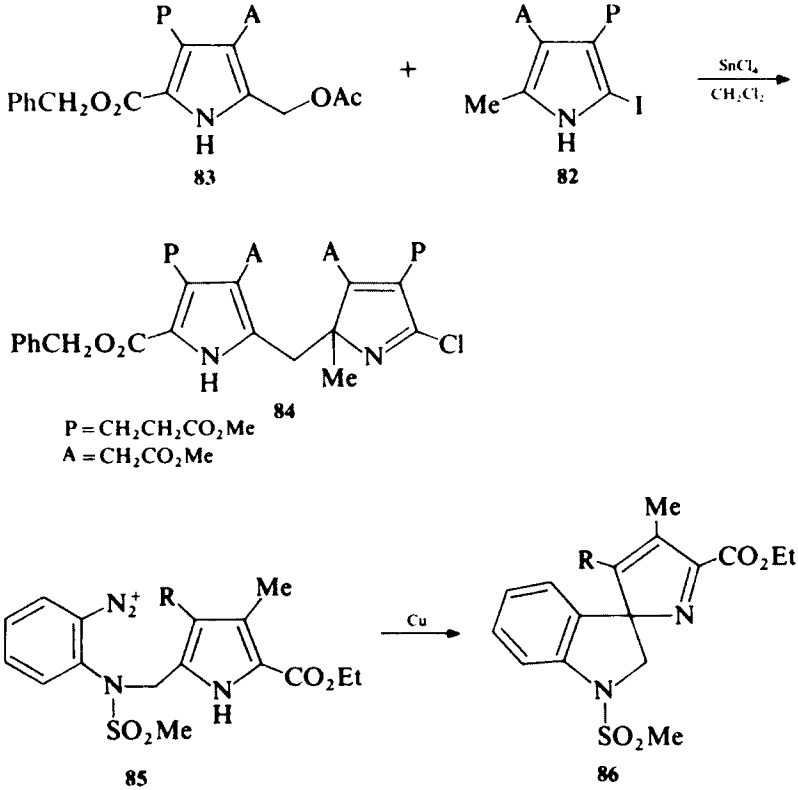


79 **80** **81**

Treatment of 2,3,4,5-tetramethyl-1*H*-pyrrole with methyl fluorosulfonate gave equal amounts of the fluorosulfonic acid salts of **70** and **73**, while the alcohols **79** (R = Me, CO_2CH_2Ph; n = 1) with trifluoromethanesulfonic anhydride, followed by sodium hydrogen carbonate, yielded a mixture of isomers **80** and **81**, with the former predominating.[166] For **79** (R = Me; n = 2), however, only the 3*H*-pyrrole isomer **80** was formed.

4.4.1.1.2. Other Alkylations and Arylations

Reaction between **82** and the acetoxymethylpyrrole **83** in the presence of tin(IV) chloride gave the 2*H*-pyrrole product **84** (43%).[167] The diazonium salts **85** decomposed into the spiro-2*H*-pyrroles **86** in high yields when R = CO_2Et[168] or COMe,[169] but not when R = Me.[169] A related spiroindolo-2*H*-pyrrole has been prepared via an intramolecular Fischer-indole-type cyclization.[92] Halogenotetrapyrrole salts have been cyclized in the presence of piperidine and nickel(II) salts to nickel(II) tetradehydrocorroles, a ring system containing a 2*H*-pyrrole moiety.[170,171] The formation of 2*H*-pyrrole **20** from methyl 2,5-dimethylpyrrole-1-carboxylate and DMAD involves electrophilic attack at C_2 followed by rearrangement.[100]

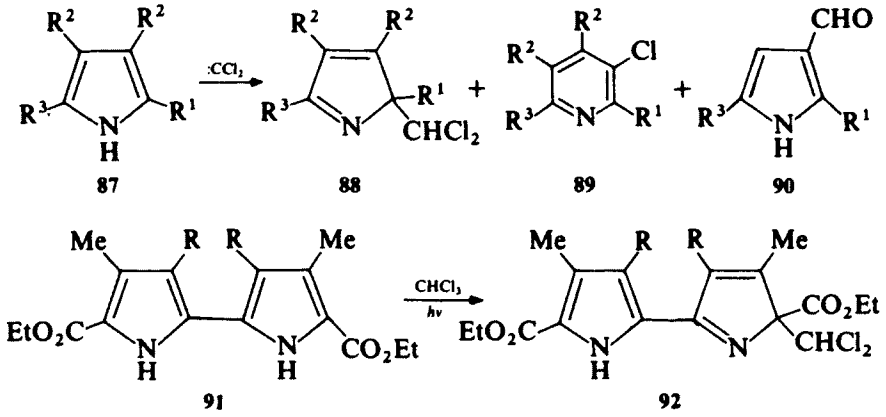


Treatment of 2-ethoxy-3,4-dimethyl-1*H*-pyrrole with DMAD at −70°C gave the adduct **68** that isomerized at room temperature to the 1-azafulvene **69**.[91]

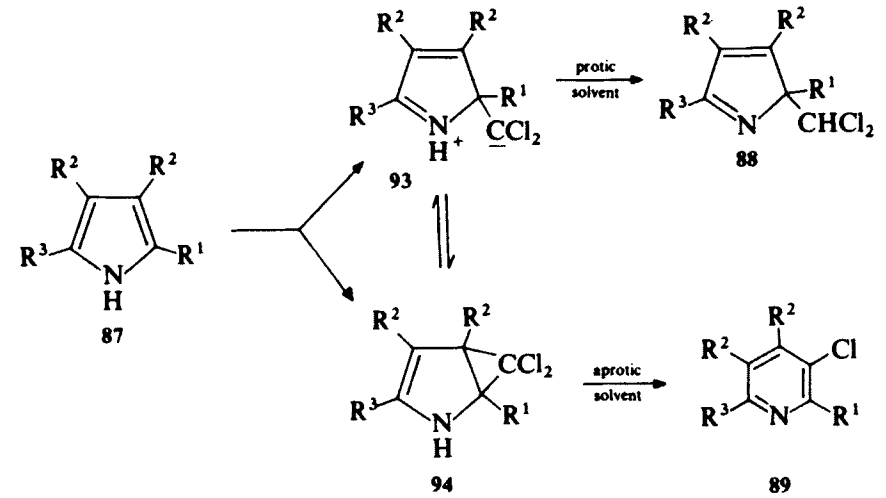
4.4..1.1.3. Carbenes

The Reimer–Tiemann reaction with 2,5-dialkyl pyrroles **87** was found by Plancher and co-workers to yield isopyrroles, believed to be the 2*H*-isomers **88**,

together with the chloropyridines **89** and (when $R^2 = H$) the 3-formyl-1*H*-pyrroles **90**.[172,173] The ratio of 2*H*-pyrrole to pyridine was later shown to depend on the solvent, the pH, the carbene source, and the amount of water present.[14,66] Optimum yields of **88** were obtained with chloroform and aqueous ethanolic potassium hydroxide, while neutral aprotic conditions favored **89**. Phase-transfer catalysis also favored the formation of **89**,[174] and the use of phenyltrichloromethylmercury as the carbene source resulted in seven products, of which two (in low yield) were 2*H*-pyrroles.[133,175] For the unsymmetrical 2-*t*-butyl-5-methyl-1*H*-pyrrole, two regioisomeric pyridines[65,133,175] and aldehydes[133,175] were found, but only one 2*H*-pyrrole. The reaction of photochemically generated dichlorocarbene with the 2,2′-bipyrrole **91** gave moderate yields of the adducts **92**.[176]

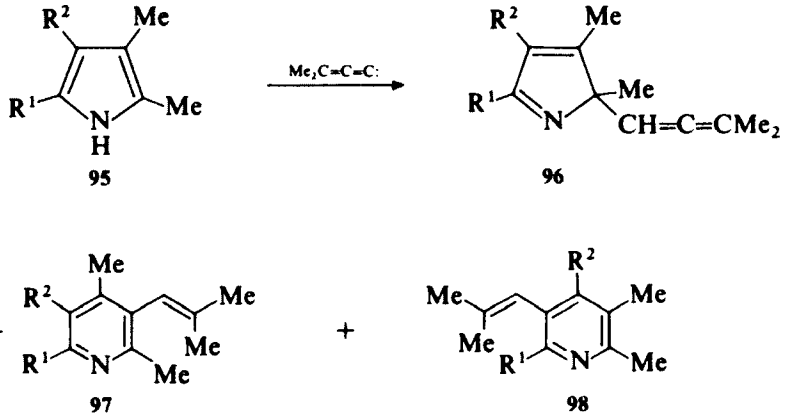


Although **88** can be converted into **89** (and other pyridines) in the presence of very strong bases,[177,178] contrary to early claims[172,173] the transformation cannot be carried out under the conditions prevailing in the Reimer–Tiemann



reaction of **87**,[179–182] thus demonstrating that **88** is not an intermediate in the formation of **89**. Much discussion, however, has been centered on whether the two products have a common intermediate, as both supporting[177,178,183] and refuting[14,66] evidence has been presented. More recent results support a common intermediate (**93**⇄**94**) and explain the solvent-dependence of product distribution.[133]

Dimethylvinylidene carbene has recently been shown to add to alkyl 1*H*-pyrroles **95** (R^1, R^2 = H, Me) to give both 2*H*-pyrroles **96** and regioisomeric pyridines **97** and **98** in low yields. The preferred site of attack is the most substituted C=C bond.[64]



4.4.1.1.4. Halogenating Agents

Pentachloro-2*H*-pyrrole **12** has been prepared from succinimide or 3,4-dichloromaleimide and phosphorus pentachloride,[184] with the conditions of the reaction being improved later.[185] The same compound is also obtained by the treatment of pyrrole or 2,3,4,5-tetrachloropyrrole with sulfuryl chloride in anhydrous ether.[186] Detailed analysis by GC, HPLC, and NMR spectroscopy has shown that any 3*H*-pyrrole **13** present is below the level of detection.[70]

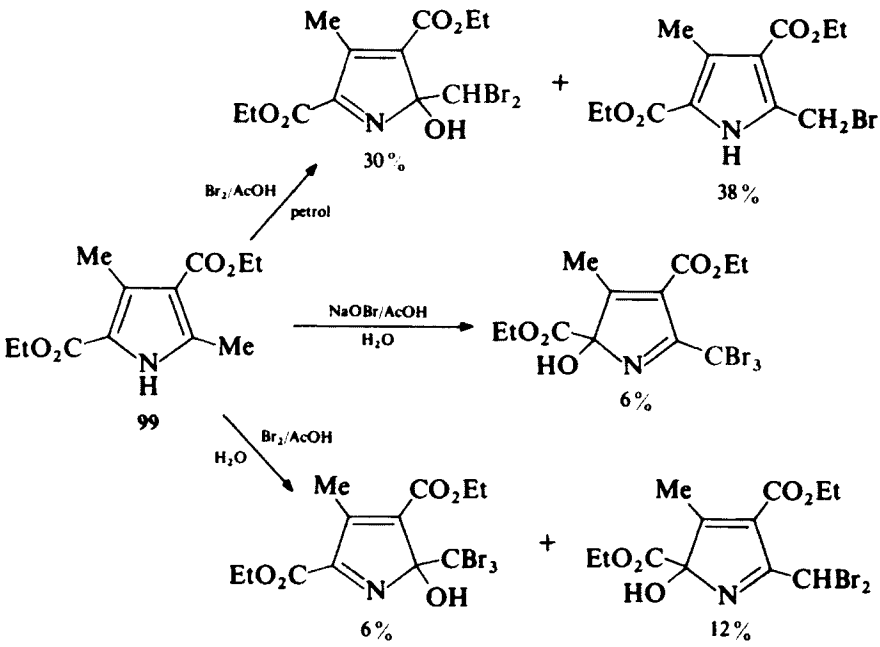
Bromination of the 1*H*-pyrrole diester **99** leads to different bromo-2*H*-pyrroles, depending on the conditions (Scheme 3).[187,188]

The 1*H*-pyrroles **100** (R^1, R^2 = SCF_3, Cl) undergo oxidative dimerization with iodine under strictly anhydrous conditions to yield the bis-2*H*-pyrroles **23**–**25**.[112,113]

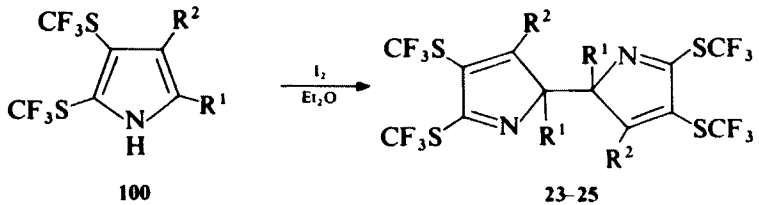
The dibromo-1-azafulvene **101** has been prepared by bromination of the 2-sulfonic acid **102**,[187] and treatment of **103** with sulfuryl chloride in dry ether led to the 2*H*-pyrrol-2-one **26**, together with **104**.[75]

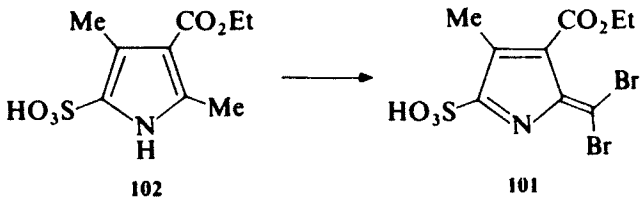
4.4.1.1.5. Other Chemical Oxidants

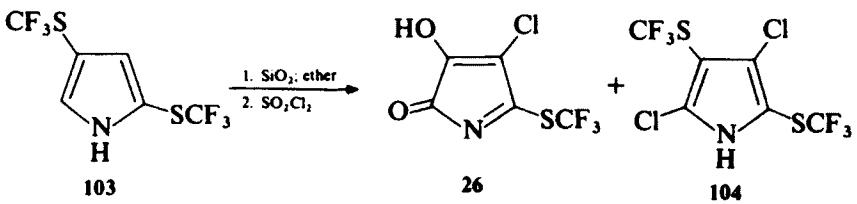
Treatment of 2,3,4,5-tetraphenylpyrrole **105** with sodium nitrite in acetic acid at 0°C resulted in a product identified as an equilibrium mixture of the 2*H*-pyrrole **106** and a ring-opened product designated as being the *cis*-oxoimine


Me
CO2Et
EtO2C
CHBr2
OH
30%
+
CH2Br
38%
Br2/AcOH
petrol
99
NaOBr/AcOH
H2O
CBr3
6%
Br2/AcOH
H2O
12%

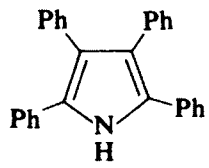
Scheme 3


CF3S
R2
R1
100
I2
Et2O
SCF3
23–25


Me
CO2Et
HO3S
102
Br
101


CF3S
SCF3
1. SiO2; ether
2. SO2Cl2
HO
Cl
O
26
104

107, in view of its facile reduction to **105** and hydrolysis to *cis*-dibenzoylstilbene **108**.[189] The reaction between **105** and pentyl nitrite at low temperature gave the same product, while at higher temperature, only **108** was isolated. The product was later shown to comprise only **106**[190] and to be identical with one of two structurally related compounds reported by Japp and Klingemann in a series of papers.[191–194] Lutz and Boykin prepared it from **105** by oxidation with chromium(VI) oxide, lead (IV) acetate, or nitric acid, as well as sodium nitrite, all in acetic acid.[190] Similar oxidations of the *N*-methyl derivative of **105** gave "pyrrolenineonium salts," which were difficult to purify, but which gave rearrangement products analogous to **106**.[190]



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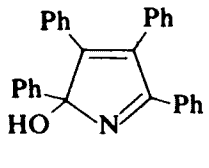
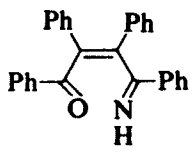
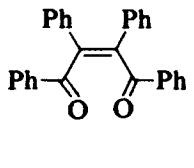


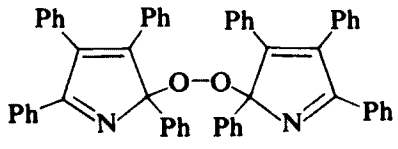
106



107



108



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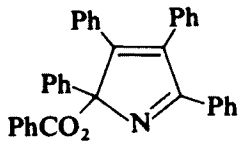
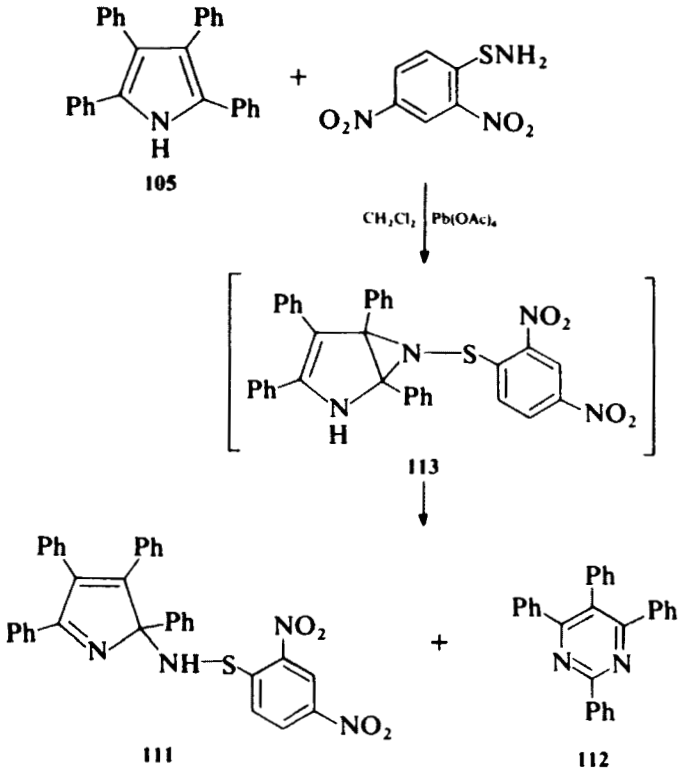


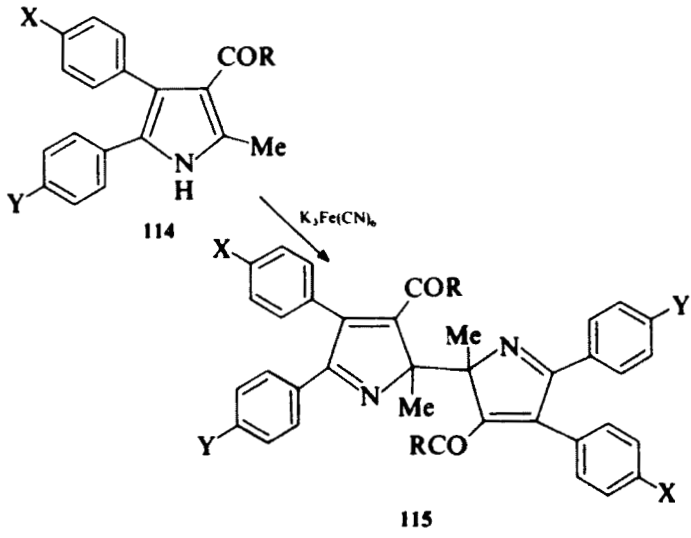
110

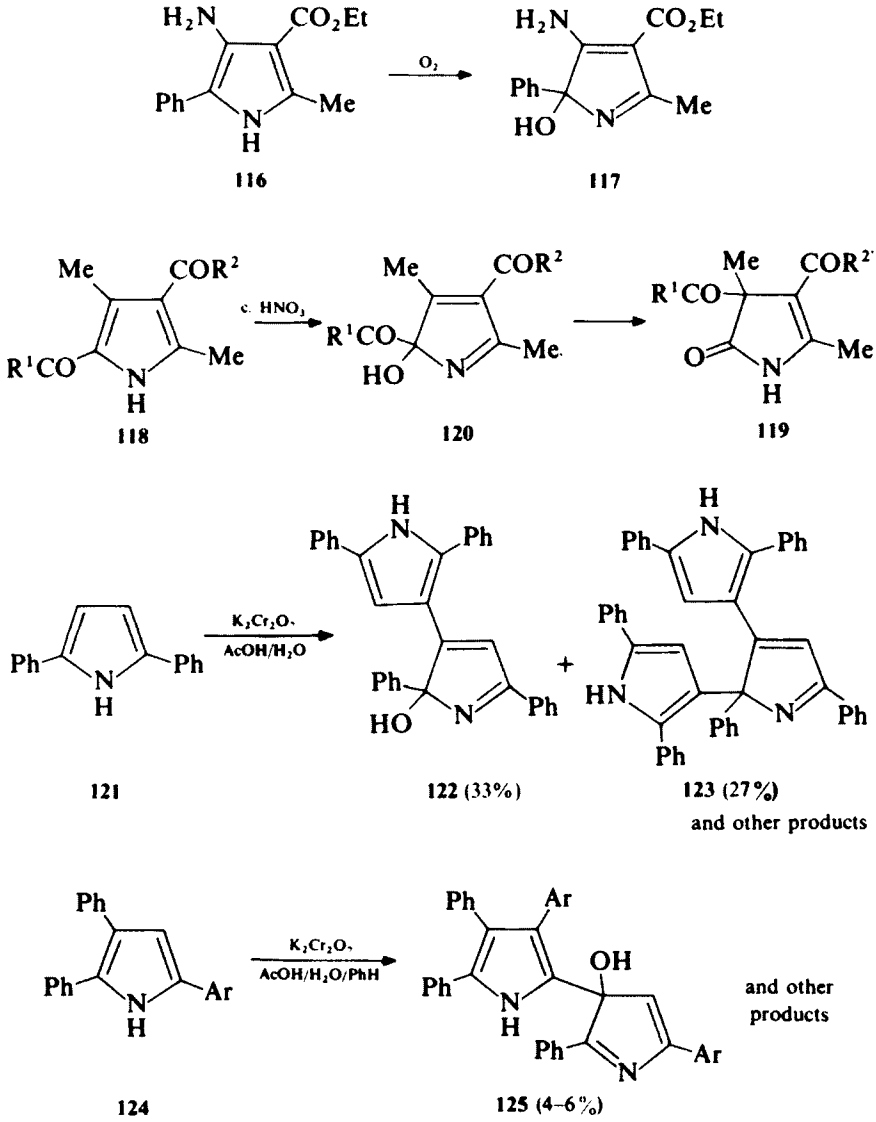
When oxidized in the presence of specific reagents, **105** yields other 2*H*-pyrrole products. Thus, lead(IV) oxide in benzene in the presence of oxygen produced a separable mixture of the two diastereomers of the peroxide **109**,[195,196] whereas dibenzoyl peroxide in benzene gave the benzoate **110** by a mechanism thought not to involve the $PhCO_2^{\cdot}$ radical.[197] Reaction with lead(IV) acetate and 2,4-dinitrobenzenesulfenamide resulted in a mixture of the 2*H*-pyrrole **111** and the pyrimidine **112**, presumably via the nitrene adduct **113**.[135]

Other tetrasubstituted 1*H*-pyrroles have been oxidized to 2*H*-derivatives. Potassium hexacyanoferrate(III) converts **114** into the dimers **115**;[121] the 3-amino compound **116** spontaneously oxidizes in air to **117**,[105] and the 2,4-diacyl compounds **118** yield the lactams **119**, presumably by rearrangement of 2-hydroxy intermediates **120**.[198]

Oxidations of less substituted 1*H*-pyrroles generally yield complex reaction mixtures,[199] but 2*H*- and 3*H*-pyrroles may be isolated when aryl groups are present in the 2 and 5 positions. Thus, with potassium dichromate in acetic acid, 2,5-diphenylpyrrole **121** gives **122** and **123** together with three other products,[200] while **124** (Ar = Ph or 4-MeC_6H_4) gives **125** together with four other products.[201] In both cases, some of the other products contain a 7a*H*-indole moiety.

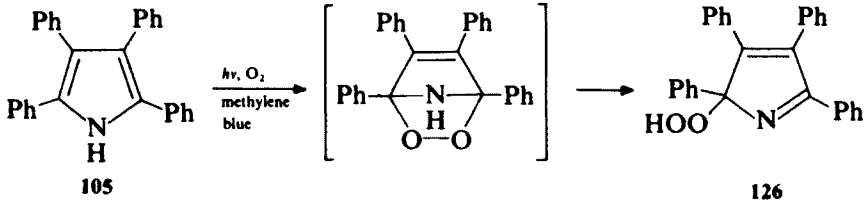

Ph
Ph
Ph
N
H
Ph
105
+
SNH2
O2N
NO2
CH2Cl2 | Pb(OAc)4
Ph
Ph
NO2
N
S
Ph
N
H
Ph
NO2
113
Ph
Ph
Ph
N
Ph
NH
S
NO2
NO2
111
+
Ph
Ph
Ph
N
N
Ph
112

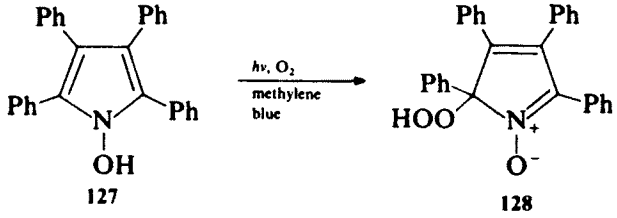

X
COR
Me
N
H
Y
114
K3Fe(CN)6
X
COR
Y
Me
N
N
Me
Y
RCO
X
115



4.4.1.1.6. Photochemical Oxidation

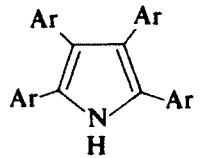
The methylene-blue-sensitized photooxidation of **105** in oxygen gives a high yield of hydroperoxide **126**;[69,195,202] the proposed mechanism involves a hetero-Diels–Alder reaction.[69] Compound **126** was presumably an intermediate in a similar photooxidation reported earlier.[203] 2,5-Diphenylpyrrole **121**,[69] 2,5-di-*tert*-butyl- and 2,3,5-tri-*tert*-butylpyrroles,[21] and a series of 2-aryl-4,5,6,7-tetrahydroindoles[204] have been similarly oxidized. Likewise, the *N*-hydroxy compound **127** produces the hydroperoxy *N*-oxide **128**.[205]



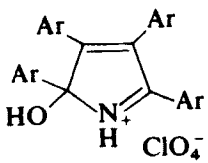


4.4.1.1.7. Electrochemical Oxidation

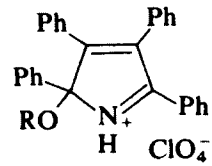
Oxidation of tetraaryl pyrroles, **105**, **129**, and **130** using a rotating platinum microelectrode gives different products in different proportions, depending on the conditions. In aqueous methanolic lithium perchlorate, the salts **132** and **133** were isolated in high yields from **129** and **130**, respectively,[206,207] while **105** gave **131**, together with increasing proportions of **134** (or **135** when methanol was replaced by ethanol) as the percentage of water present decreased.[208] In wet



105 Ar = Ph
129 Ar = 4-MeC$_6$H$_4$
130 Ar = 4-MeOC$_6$H$_4$



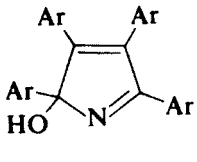
131 Ar = Ph
132 Ar = 4-MeC$_6$H$_4$
133 Ar = 4-MeOC$_6$H$_4$



134 R = Me
135 R = Et

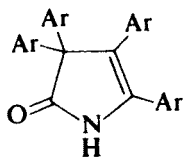
nitromethane, containing tetraethylammonium perchlorate and sodium carbonate, the products depend on the temperature. At low temperature, the 2-hydroxy compounds **106**, **136**, and **137** are the only products, while at 90°C the pyridines **138–140** (R = H) are the major products, together with smaller amounts of the lactams **46**, **141**, and **142** and the diketones **108** and **143**; the two latter species arise from decomposition of the 2-hydroxy compounds that are not detected.[206,207,209] The results have been explained in terms of the mechanism shown in Scheme 4.

Oxidation, from half-wave potentials relative to Ag/AgCl, occurs in two steps, with values for E_1 and E_2 being respectively 1.17 and 1.77 V for **105**,[208] 1.08 and 1.69 V for **129**,[206] and 0.93 and 1.37 V for **130**,[207] and correlating well with σ^+ constants.[206] The intermediate cation radical **144** has been detected by ESR

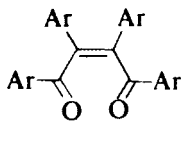


106 Ar = Ph
136 Ar = 4-MeC_6H_4
137 Ar = 4-$MeOC_6H_4$

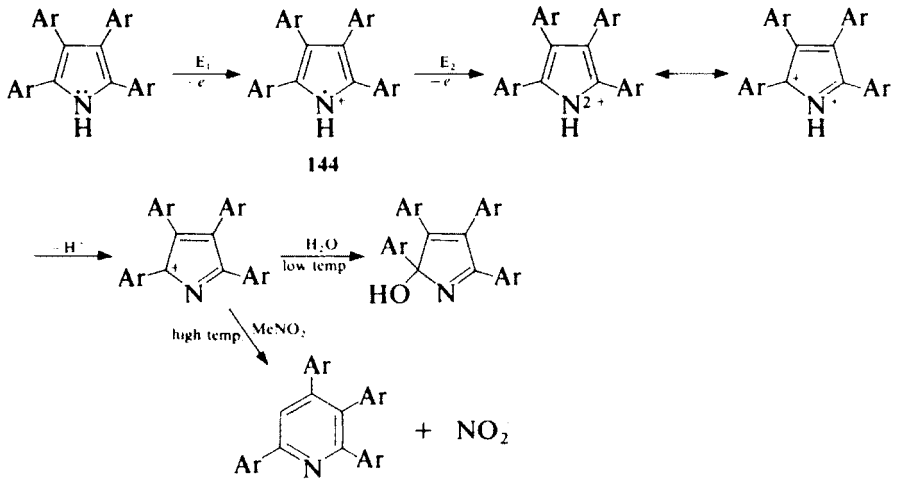
138 Ar = Ph
139 Ar = 4-MeC_6H_4
140 Ar = 4-$MeOC_6H_4$



46 Ar = Ph
141 Ar = 4-MeC_6H_4
142 Ar = 4-$MeOC_6H_4$



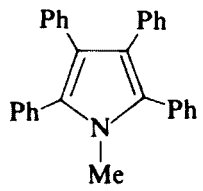
108 Ar = Ph
143 Ar = 4-MeC_6H_4



144

Scheme 4

spectroscopy[207,208] and trapped as the peroxide **109**.[208] The pyridine C_5 atom comes from the nitromethane, as demonstrated by the formation of **138** (R = D, Me) when the oxidation was carried out in CD_3NO_2 and $EtNO_2$, respectively;[207] a mechanism has been proposed.[209] *N*-Methyl and *N*-ethyl derivatives of **105**, **129**, and **130** behave analogously, and the salts **146** and **147**, and the lactam **148** have all be isolated from electrochemical oxidations of **145** under different conditions.[210]



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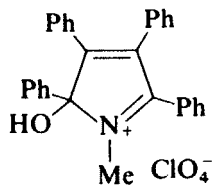

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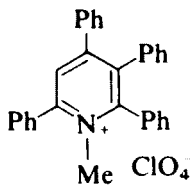

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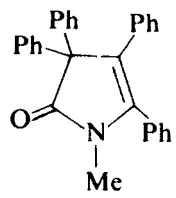


148

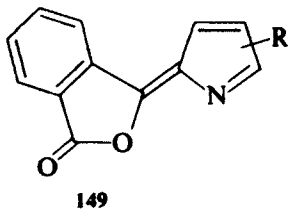
4.4.1.1.8. Protonation

Protonation of 1*H*-pyrroles is discussed in detail in Chapter 3. For simple alkyl and *N*-aryl pyrroles, the α-protonated (2*H*-pyrrolium) form is generally

thermodynamically the most stable in strongly acid solutions, but the β-protonated (3*H*-pyrrolium) form may also be observable by UV and NMR spectroscopy and, on occasions, is the more stable.[32,33,211-213] 2-Amino-1*H*-pyrroles bearing nitrile or ester group at C_3 protonate at C_5 in strong acid to give 5-amino-2*H*-pyrrolium cations.[87,214] However, whereas 1*H*-pyrrole-2- and -3-carboxylic esters protonate at C_2 and C_5, respectively, to give the 2*H*-pyrrolium cations, the 2- and 3-acyl compounds protonate on the carbonyl oxygen atom to give 1- and 2-azafulvenium cations, respectively.[86,89] A series of stable *tert*-butyl-substituted 2*H*-pyrrolium salts has been isolated by treating the 1*H*-pyrroles in dry ether with fluoroboric acid.[85]

4.4.1.1.9. Carbonyl Compounds with Acid or Base

The reaction between pyrrole or its simple alkyl derivatives and phthalic anhydride in acetic acid was reported by Ciamician and Dennstedt,[215] and subsequently by many others,[216-219] to give products of the general structure **149**. The products were also reported from pyrrolylmagnesium halides and phthalic acid derivatives.[220,221] The structures were later shown to be the *N*-acyl isomers (**150**),[222] despite an earlier report to the contrary.[223]



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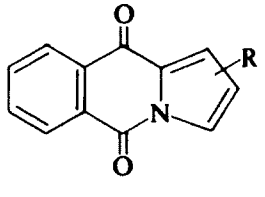
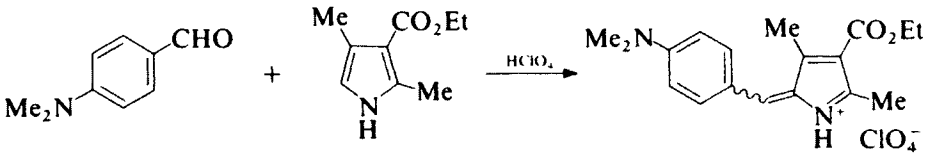
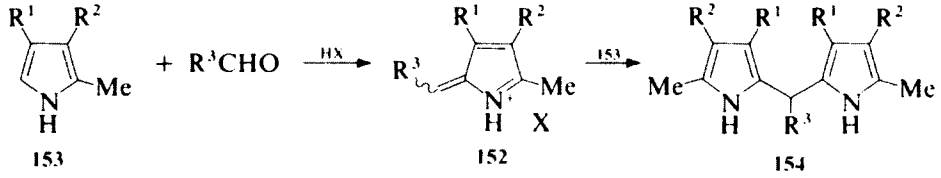


150

1*H*-Pyrroles, having at least one unsubstituted carbon atom, react with 4-dimethylaminobenzaldehyde in the presence of strong mineral acids to give deep-red solutions (the Erlich test). The products are azafulvenium salts, many of which, including **151**[224] have been isolated as crystalline solids. The reaction has also been achieved with 2,3,4,5-tetramethylpyrrole, with concomitant formation of methanol,[225] and the aminobenzaldehyde has been replaced successfully by furfural,[226] unsaturated aldehydes,[53] and cyclic ketones,[227] including cyclopropenone,[77] nin-hydrin,[228] and a combination of an aldehyde and a ketone.[229] Generally, the colored salt is formed, but if the reaction is carried out in acetic acid, the free-base azafulvene may be isolated.[226,228] On occasions the azafulvenium salt **152** reacts further with the 1*H*-pyrrole **153** to



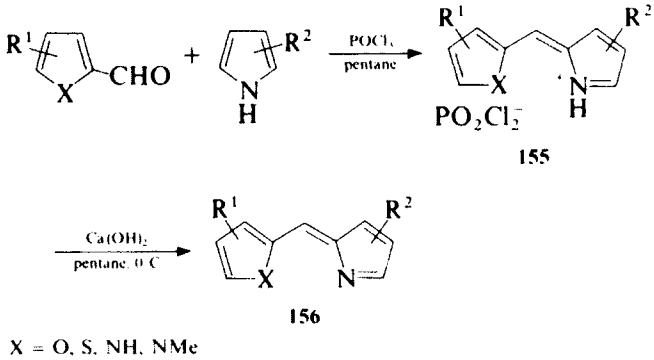
151



153 152 154

give products of type **154**; either or both products may be isolated.[228,230,231] Treibs and co-workers have found that **152** is favored either when the pyrrole is strongly basic (R^1, R^2 = alkyl), or when it is weakly basic ($R^1 = CO_2Et$) and where R^3 is able to stabilize a carbonium ion and HBr is present.[231]

Furan-, pyrrole-, and thiophene-2-aldehydes also react with 1*H*-pyrroles in the presence of phosphorus oxychloride to give the salts **155**, which may be converted into the azafulvenes **156**.[232] 2-Alkoxy-1*H*-pyrroles unsubstituted at C_5 react with benzaldehydes in ethanolic sodium hydroxide, forming 2-alkoxy-1-azafulvenes.[45,46]



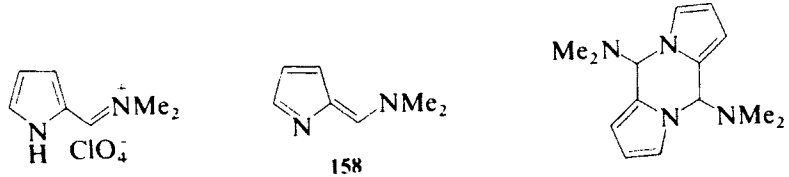
155

156

X = O, S, NH, NMe

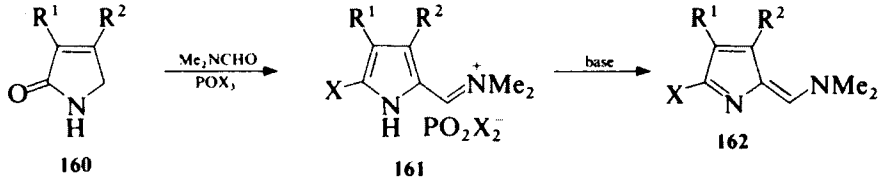
4.4.1.1.10. Amides and Acid Halides

The Vilsmeier reaction between pyrrole and the dimethylformamide–phosphorus oxychloride complex gives an intermediate iminium salt that has been isolated as the perchlorate salt **157**.[233] A claim to have isolated the free azafulvene **158**[233] is probably erroneous, as the product most likely is the dimer **159**.[234] The azafulvene **158** has been generated in situ by this approach, however, and further elaborated.[235,236]



157 158 159

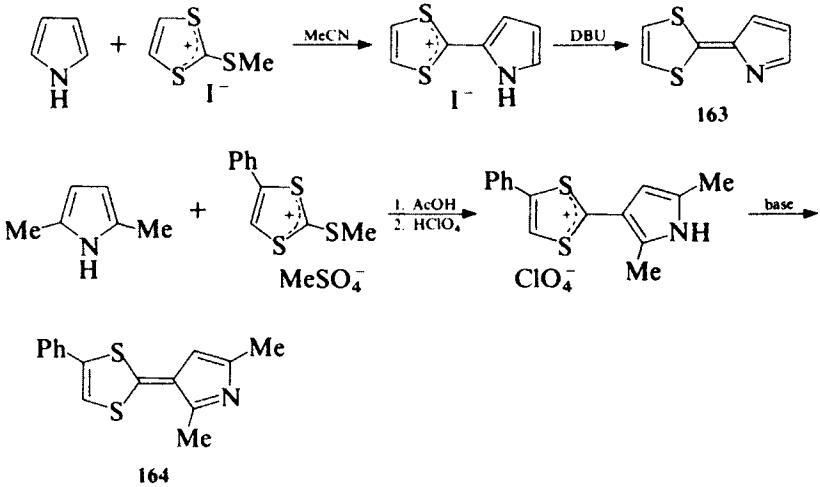
The pyrrolones **160** under Vilsmeier conditions also give isolable intermediate salts **161**, which may be converted into stable monomeric halogeno azafulvenes **162**.[74,94,237] Other stable halogeno 6-amino-1-azafulvenes have also been prepared.[48]



Aromatic amides also react with pyrroles under similar conditions;[43,238–240] both the salts and the free bases have been isolated.[43]

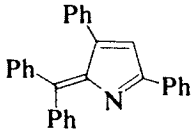
4.4.1.1.11. *S*-Alkyl Cyclic Onium Salts

S-Alkyl cyclic onium salts react with pyrroles in acetonitrile or acetic acid to yield azafulvenium salts, which, in turn, on treatment with base, give parent azafulvenes; examples are 1-azafulvene **163**[47] and 2-azafulvene **164**.[42] In addition to variously substituted 1,3-dithiolium salts,[42,47,51] successful reactions have been carried out with 1,2-dithiolium,[42] 1,3-thiaselenonium,[241] 1,3-benzodithiolium,[47] 1,2,4-dithiazolium,[42] pyrylium,[42] and cyclopropenium[42,51] salts. Intermediate 1 : 1 charge-transfer complexes between the pyrrole and the onium salt have also been isolated.[241]

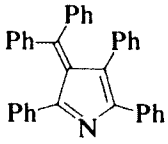


4.4.1.1.12. 1,1-Dichloro Compounds

1,1-Dichlorodiphenylmethane and dichlorodiphenylcyclopropene react with 2,4- and 2,5-diphenylpyrrole, and 2,3,5-triphenylpyrrole in acetonitrile, to give salts that may be converted into compounds such as azafulvenes **165–167**.[42]



165



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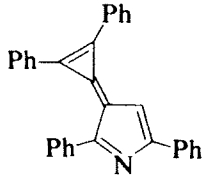
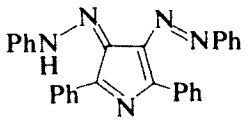


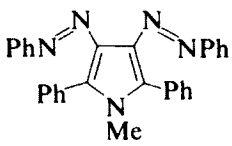
167

4.4.1.1.13. Diazonium Salts

2,5-Diphenylpyrrole couples with benzenediazonium chloride at pH 3.0 to give the azahydrazone **65**. Its structure was confirmed by comparing its UV spectrum with that of **168**.[120] At pH 6.0, 2,5-diphenyl-3-phenylazopyrrole is formed.



65

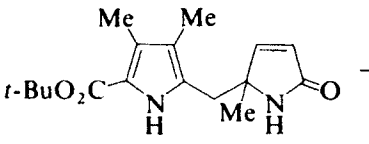


168

4.4.1.2. Transformation of 1H-Pyrrole Ring Substituents

4.4.1.2.1. Alkylation and Acylation of C=X Groups

Pyrroles with a ring C=O group are *O*-alkylated by trialkyloxonium fluoroborates to alkoxy 2*H*-pyrroles.[45,46,78,242,243] Compound **169** is converted into **170**,[78,242] while **171** gives a mixture of **172** and **173**.[243]



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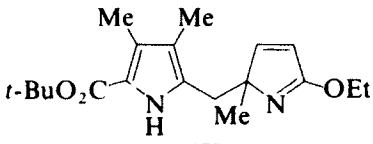

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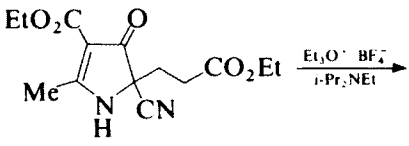

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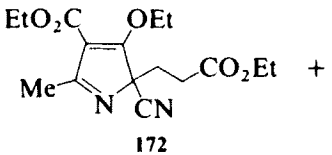

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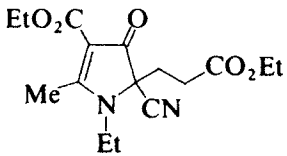
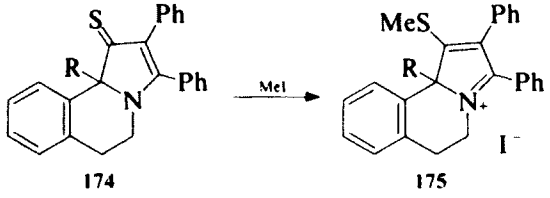
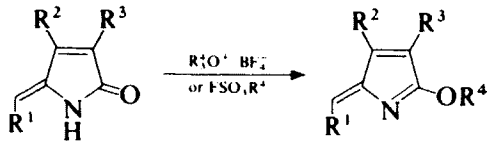


173

With acetic anhydride, however, **171** yields the *N*-acetyl derivative,[243] and not the *O*-acetyl isomer as previously reported.[244] Treatment of the thiones **174** (R = Me, Ph) with methyl iodide produced the salts **175** in quantitative yields.[245]

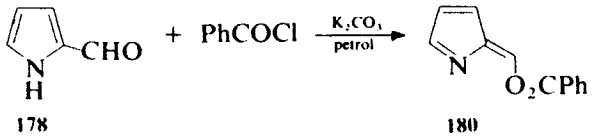


174 **175**

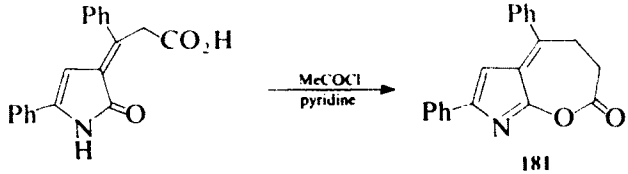


176 **177**

Lactams of the general structure **176** are *O*-alkylated by trialkyloxonium fluoroborates or alkyl fluorosulfonates, yielding the 1-azafulvenes **177**.[46,49,92] *O*-Acylation of 2-formylpyrrole **178**[246] and the lactam **179**[247] are reported to yield the azafulvenes **180** and **181**, respectively.

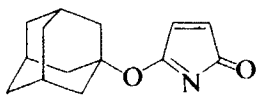


178 **180**



179 **181**

Treatment of silver(I) maleimide with 1-bromoadamantane in benzene at room temperature produces **182** (98%), while heating under reflux in toluene gives the *N*-isomer **183**.[55]



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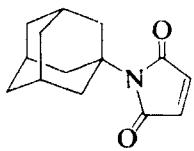
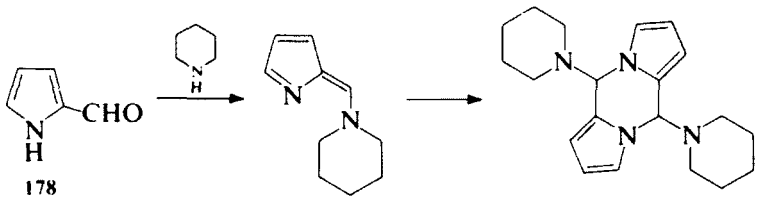


183

4.4.1.2.2. Amination of Aldehydes

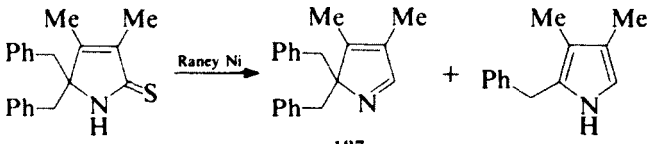
In a paper that appears to have been overlooked by later workers, Herz and Brasch reported that treatment of 2-formylpyrrole with piperidine led to **185**, through spontaneous dimerization of the unstable intermediate 1-azafulvene **184**.[234] The reaction was rediscovered by Hensel,[248] but again overlooked by Kira and co-workers, who claimed to have isolated a series of monomers[249] (see also Section 4.4.1.1.10). It was later shown that structures **184** and **185** (and their analogs) exist in thermal equilibrium in refluxing benzene.[250] A stable 2-chloromonomer **162**, however, has been prepared by this method.[92]



178 **184** **185**

4.4.1.2.3. Desulfurization of Thiolactams

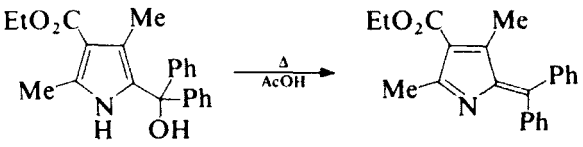
Desulfurisation of **186** with Raney nickel gave the 2*H*-pyrrole **187** and a small amount of **188**;[78] an analogous desulfurization has been carried out using nickel boride.[167]



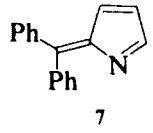
186 **187** **188**

4.4.1.2.4. Elimination from Side Chains

The tertiary alcohol **189** was dehydrated to the 1-azafulvene **190** in refluxing acetic acid.[251] Also prepared from analogous precursor alcohols were the azafulvenes **7**[41] and **191**[252] and the yellow salts **192**.[253] Reduction of 2- and 3-pyrryl ketones with sodium borohydride in refluxing isopropanol is believed to proceed via 1- and 2-azafulvene intermediates.[254]



189 **190**



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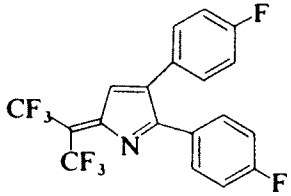

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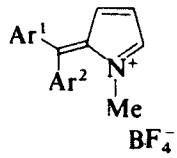
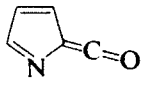


192

Flash-vacuum pyrolysis of pyrrole-2-carboxylic acid or its methyl ester yields the ketene **193**, detectable at $-190°C$.[73]



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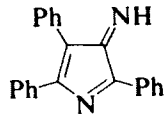
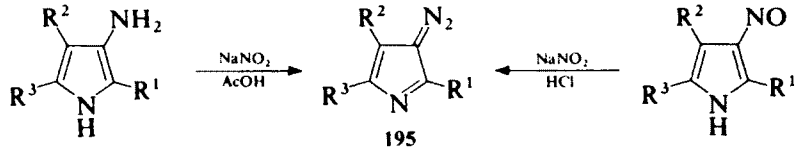


194

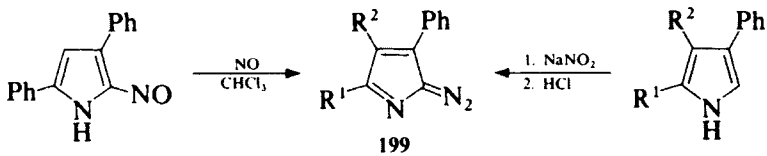
4.4.1.2.5. Transformations of Amino and Nitroso Groups

Oxidation of 3-amino-2,4,6-triphenylpyrrole with potassium hexacyanoferrate(III) in alkaline medium, or with lead(IV) oxide in a neutral medium, is reported to give the red imine **194**.[255]



196 195 197

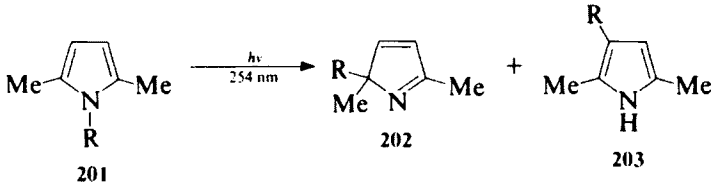
3-Diazopyrroles **195**, bearing a wide range of substituents, have been prepared by nitrosation of the 3-amino compounds **196**;[58,59,76,98,119,256–260] nitrosation of the 3-nitroso compounds **197** gives the same products.[58,261] Treatment of 2-nitrosopyrrole **198** with NO[56] yields the 2-diazo compound **199** (R^1 = Ph, R^2 = H).[56] Analogs may be prepared from the 1*H*-pyrroles **200** by sequential treatment with sodium nitrite in aqueous acetone and hydrochloric acid.[56,262]



198 199 200

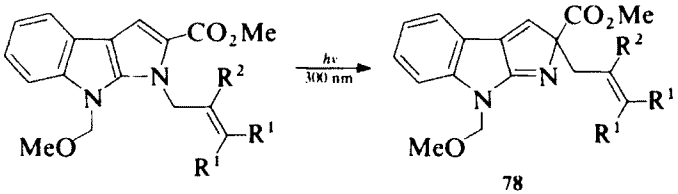
4.4.1.3. By Rearrangement of 1H-Pyrroles

Thermal rearrangement of *N*-alkyl pyrroles leads to a mixture of 2- and 3-alkyl isomers. It appears that 2*H*-pyrroles are intermediates, since thermolysis of these compounds at the same temperatures leads to the same product distribution.[79,263] Photolysis of 1,2,5-trialkylpyrroles (e.g., **201**) gives the 2*H*-pyrrole **202**, together with the 3-alkyl isomer **203**. In this case, **202** is not an intermediate in the formation of **203**, since the latter is not formed on prolonged photolysis of



201 **202** **203**

the 2*H*-pyrrole.[7,264] When R is optically active, migration occurs with some retention of configuration;[264] when R in **201** is 1-methyl-2-propenyl, the products are **202** and **203** in which the configuration of the R group is unchanged, together with R = *cis*-2-butenyl and *trans*-2-butenyl.[7] In contrast, the photochemical rearrangement of **77** to **78** (R^1, R^2 = H or Me) took place without allylic inversion.[164]

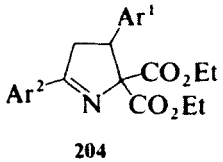


77 **78**

4.4.1.4. From Pyrrolines

4.4.1.4.1. Oxidation

Oxidation of the pyrroline diester **204** (Ar^1 = Ar^2 = Ph) by chloranil in boiling xylene was reported to give the corresponding 2*H*-pyrrole **205**.[265,266] The product was later shown to be the rearranged isomer **206** (Ar^1 = Ar^2 = Ph).[267,268] However, a number of pyrrolines **204** have been oxidized successfully to 2*H*-pyrroles **205** using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in benzene at 25°C.[268] The diisobutylaluminium hydride (DIBAL) reduction product **207** of **170** was oxidized to **208** via the *N*-chlorocompound using *t*-butyl hypochlorite and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).[78,242] The Pummerer rearrangement of the sulfoxide **209** led to three products, including the 2*H*-pyrrole **210** (33%).[269]



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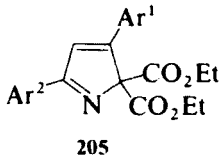

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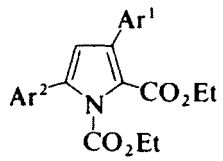

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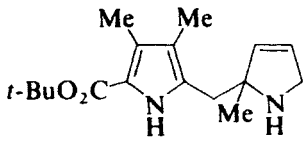

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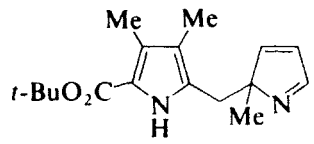

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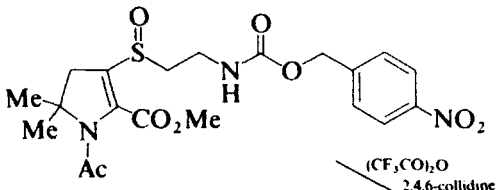

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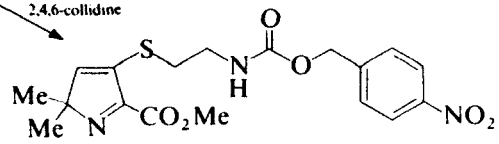
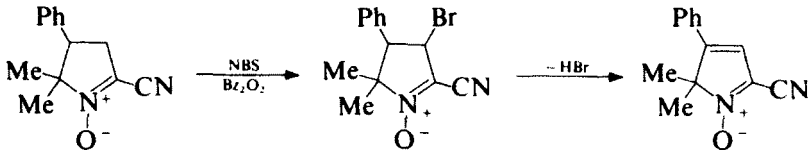
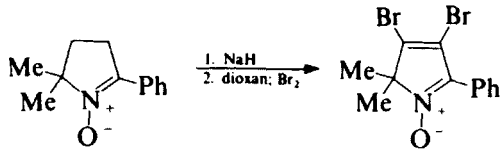


210

Pyrroline *N*-oxides have been oxidized to 2*H*-pyrrole *N*-oxides by *N*-bromosuccinimide (NBS) under various conditions,[8,39,40,270,271] by dioxan dibromide,[38] and by selenium dioxide.[90] Sometimes the intermediate bromopyrroline, such as **211** has been isolated and subsequently dehydrobrominated to **212**;[39,270] at other times bromo-substituted products, such as **213**,[38] were isolated.[40,271] Selenium dioxide oxidation of **214** gave a mixture of **215** and **216**.[90]



211 212



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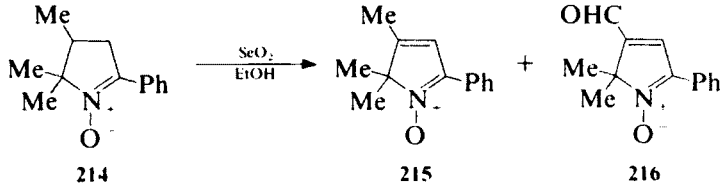
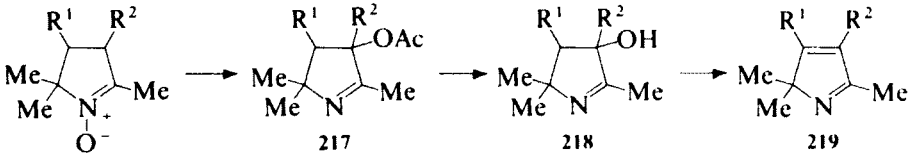


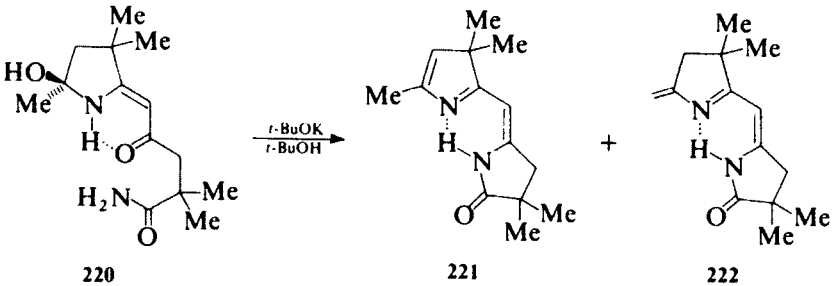
4.4.1.4.2. Rearrangement of *N*-Oxides

Pyrroline *N*-oxides on heating with acetic anhydride, either with[272,273] or without[271,274] subsequent treatment with acid, or on treatment with benzoyl chloride,[40,274] are converted into 2*H*-pyrroles. The reaction appears to proceed via the 4-acyloxy intermediate **217**, which has been observed[40] and then has been converted, either by hydrolysis to **218** and subsequent dehydration or directly into **219**. Intermediates **218** have been isolated.[272,273] A different mechanism has also been proposed.



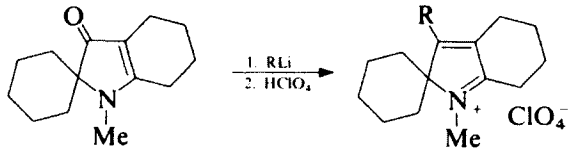
4.4.1.4.3. Dehydration of Alcohols

The hydroxypyrroline **218** ($R^1 = R^2 = R^4 = R^5 = Me$; $R^3 = H$) has been dehydrated to the corresponding **219** with sulfuric acid,[272] while treatment of the analogous hydroxy *N*-oxides with *p*-toluenesulfonic acid gives high yields of either the 2*H*-pyrrole *N*-oxides or the isomers with an exocyclic double bond, depending on the nature of R^4.[37] The reaction between **220** and strong base led to an inseparable mixture of the 3*H*-pyrrole **221** and its isomer **222** in a ratio of 3.5 : 1.[275] The dehydration of hydroxy pyrrolines to other 3*H*-pyrroles is discussed in Section 4.4.3.1.2.



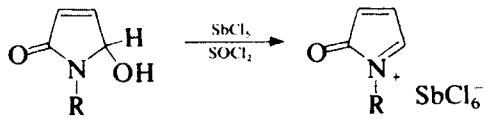
4.4.1.4.4. Solvolysis of Alcohols

The 2*H*-pyrrole salts **223** (R = Me, *t*-Bu, Ph) were prepared by solvolysis of tertiary alcohols formed by adding organolithium to the pyrrolone **224**.[35]



224 **223**

Isolation of the 2*H*-pyrrole-2-one salts **17** and **18** (R = H, Me) from the lactams **225** was possible since dimerization was opposed by repulsion of the positive charges.[99]



225 **17, 18**

4.4.2. Ring Synthesis by Formation of One Bond

In principle, ring synthesis in this category may be from C–C–C–C–N, C–C–C–N–C, or C–C–N–C–C fragments, by formation of a bond respectively between N and $C_2(C_5)$, between C_2 and C_3, between C_4 and C_5, or between C_3 and C_4. Examples of all are known except C_4–C_5 bond formation.

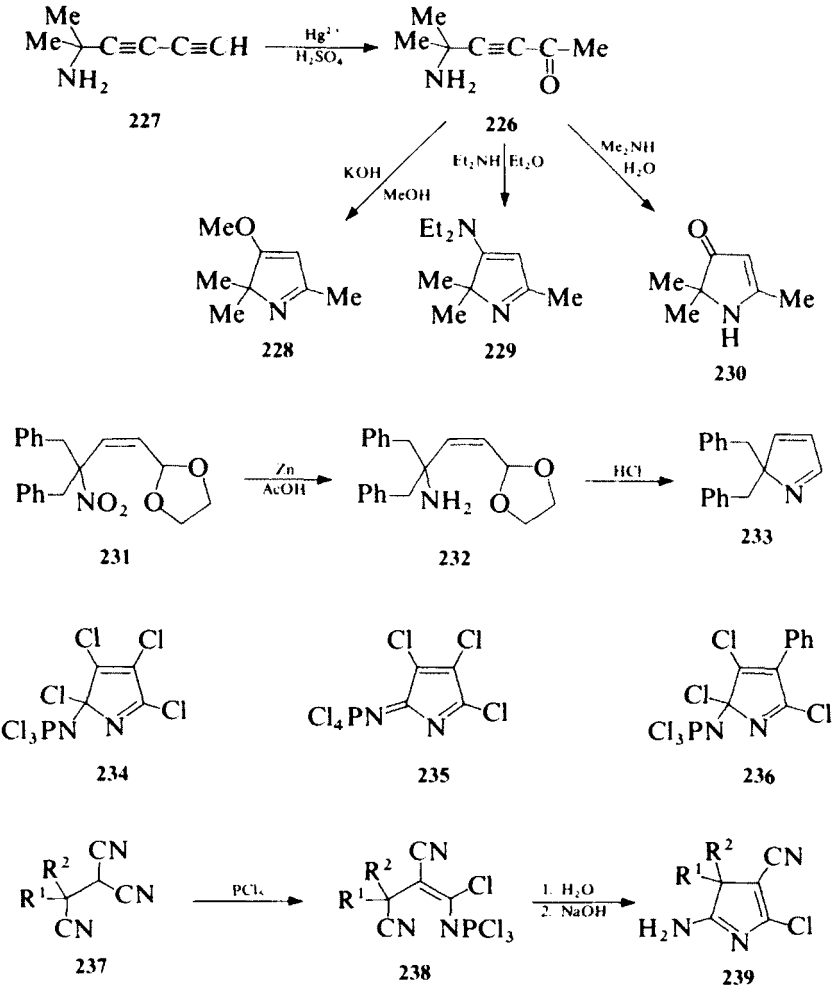
4.4.2.1. The N–C_2 or N–C_5 Bonds

4.4.2.1.1. 4-Amino Carbonyl Compounds

The acetylenic ketone **226**, formed by Hg(II)-catalyzed hydrolysis of diacetylene **227**, may be cyclized to yield the products **228–230** depending on the conditions.[22,276] Reduction of the nitroacetal **231**, followed by acid-catalyzed cyclization of **232**, gave the simple disubstituted 2*H*-pyrrole **233**.[78,242]

4.4.2.1.2. 1,2-Dinitriles

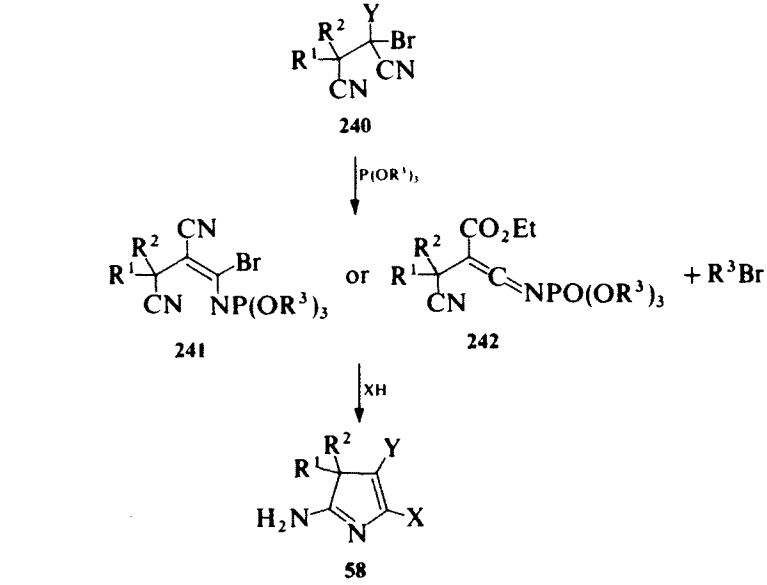
Treatment of succinonitrile, maleonitrile, or fumaronitrile with excess phosphorus pentachloride produced the 2*H*-pyrrole **234**,[277] initially formulated incorrectly as the 2*H*-pyrrol-2-imine **235**.[278] 2-Phenylsuccinonitrile likewise gave the analog **236**.[277] The use of 2,2-disubstituted succinonitriles **237** led, via isolable intermediates **238**, to the 3*H*-pyrroles **239**. Their hydrochloride salts were also prepared.[149,150] In an extensive study, Foucaud and co-workers

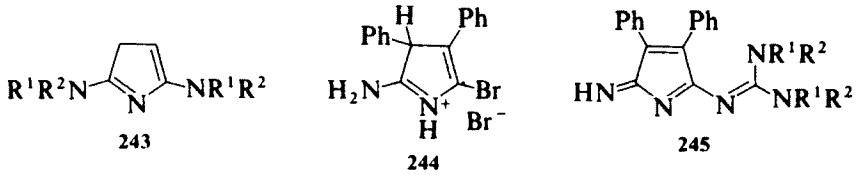


treated the bromodinitriles **240** (Y = CN, CO_2Et) with phosphite esters to give intermediates **241** (Y = CN) or **242** (Y = CO_2Et), which were cyclized to 3*H*-pyrroles **58** (X = Br, OMe, NH_2, $NHCH_2Ph$), together with other products.[30,148,151,152] Other analogs of **58** have also been prepared by related routes.[82,279] Succinonitrile has been reportedly transformed into the 3*H*-pyrroles **243** with secondary amines,[29] while 2,3-diphenylsuccinonitrile with HBr in acetic acid gave what was probably the salt **244**.[280] The reaction between 2,3-diphenylfumaronitrile and guanidines in ethanol yielded the products **245**.[281]

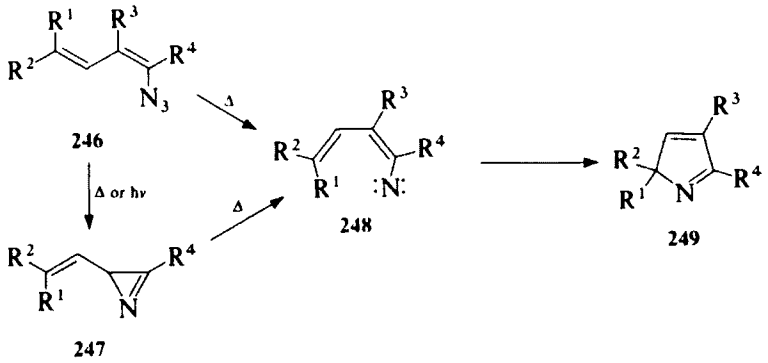
4.4.2.1.3. 1,3-Dienyl Nitrenes

Thermolysis or photolysis of 1-azido-1,3-butadienes **246**, or thermolysis of the 3-vinylazirines **247**, leads to 1,3-dienylnitrenes **248**, which cyclize spontaneously



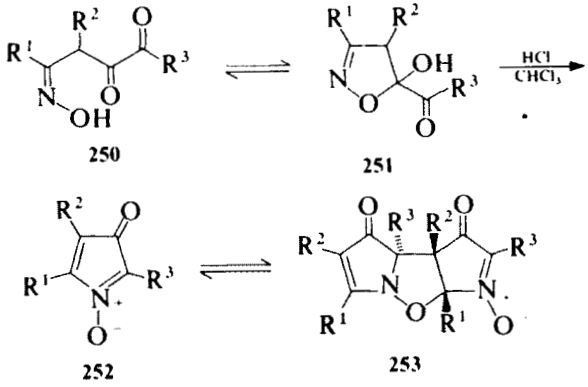


to yield the 2*H*-pyrroles **249**.[15,282–289] Sometimes the product **249** rearranges to a 1*H*-pyrrole under the reaction conditions,[15,283,285–289] and pyridines are frequently by-products, when R = Me or CH_2. Molybdenum carbonyl complexes of nitrenes **248** also give 1*H*-pyrrole products, presumed to arise from rearrangement of an initially formed 2-benzoyl-2*H*-pyrrole.[290,291]



4.4.2.1.4. 3,4-Diketo Oximes

The oximes **250**, which appear to exist in equilibrium with the hydroxyisoxazoles **251**, are readily converted by acid to the purple *N*-oxides **252**.[292–294] Some examples of **252** have been shown to be in equilibrium with the yellow dimers **253**, from which they can be separated.[294]

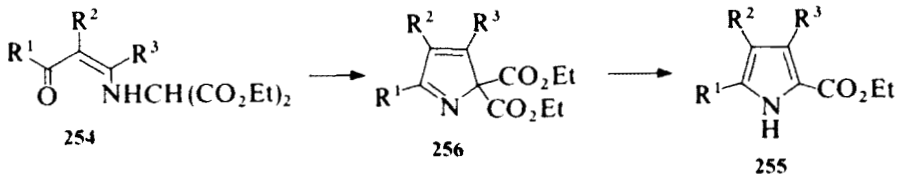


250 **251** **252** **253**

4.4.2.2. The C_2–C_3 Bond

4.4.2.2.1. Enaminones

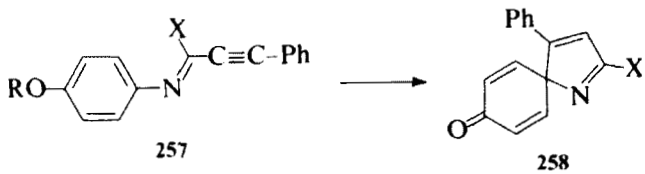
Enaminones **254**, derived from 1,3-diketones and diethyl aminomalonate, were found by Umio and co-workers to be cyclized to 1*H*-pyrrole esters **255** with ethyl polyphosphate. However, on occasions the 2*H*-pyrrole intermediates **256** were isolated.[295–298] This method has been used to prepare **205** ($Ar^1 = Ar^2 = Ph$)[268] and, with modifications, as a general synthesis for 1*H*-pyrrole-2-carboxylic esters **256**.[299,300]



254 **256** **255**

4.4.2.2.2. Acetylenic Aryl Imines

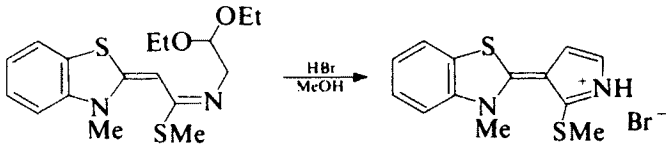
The acetylenic imines **257** [R = Me, Et; X = NMePh, $N(CH_2)_4$, OEt] have been cyclized in strong acid to the spiro-2*H*-pyrroles **258**, together with smaller amounts of quinolines.[104,301,302]



257 **258**

4.4.2.3. The C_3–C_4 Bond

The acetal **259** on treatment with acid was converted into the 2-azafulvene **260**.[96]



259 **260**

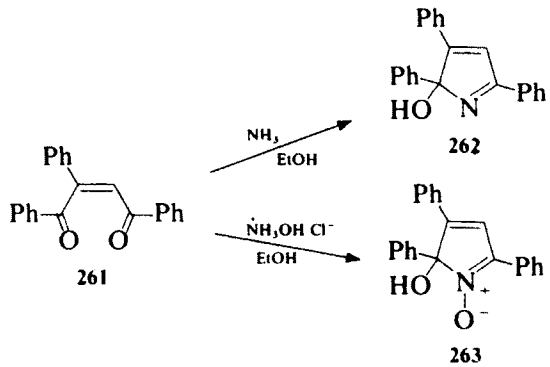
4.4.3. Ring Synthesis by Formation of Two Bonds

Known syntheses in this category include combinations of 4 + 1 atom fragments (formation of N–C_2 and N–C_5; C_2–C_3, and C_3–C_4; C_3–C_4 and C_4–C_5 bonds) and 3 + 2 atom fragments (formation of N–C_2 and C_3–C_4; N–C_2 and C_4–C_5; C_2–C_3 and C_4–C_5 bonds). The first and the last procedures include important general methods.

4.4.3.1. The N–C_2 and N–C_5 Bonds

4.4.3.1.1. From Unsaturated 1,4-Diketones

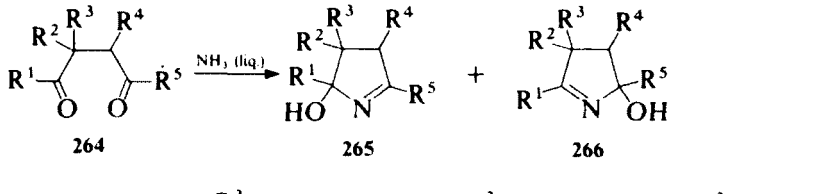
The reaction between the diketone **261** and ammonia gave a product described by Japp and Klingemann as "Dibenzoyl cinnamenimide," to which an incorrect structure was assigned by them[191,192,194] and others.[303] It was later shown to be **262**.[190] The tetraphenyldiketone **108** was likewise converted into **106**.[69,190,193,202] A similar reaction of **261** with hydroxylamine yielded the *N*-oxide **263**,[303–305] although this also was initially assigned an incorrect structure.[303]



261 **262** **263**

4.4.3.1.2. From Saturated 1,4-Diketones

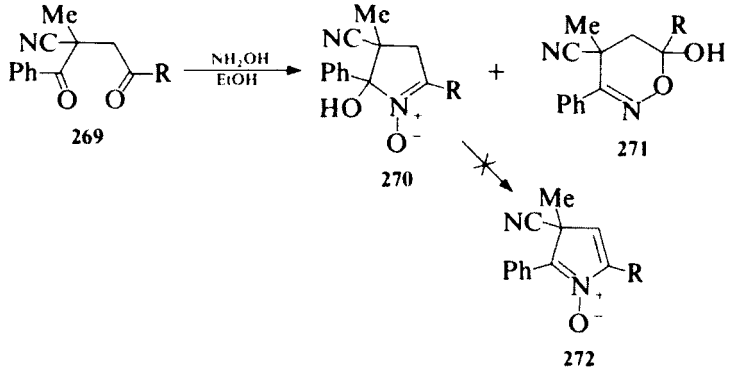
These undergo the Paal–Knorr reaction with ammonia and are converted into 1*H*-pyrroles. Examples disubstituted at C_2 (**264**), however, yield isolable intermediate regioisomeric hydroxypyrrolines **265** and **266**, which may be dehydrated subsequently to yield 3*H*-pyrroles **2**.[13,28,132,154] When R^1 or R^4 is a group bearing one or more α-hydrogen atoms, isomers **267** and/or **268** having exocyclic C=C bonds are also formed (see Section 4.3.3.4). These compounds exist in thermal equilibrium with **2**, which may, on occasions, be separated from



264 **265** **266** **2** **267** **268**

them successfully. For some substituents, 3*H*-pyrroles **2** may be prepared directly from **264** by reaction with ammonium acetate in acetic acid, although this may bring about rearrangement to the 2*H*-pyrrole **1**.[13,28] Whereas the reaction is successful using **264** with a wide range of substituents R^1–R^5, including ester and nitrile functions, it fails when R^2 is an acyl group, yielding either a 1*H*-pyrrole and an amide,[154,306] or, when R^1CO and R^2 form part of a cyclic 1,3-diketone, 1-acyl-1*H*-pyrroles via rearrangement of the intermediate **265**.[307,308] This is, nevertheless, currently the most useful route available to 3*H*-pyrroles.

With hydroxylamine, the diketones **269** (R = *t*-Bu, Ph) were converted into a mixture of the hydroxypyrroline *N*-oxides **270** and the isomeric oxazines **271**.

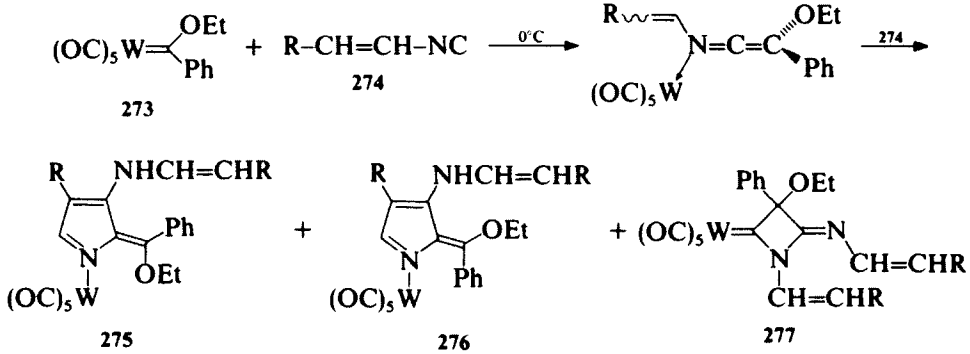


269 **270** **271** **272**

The *N*-oxides **270** were the major products at − 10°C, while **271** predominated at 40°C. All attempts to dehydrate **270** to the 3*H*-pyrrole *N*-oxides **272** were unsuccessful, yielding only **271** or complex mixtures.[309]

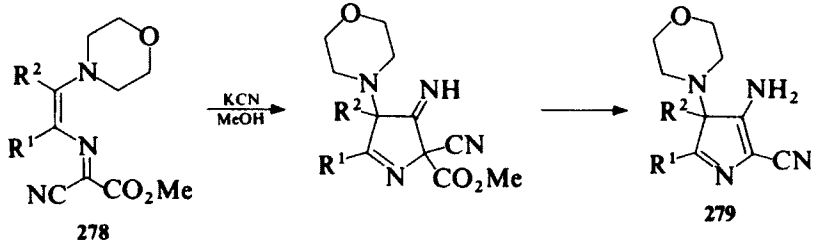
4.4.3.2. The C_2–C_3 and C_3–C_4 Bonds

Only one report has appeared. The tungsten carbene carbonyl complex **273** adds to the isonitriles **274** (R = H, Me) to yield the stereoisomeric azafulvenes **275** and **276**, together with the azetidine **277**. The red azafulvene complexes are reportedly far more stable than the parent heterocycles.[93]



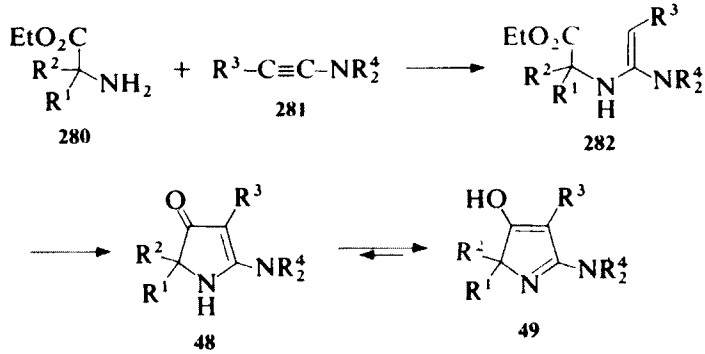
4.4.3.3. The C_3–C_4 and C_4–C_5 Bonds

Again there has been only one report of cyclization in this category. Compounds **278** add cyanide ion and cyclize with loss of an ester group to give the 3*H*-pyrroles **279**.[31]

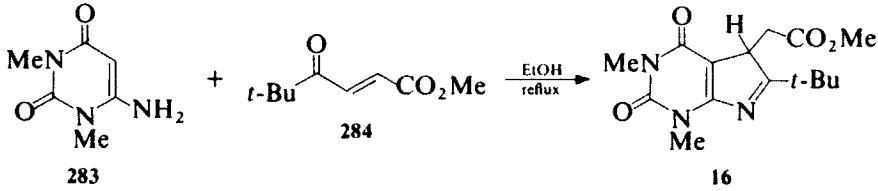


4.4.3.4. The N–C_2 and C_3–C_4 Bonds

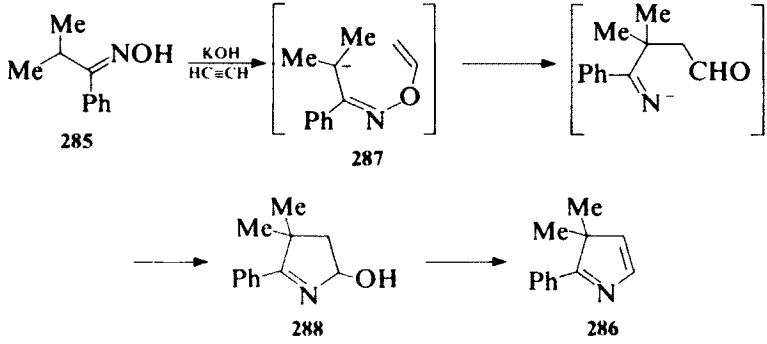
α-Amino esters **280** (R^1, R^2 = H, alkyl, Ph) add to 1-alkynamines **281**, forming the aminals **282**, which may be cyclized to an equilibrium mixture of **48** and **49** (see Section 4.3.3.2).[23,24,310]



Reaction between the aminouracil **283** and the unsaturated ester **284** yields the 3*H*-pyrrole **16**,[84] which has been referred to in Section 4.3.3.1.



Treatment of the ketoxime **285** with acetylene in strong base gave a low yield of 3*H*-pyrrole **286**, possibly via rearrangement of **287**. The intermediate **288** has been isolated and converted independently into **286**.[71]

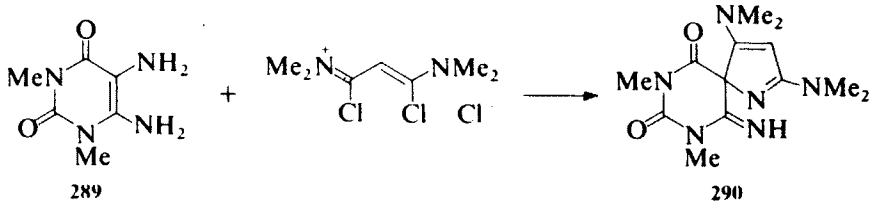


The HI salt of 3-amino-3-methylbutanone is reported to give a number of products on treatment with base, including one identified as a 2*H*-pyrrole or a 2,5-dihydropyridine.[311]

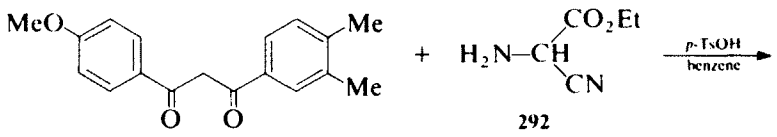
4.4.3.5. The N–C_2 and C_4–C_5 Bonds

The diaminouracil **289** has been converted into the spiro-2*H*-pyrrole **290**.[106] Cyclization of 1,3-diketone **291** with the aminoester **292** gave the isomeric

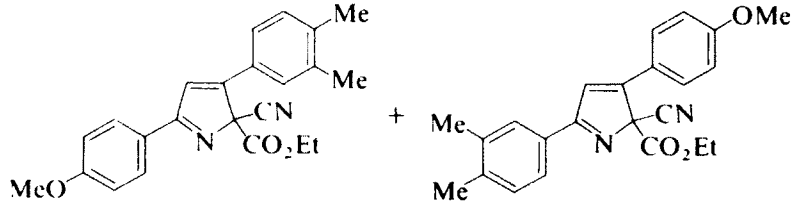
2*H*-pyrroles **293** and **294** directly, without isolation of the intermediate enaminone[103] (see Section 4.4.2.2.1). 2,2-Disubsituted 1,3-diketones **295** condense with the aminoester **296** to yield, via observable intermediate hydroxypyrrolines, low yields the regioisomeric 3*H*-pyrroles **297** and **298**, together with products from cleavage of the diketone **295**.[312]



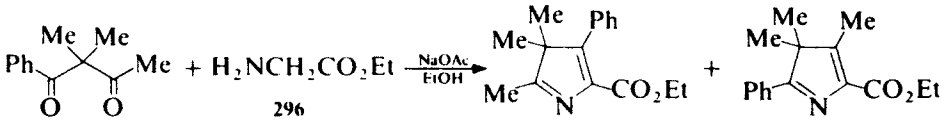
289 **290**



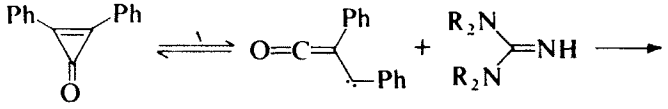
291 **292**



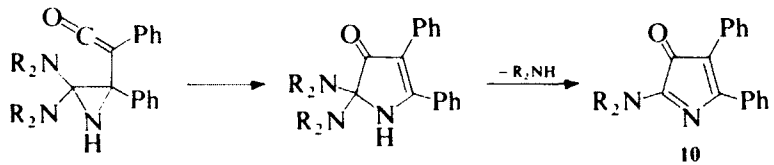
293 **294**



295 **296** **297** **298**

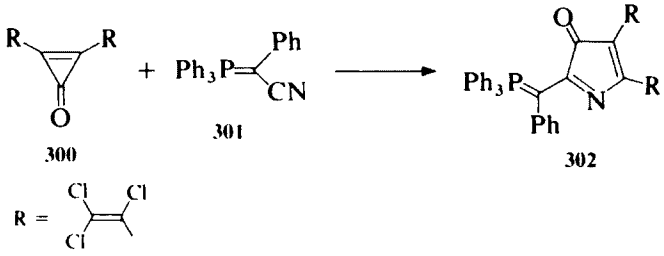


299



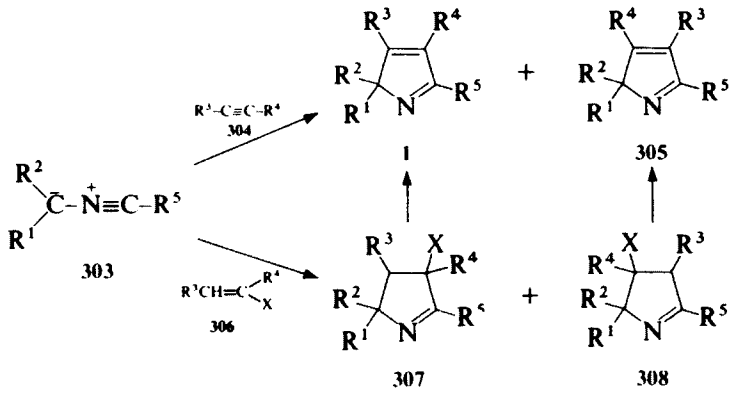
10

2-Amino-3*H*-pyrrol-3-ones **10** have been prepared from diphenylcyclopropenone **299** and guanidines by the proposed mechanism shown.[57,60] The use of a benzamidine in place of a guanidine yields the triphenyl compound **9**,[57] detectable only in solution. Reaction between the cyclopropenone **300** and the ylid **301** gives the isolable blue 3*H*-pyrrol-3-one **302**.[313]



4.4.3.6. The C_2–C_3 and C_4–C_5 Bonds by 1,3-Dipolar Cycloaddition

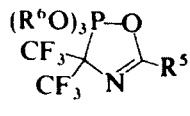
By far the majority of ring syntheses by formation of the C_2–C_3 and C_4–C_5 bonds have involved 1,3-dipolar cycloaddition reactions. The 1,3-dipole **303** is a nitrile ylid and is normally generated in the presence of an alkyne **304**, to give, where $R^3 \neq R^4$, mixed regioisomeric 2*H*-pyrrole products **1** and **305**. On occasions, the alkyne has been replaced by an alkene **306**, whereupon the initial cycloadducts **307** and **308** may be converted into **1** and **305** by oxidation (X = H) or elimination (X is a leaving group). A very large number of 2*H*-pyrroles have been prepared by this general approach.



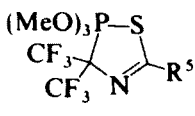
4.4.3.6.1. Generation of the 1,3-Dipole

This was first achieved for 2*H*-pyrrole synthesis by thermal elimination of trialkyl phosphate from the oxazaphospholes **309** (R^6 = Me, Et).[314] Subsequently, R^6 has always been Me, and the elimination has been carried out both thermally[67,109–111,315,316] and photochemically.[316,317] Other successful

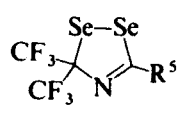
preparations by thermal elimination have involved loss of $(MeO)_3PS$ from **310**,[318] selenium from **311**,[108] cyclohexyl isocyanide from **312**[319] and carbon dioxide from oxazolones **313**[320-322] and **314**.[323] Decomposition of an oxazolone **313** ($R^1 = R^2 = CF_3$; $R^5 = H$) in the presence of trimethyl phosphite gave the dipole **315**, which led successfully to 2*H*-pyrroles having $R^5 = H$.[68] Photochemical elimination from an oxazolone **313** has also been reported.[18]



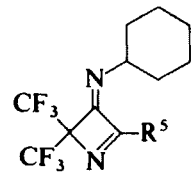
309



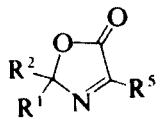
310



311



312



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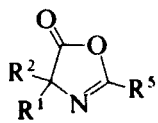
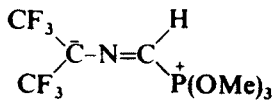
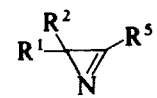


314



315



316

1-Azirines **316** undergo photochemical cleavage of the C_2–C_3 bond to generate the dipoles **303**.[10,16-19,115,324-330] Irradiation has been carried out in a variety of aprotic solvents, generally with a high pressure mercury lamp, although a low-pressure lamp has been used.[328,329] Irradiation at $-185°C$ led to the successful trapping of dipoles **303** ($R^1 = R^2 = Me$; R^5 = substitued phenyl) in 2-methylpentane glasses, permitting their identification by UV spectroscopy.[19]

Generation of the 1,3-dipole by elimination of HCl from an imidoyl chloride with base has been reported only twice in this series.[331,332] In one case the final adduct was a spiropenicillin.[331]

4.4.3.6.2. The Dipolarophile

This has generally been an alkyne; the most widely used is dimethyl acetylenedicarboxylate (DMAD).[17,18,68,108,314,316-322,325,326,328-332] Other alkynes used have been methyl propynoate,[19,68,315,316,318,320,323] ethyl propynoate,[328,329] ethyl phenylpropynoate,[19] ethyne,[67] phenylethyne,[67] diphenylethyne,[67,314] and *N*,*N*-diethyl-1-propynamine.[108,111] On occasions isomeric open-chain 1:1 adducts are also formed,[67,328,329] and, in other cases, 6-membered ring heterocycles have been observed, both in addition to,[111] and in place of,[108,322] the expected 2*H*-pyrroles.

The dipolarophile may also be an alkene **306**, which, in all of those reported, bears an electron-withdrawing substituent. Reactions where the initial adducts **307** and **308** have been converted into 2*H*-pyrroles have employed dimethyl fumarate,[315,316] fumaro-nitirile,[109,110] vinylphosphonium salts,[10,324] vinyl sulfones,[10] more highly substituted alkenes,[16] or electron deficient heterocycles.[115,237] Generally, conversion to the 2*H*-pyrroles **1** and **305** has been

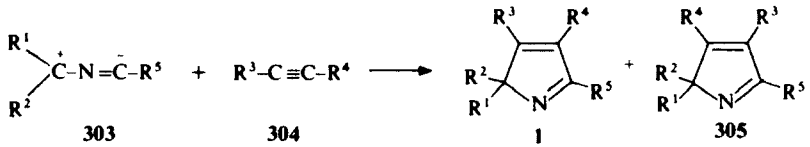
achieved by loss of HX, but direct oxidation[109,110,327] and bromination followed by elimination of HBr[115,315,316] have been reported.

4.4.3.6.3. Regiochemistry

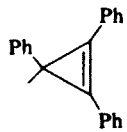
Where R^3 and R^4 in the alkyne **304** are different, two regioisomers may be formed. Generally, both are observed, the relative amounts depending on dipole and dipolarophile HOMO and LUMO energies, as well as steric factors. In some instances, only one isomer is found.[68,323,328,329] Examples where product distribution has been reported are given in Table 4.33.

Where alkenes are used as dipolarophiles, propenoate esters and propenenitrile give a mixture of **307** and **308**.[315,316] However, the additions of vinylphosphonium salts,[10] vinyl sulfones,[10,115] and certain other alkenes[16] are highly regioselective and provide a convenient indirect route to specific 2*H*-pyrrole regioisomers **1** or **305**.

TABLE 4.33. DISTRIBUTION OF REGIOISOMERIC 2*H*-PYRROLES FORMED BY 1,3-DIPOLAR CYCLOADDITION



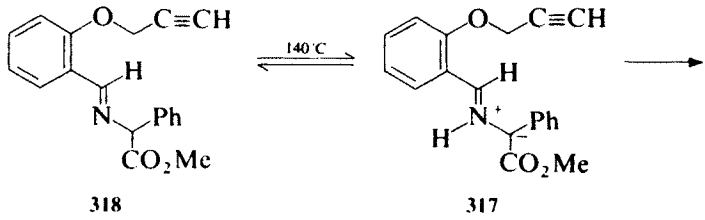
303 **304** **1** **305**

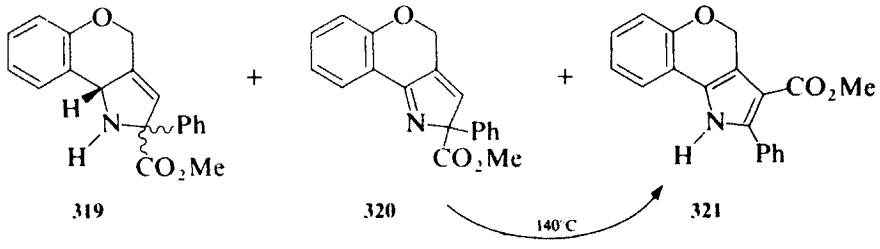
1,3-Dipole			Dipolarophile			
R^1	R^2	R^5	R^3	R^4	Ratio **1**:**305**	Ref.
Me	Me	Ph	H	CO_2Me	0.04:1	19
Me		Ph	H	CO_2Me	0:1	323
Me	Me	Ph	Ph	CO_2Et	0.35:1	19
Me	Me	NMePh	H	CO_2Et	0:1[a]	328,329
CF_3	$(CH_2)_2COMe$	*i*-Pr	H	CO_2Me	1.50:1	320
CF_3	CF_3	*t*-Bu	H	Ph	0.48:1[b]	67
CF_3	CF_3	Ph	H	Ph	1.25:1[b]	67
CF_3	CF_3	4-MeC_6H_4	H	Ph	1:1[b]	67
CF_3	CF_3	4-ClC_6H_4	H	Ph	1.05:1[b]	67
CF_3	CF_3	4-FC_6H_4	H	Ph	1.14:1[b]	67
CF_3	CF_3	H[a]	H	CO_2Me	1:0[c]	68
CF_3	CF_3	*t*-Bu	H	CO_2Me	3.54:1	315,316
CF_3	CF_3	Ph	H	CO_2Me	2.33:1	315,316
CF_3	CF_3	*t*-Bu	Me	NEt_2	0.54:1[d]	111

[a] Open-chain isomer (5%) also formed.
[b] Open-chain isomer (21–34%) also formed.
[c] The dipole is **315**.
[d] 1,3-Oxazine also formed.

4.4.3.6.4. Alternative Routes by 1,3-Dipolar Cycloaddition

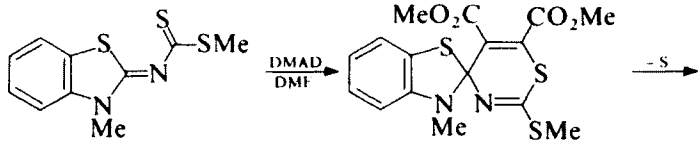
The addition of an alkyne to an azomethine ylid, followed by oxidation, offers an alternative route to 2*H*-pyrroles. The ylid **317**, in thermal equilibrium with the imine **318**, undergoes intramolecular cycloaddition to give the products **319–321**. The yield of **320** increases in the presence of air.[333]

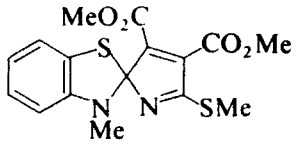




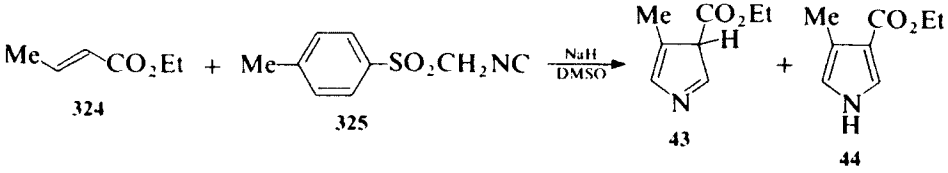
4.4.3.7. The C_2–C_3 and C_4–C_5 Bonds by Other Processes

Benzothiazole **322** undergoes a hetero-Diels–Alder reaction with DMAD, yielding the spiro-2*H*-pyrrole **323** via extrusion of sulfur from a 1,3-thiazine intermediate.[334,335]



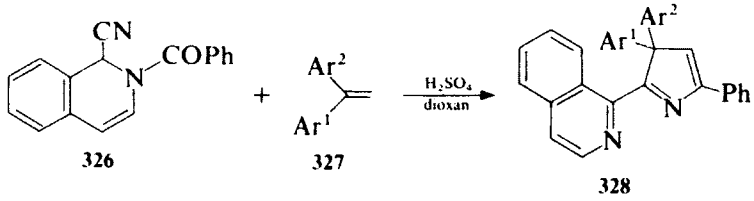


Reaction between ethyl but-2-enoate **324** and the isocyano sulfone **325** under strongly basic conditions gave a mixture of **43** and **44**. Under the reaction conditions, the former was slowly converted into the latter.[141]



4.4.4. Ring Synthesis by Formation of Three Bonds

In the first authentic synthesis of 3*H*-pyrroles, the ring was assembled from the Reissert compound **326** and the 1,1-diarylethenes **327**, with C_5 of the product **328** arising from the benzoyl carbonyl group. The 3-(4-methoxyphenyl) compound was also prepared,[27,326] and a 2-(1-phthalazinyl) analog has been reported.[337]



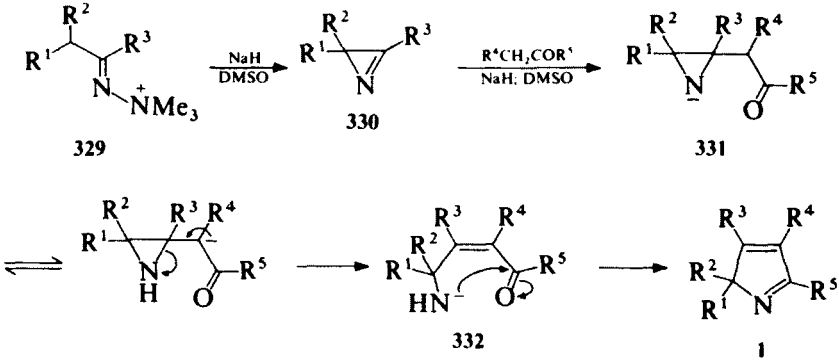
A report describing the preparation of 2*H*-pyrrole **293** from a chalcone, ethyl cyanoacetate, and ammonium acetate[338] has been shown to be in error.[103]

4.4.5. Ring Synthesis by Transformation of Other Heterocycles

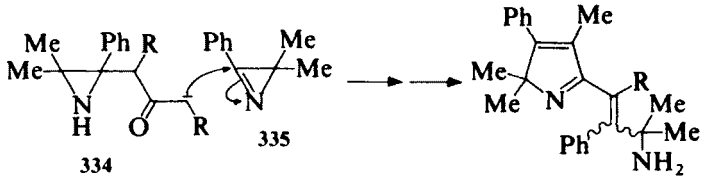
Syntheses have been reported from 3-, 5-, and 6-membered ring heterocycles and include ring expansions, ring contractions, and reactions involving major reorganisation of the heterocycle and its substituents. The thermal and photochemical generation of 1,3-dipoles from certain 3-, 4-, and 5-membered ring heterocycles has already been discussed in Section 4.4.3.6.1.

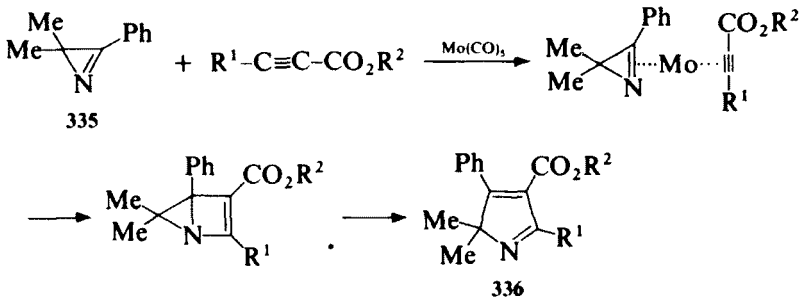
4.4.5.1. Azirines and Aziridines

Mison and co-workers have reported what they claim, with considerable justification, to be the most convenient general synthesis for 2*H*-pyrroles.[12,81] A hydrazonium salt **329** is converted into an azirine **330**, which reacts with a carbanion derived from a ketone to yield the 2*H*-pyrrole **1**. The reaction is successful for phenyl and a very wide range of alkyl substituents.[80,83,101,339,340] With aldehydes, using KH in THF, the 2*H*-pyrroles **1** (R^5 = H)[341] and, with benzyl cyanide, **1** (R^4 = Ph, R^5 = NH_2)[12,81] are formed. When R^2 = H, the products are 1*H*-pyrroles.[12,324]



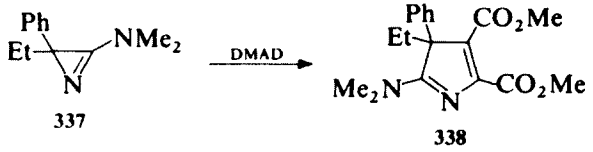
Attempts to extend the synthesis to examples of **1** having acyl or ester substituents, however, were unsuccessful.[343] Byproducts arising from protonation of the intermediate **331** or the trans form of **332** may also be isolated.[12,81] The 2*H*-pyrroles **333** (R = H or Me) are side products when the ketone is propanone or 3-pentanone and appear to arise from attack of the carbanion **334** on a second molecule of the azirine **335**.[343] An analogous reaction between enamines of ketones and the azirines **330** fails to give 2*H*-pyrroles, although the 1*H*-isomers are isolated when R^2 = H.[345]

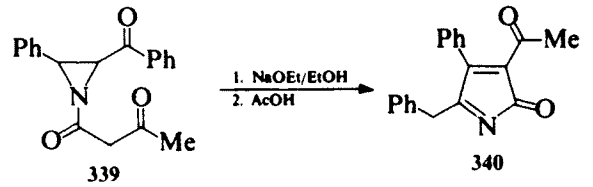




The azirine **335** reacts with alkynoate esters by C=N bond fission in the presence of molybdenum hexacarbonyl, yielding the 2*H*-pyrroles **336**, which are regioisomers of those formed photochemically via C–C bond fission in the absence of the catalyst.[16,346]

Thermolysis of the azirine **337** with DMAD proceeds via C–N bond fission, yielding the 3*H*-pyrrole **338**.[17,138]

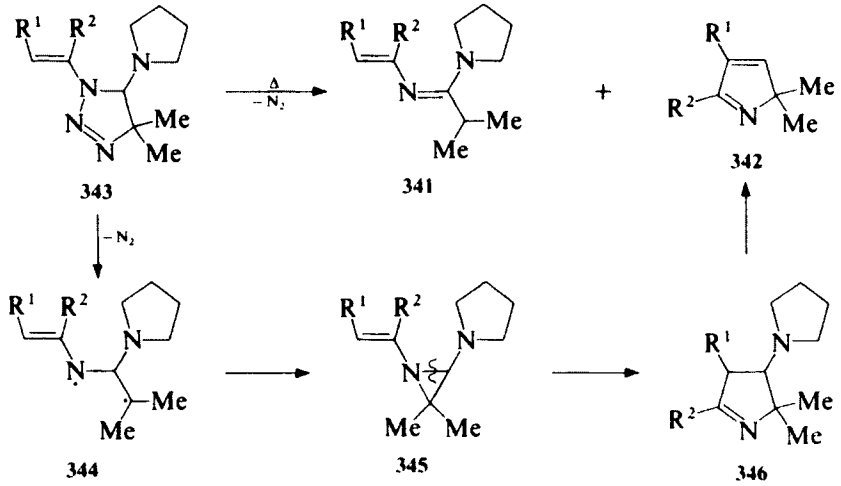




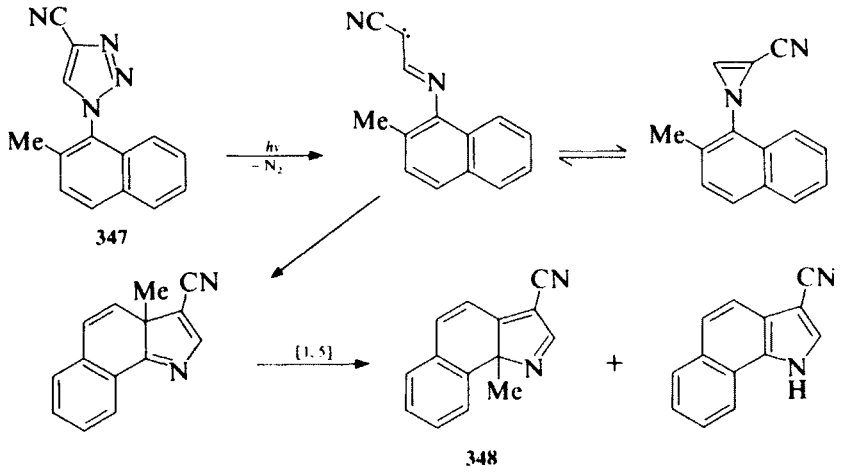
Rearrangement of the aziridine **339** with loss of water is reported to give the 2*H*-pyrrol-2-one **340**. However, the structure is inconsistent with the AB quartet at δ 3.60 in the ^{1}H NMR spectrum.[347]

4.4.5.2. 1,2,3-Triazoles

Products **341** and **342** have been isolated from the thermolysis of the triazole **343** (R^1 = H, R^2 = Ph); **342** is favored by less polar solvents and presumed to be formed via the diradical **344**, the aziridine **345**, and the pyrroline **346**. For **343**, (R^1 = Ph, R^2 = H), only the 2*H*-pyrrole **342** was found.[9] Photolysis of the same two triazoles **343** in methanol resulted in isolation of **346**, which decomposed on alumina to produce the 2*H*-pyrroles **342** in yields better than those obtained via thermolysis.[348,349]



The 4-cyanotriazole **347** (or less favorably its 5-cyanoisomer) yields, on photolysis, the 2*H*-pyrrole **348** via the sequence of transformations shown.[350]



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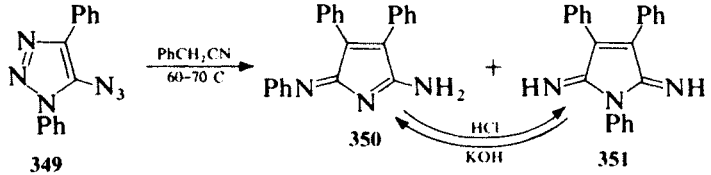
The mixed products **350** and **351**, which are interconvertible via Dimroth rearrangements, are formed on thermolysis of **349** in benzyl cyanide.[351]



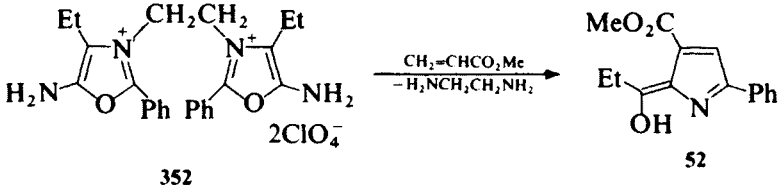
349

350

351

4.4.5.3. Other 5-Membered Rings

Treatment of the bisoxazolium salt **352** with methyl propenoate under reflux gives the enol **52**.[44] Compound **353** undergoes ring opening to the 2-azafulvene **354** with PCl_5 in $POCl_3$.[52] The isothiazole **355** is converted by reaction with cyanide into the 3*H*-pyrrol-3-imine **64**.[97]



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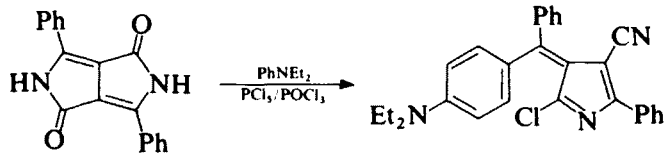

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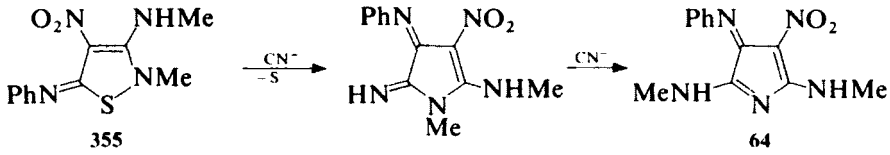
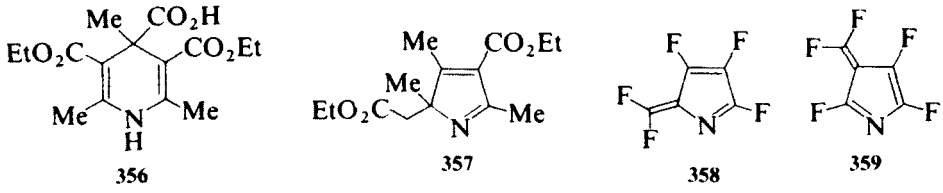


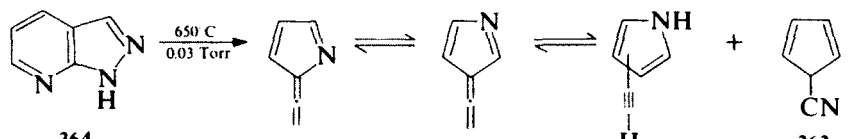
355 64

4.4.5.4. *Pyridines*

Thermolysis of the dihydropyridine **356** gave the 2*H*-pyrrole **357** together with small amounts of other products, including **67**.[36] The pentafluoroazafulvenes **358** and **359** were identified as transient intermediates in the gas-phase photolysis of pentafluoropyridine (see Section 4.2.4).[116] Photolysis of 3-diazo-2-pyridone and 3-diazo-4-pyridone in aqueous acid yield, respectively, 1*H*-pyrrole-2- and -3-carboxylic acids.[352] The intermediates are believed to be the 1-azafulvene **193** and its 2-aza-isomer. An equilibrium mixture of the azafulvenes **360** and **361**, and the isomeric ethynylpyrroles **362**, together with nitrile **363**, were identified by IR and ^{1}H NMR spectroscopy as the products from flash-vacuum pyrolysis of **364**.[353]

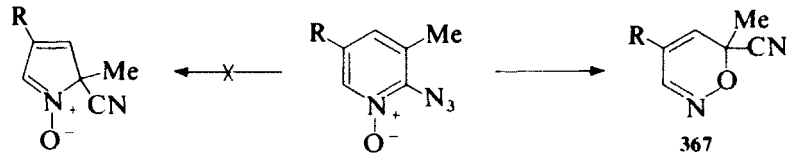


356 357 358 359



364 360 361 362 363

2*H*-Pyrrole *N*-oxides **365** (R = H, Br), originally identified as the products from thermolysis of the pyridine *N*-oxides **366**,[354,355] were later shown to be oxazines **367**.[356]



365 366 367

4.5. REACTIONS

The reactivity of the three classes of compounds discussed in this chapter is in marked contrast to that of the 1*H*-pyrroles. Electrophilic attack tends to be at the basic ring nitrogen atom, while nucleophilic attack occurs at ring carbon atoms (and C_6 in the azafulvenes) such that the nitrogen atom can function as an electron sink. Rearrangements, particularly to the thermodynamically more stable 1*H*-pyrroles, are a characteristic feature of the 2*H*- and 3*H*-pyrroles, while the many cycloaddition reactions of all three classes result from their close structural relationships with cyclopentadienes, fulvenes, and cyclopentadienones, respectively, or from the presence of an *N*-oxide function.

Under each heading, discussion of compounds will again be in the following order: 2*H*- and 3*H*-pyrroles; 1- and 2-azafulvenes; 2*H*- and 3*H*-pyrroles with an exocyclic C=X bond.

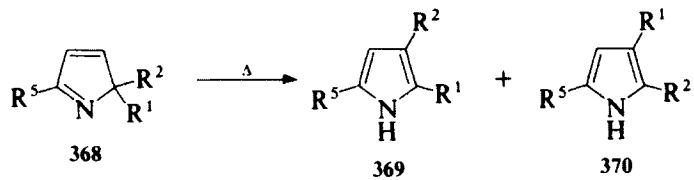
4.5.1. Thermal and Photochemical Transformations, Formally Involving No Other Species

In this section both isomerization and fragmentation reactions are discussed. Acid- and base-catalyzed processes are also included where the products contain no more or no less atoms of any kind than the reactant molecule. Intramolecular Diels–Alder reactions are covered in Section 4.5.7.2.2 together with other cycloadditions.

4.5.1.1. 2H- and 3H-Pyrroles to 1H-Pyrroles

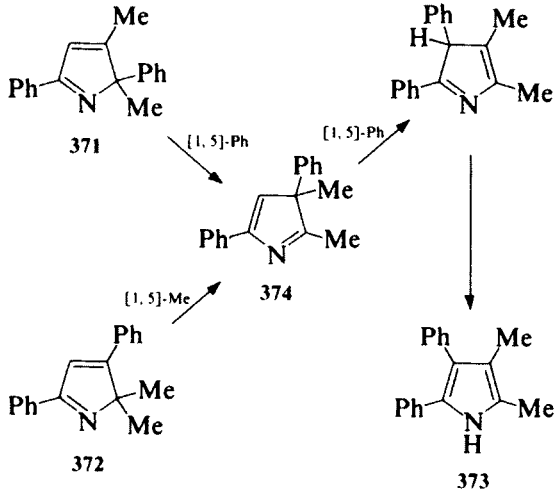
4.5.1.1.1. Simple Alkyl or Aryl Group Migration

Thermolysis of 2*H*-pyrroles **368**, unsubstituted at C_3 and C_4, results in rearrangement to the isomeric products **369** and **370** in high yields; no *N*-substituted isomers are found.[15,78,242,264,284] The reaction appears to proceed via a [1,5]-sigmatropic shift to give a 3*H*-pyrrole intermediate, followed by a [1,3]- or tautomeric hydrogen shift to form the products. When R^1 and R^2 are different, product selectivity is higher at lower temperatures,[79,284] and migratory aptitudes are benzyl > methyl > phenyl. The 1-phenylethyl group migrates with some retention of configuration.[264] For 2,2,3,5-tetrasubstituted compounds, further rearrangements occur, with both **371** and **372** yielding

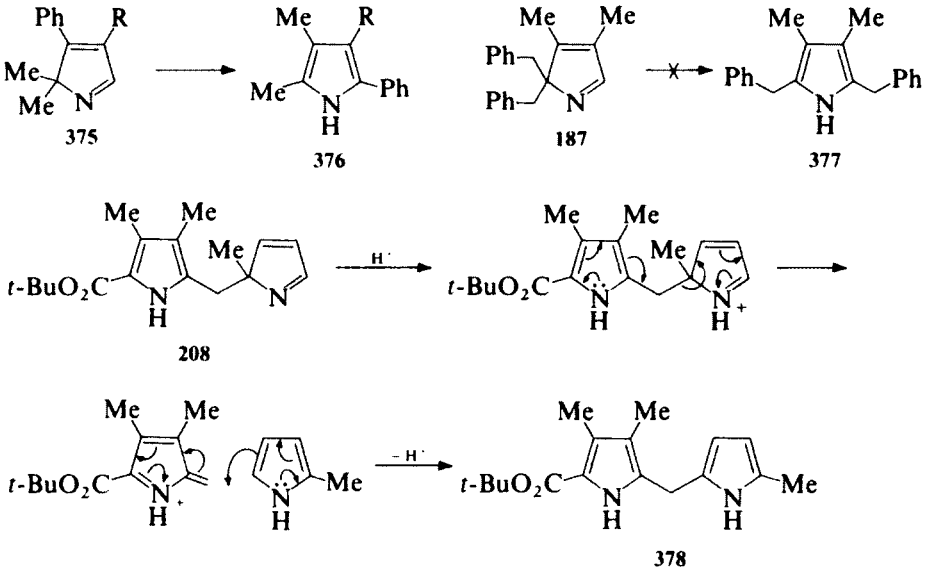


368 **369** **370**

(benzene–pyridine; 270°C) the same product **373**.[339] Interestingly, for the 3*H*-pyrrole intermediate **374**, the migratory aptitude appears to be Ph > Me. Similarly, at 260°C, the 2,2,3,4-tetrasubstituted compounds **375** (R = Et, Ph) give high yields of **376** via three consecutive [1,5]-sigmatropic shifts.[341]



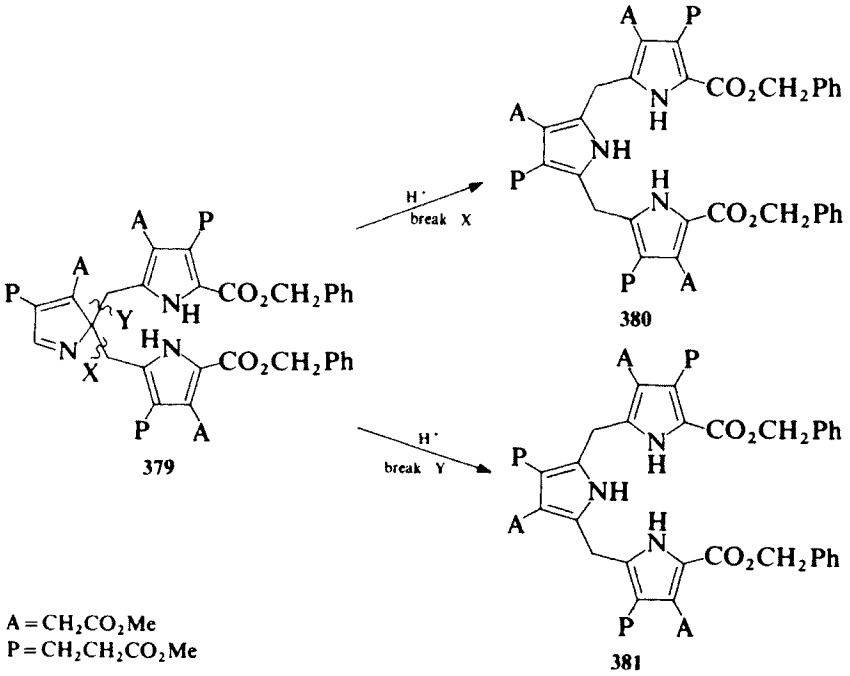
In contrast, while 2,2-dibenzyl-2*H*-pyrrole **233** rearranges to the 2,3-isomer both thermally, and with acid catalysis, the 3,4-dimethyl analog **187** is unchanged by acid and gives mixed products on heating at 130°C, but none of **377**.[78,242] Further, the thermal and acid-catalyzed rearrangement of **208** to **378**,



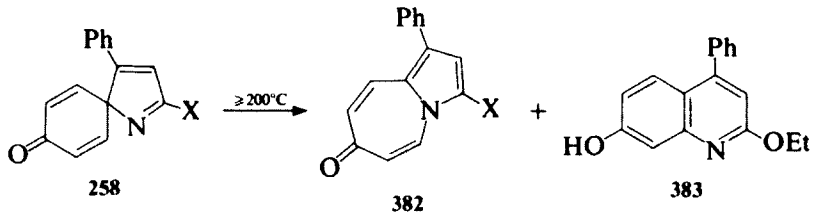
+other products

Scheme 5

as the major of four products, appeared to proceed via a fragmentation–recombination mechanism (Scheme 5). These results led Battersby and co-workers to conclude that if a 2*H*-pyrrole is an intermediate in the biosynthesis of Uroporphyrinogen-III, its rearrangement to the latter is more likely to occur by fragmentation–recombination than by three consecutive [1,5]-sigmatropic shifts.[78,242] In a recent elegant piece of work, they further demonstrated the acid-catalyzed rearrangement of **379** to **380** and **381**, together with crossover products, via the fragmentation–recombination pathway, showing that bond cleavage at X (corresponding to that required in Uroporphyrinogen-III synthesis) was favored over cleavage at Y by a factor of about 7:3. This was explained in terms of the different electronic stabilizing effects of the acetate and propionate side chains on intermediate azafulvenium ions.[167]

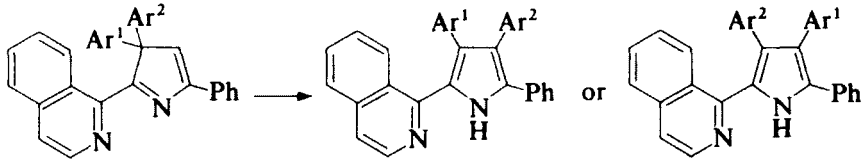


The spiro-compounds **258** behave differently; rearrangement are to nitrogen, giving the products **382**, together with quinoline **383** when X = OEt.[104,302] A



similar thermal and acid-catalyzed rearrangement to nitrogen is found with the spiro-compound **86** (R = CO_2Et).[168]

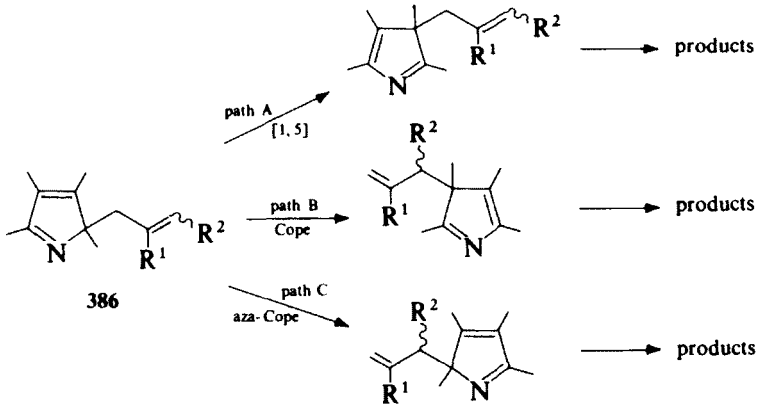
3*H*-Pyrroles **328** (Ar^1 = Ar^2 = Ph) rearrange on heating with strong acid or strong base to **384**. The mechanism appears to be ionic, as the isolated product is **384** under acidic conditions, when Ar^1 = Ph and Ar^2 = 4-$MeOC_6H_4$, while in base it is **385**.[27,336]



328 **384** **385**

4.5.1.1.2. Allyl and Substituted Allyl Group Migration

When the migrating group is an allyl or substituted allyl function, three initial rearrangement steps are possible with 2*H*-pyrroles (Scheme 6) involving a [1,5]-sigmatropic shift to C_3 (path A), a [3,3]-sigmatropic (Cope) rearrangement to C_4 (path B), or a similar (aza-cope) rearrangement to C_5 (path C). The results of three studies[83,341,357] may be rationalized.[358] For **386** (R^1 = H, R^2 = trans-Me), path A is followed when C_3 and C_4 are unsubstituted; path C when C_4 and C_5, or only C_5, are unsubstituted; and path B when only C_4 is unsubstituted.[341] In all cases, the final product is a 1*H*-pyrrole from a subsequent hydrogen shift. For **386** (R^1 = Me; R^2 = H), path C is followed exclusively, even when C_3 is unsubstituted, and the resulting 2-trans-crotyl-2*H*-pyrrole rearranges further by paths A, B, or C as described above. A comparison of the frontier orbital coefficients at C_4 and C_5 in **386** show that the transition state of path C is favored over that of path B.[341]

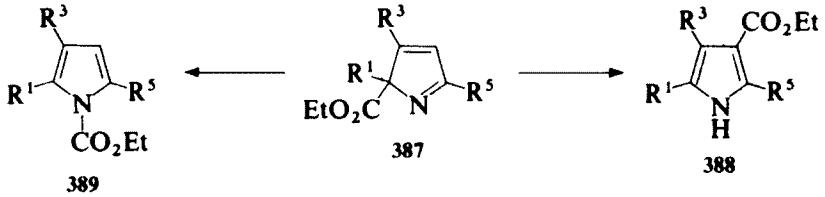


Scheme 6

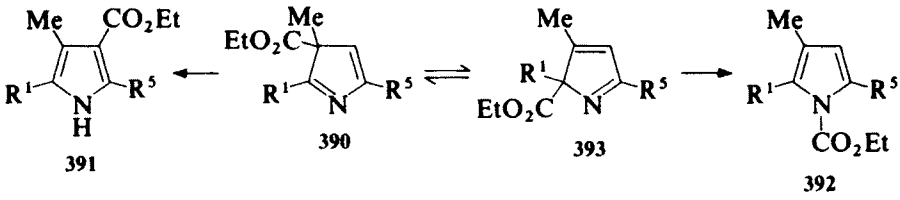
4.5.1.1.3. Other Group Migration

For 2*H*-pyrroles unsubstituted at C_3, thermal rearrangement is exclusively to C_3.[285-289,333] Ester groups migrate more readily than nitrile[285] or phenyl groups,[333] and the order of migratory aptitudes RSO > RS ~ H > RSO_2 > RCO > EtO_2C was established in a recent study.[287,289] There is evidence that under some conditions the benzoyl group may shift competitively to N and C_3.[290,291]

When C_3 is substituted, the 2-esters **387** give two products, **388** and **389**, with the migration to C_4 predominating for R^3 = Me,[28,132] while the *N*-ester **389** is the major product when R^3 = Ar.[89,103,268] For a series of 2,2-diesters **19**, (**387**, $R^1 = CO_2Et$, R^3, R^5 = substituted aryl), the rearrangement temperature was 140 ± 2°C, regardless of the aryl substituents, indicating a concerted [1,5]-sigmatropic rearrangement with negligible charge separation in the transition state.[268]



The intermediacy of 3*H*-pyrroles in the conversion of **387** into **388** and the reversibility of a 2*H*- to 3*H*-pyrrole interconversion were demonstrated by the thermolysis of **390** to a mixture of **391** and **392**.[28,132] When the reaction was interrupted, compounds **390**–**393** were all present. When **393** was heated for a short time, the same four compounds were observed.



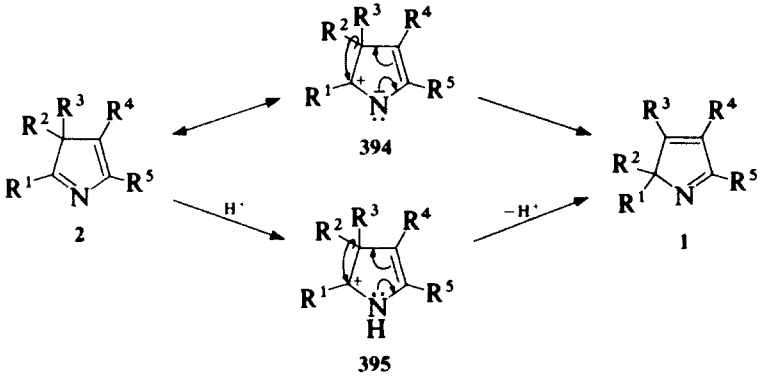
4.5.1.2. 2H- and 3H-Pyrrole Interconversions

4.5.1.2.1. Sigmatropic Rearrangements

In addition to the interconversion of **390** and **393**, pentachloro-3*H*-pyrrole **13** is known to exist in thermal equilibrium with the 2*H*-isomer **12** at undetectably low concentrations.[70,359] 1-substituted and 1,19-disubstituted octadehydrocorrins, which contain 2*H*-pyrrole moieties, rearrange thermally to the 3*H*-pyrrole 3,3-isomers. Migratory aptitudes have been determined as CH_2=$CHCH_2$ > CO_2Et > Et > Me.[360]

4.5.1.2.2. Other Mechanisms

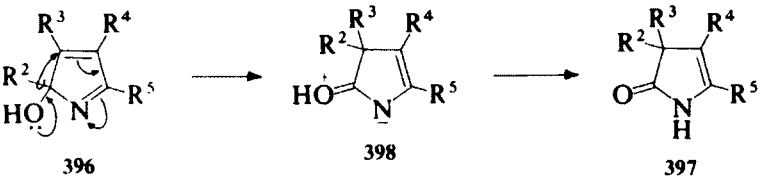
Thermolysis of 3,3-dialkyl- or 3-alkyl-3-phenyl-3*H*-pyrroles **2** in polar aprotic or protic solvents yields exclusively 2*H*-pyrroles **1**.[13,131] The rearrangement is irreversible and unaffected by peroxide catalysts,[131] but the rate is strongly enhanced by acids.[13,131,166] Migratory aptitudes are Et > Me[131] and Ph > Me.[13] The mechanism is probably of the Wagner–Meerwein type, proceeding via intermediates **394** or **395**. Kinetics have been studied.[131]



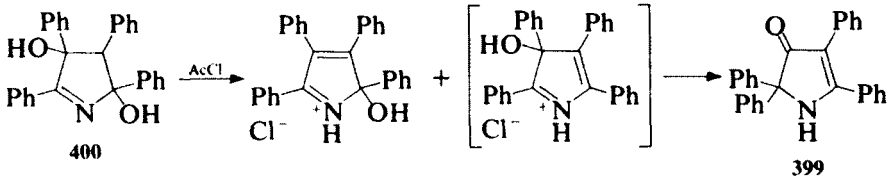
3*H*-Pyrrole salts rearrange on gentle heating.[131] Wong and Ritchie reported that the picrate salts of isomeric 3*H*- and 2*H*-pyrroles have the same melting points and show almost no depression with mixed melting point.[26] It has since been shown that 3*H*-pyrrole picrates rearrange to the 2*H*-isomers on recrystallization from hot ethanol but may be crystallized unchanged at lower temperatures.[13]

4.5.1.3. Hydroxy 2H- and 3H-Pyrroles to Pyrrolones

Thermal rearrangement of the 2-hydroxy compounds **396** to the isomeric lactams **397** is a very general reaction, proceeding in a number of solvents, as well as under acid or base catalysis. The mechanism appears to be ionic, involving an intermediate **398** or its protonated or deprotonated form. The migrating group has most commonly been phenyl,[69,190–193,195,200,202,203,209,303] but also 4-methylphenyl,[206] 4-methoxyphenyl,[207] *t*-butyl,[21] other alkyl,[204] and acyl, ester, or amide.[198] The salt **146** also rearranges to the lactam **148**.[190,210]

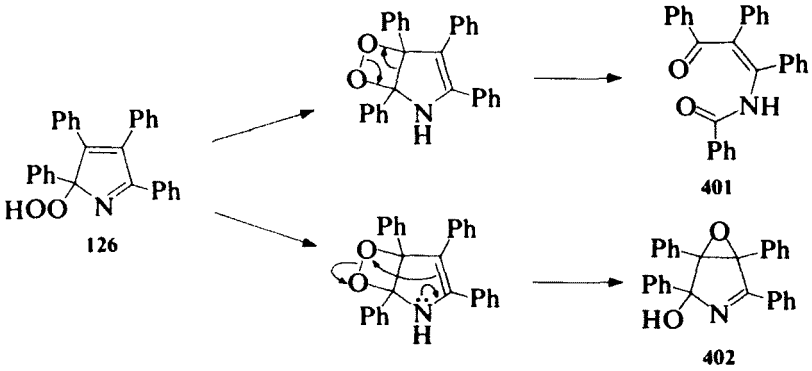


Formation of the pyrrolone **399** from the dihydroxypyrroline **400** is thought to proceed via a 3-hydroxy-3H-pyrrole salt.[361]



4.5.1.4. Other Rearrangements of 2H-Pyrroles

On heating in methanol, the hydroperoxy compound **126** rearranges by two independent pathways to **401** and **402**.[69,195,196,203]



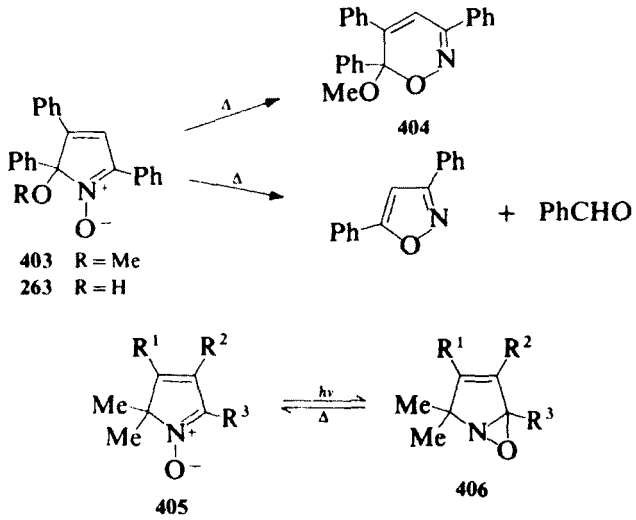
The reversible dissociation of structures **30** (e.g., **23–25**, **115**) to the radicals **31** has been discussed in Section 4.2.5. At higher temperatures, the 1,1′-bipyrrole isomer is formed irreversibly.[112]

On heating, the 2-amino compound **111** is converted quantitatively into the pyrimidine **112** and 2,4-dinitrobenzenethiol.[135]

4.5.1.5. 2H-Pyrrole 1-Oxides

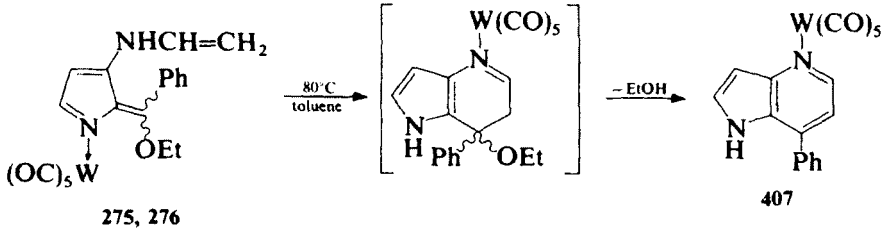
Distillation of the *N*-oxide **403** at low pressure yielded the oxazine **404**, while the hydroxy compound **263** underwent fragmentation.[362] The *N*-oxide **365** appears to exist at very low concentration in equilibrium with the oxazine **367**.[356]

Conversion of **405** into isolable oxaziridines **406** has been achieved photochemically. In some cases the reaction may be reversed thermally.[363,364]



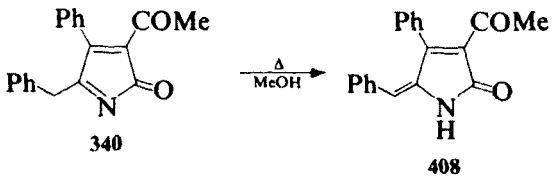
4.5.1.6. *1-Azafulvenes*

On heating (80°C) the isomers **275** and **276** (R = H) rearrange, with loss of ethanol, to the pyrrolo–pyridine complex **407**.[93] Photoisomerization of structures **156** (X = O, S, NMe) to a mixture of *E*- and *Z*-forms has been reported.[232] The thermal equilibrium between structures **184** and **185** (and their analogs) has been mentioned in Section 4.4.1.2.2.[250,365]



4.5.1.7. *2H-Pyrrol-2-ones and 2H-Pyrrol-2-imines*

Pyrrolone **340** is reported to isomerize in boiling methanol to **408**,[347] while the rearrangement of **182** to **183** in boiling toluene is catalyzed by silver



bromide.[55] The interconversion of **350** and **351** by Dimroth rearrangement was referred to in Section 4.4.5.2.[351]

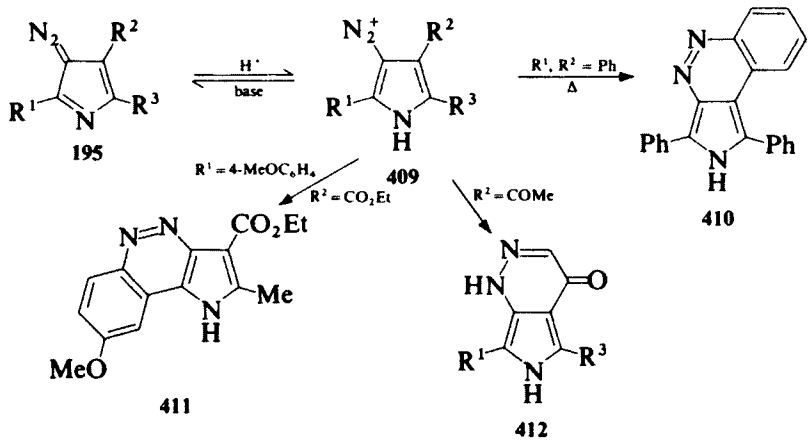
4.5.2. Electrophilic Reactions

4.5.2.1. Protonation

Protonation at ring nitrogen occurs readily in both 2*H*-[23,89,190,195,206,209] and 3*H*-pyrroles[13,150] to give isolable salts; the reaction is readily reversed by base. The basicity of these compounds has frequently been utilized in separating them from reaction mixtures containing 1*H*-pyrrole precursors or coproducts. Values for pK_a have been measured in solution (Section 4.2.6),[11] and structures of type **49** have been patented as hydrogen halide acceptors.

Some 1- and 2-azafulvenes have also been reported to give isolable salts with acid, the free bases being readily regenerated with tertiary amines.[47,51]

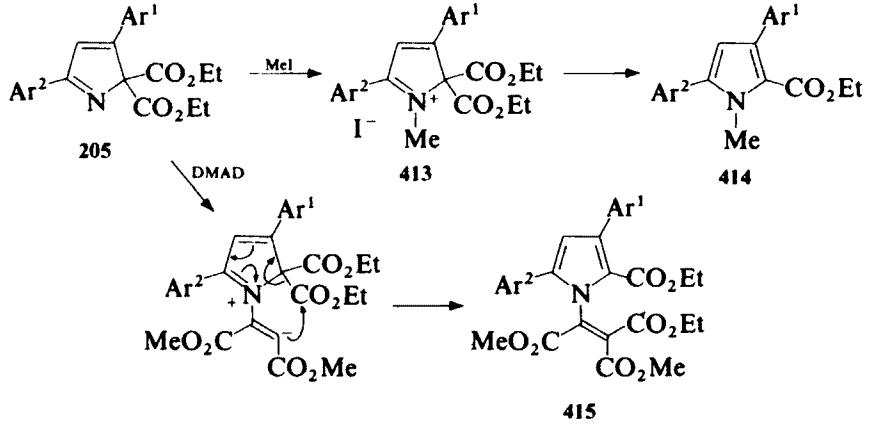
3-Diazopyrroles **195** also protonate on the ring to form 1*H*-pyrrole diazonium salts **409**, many of which have been isolated.[256–258,260,366–368] On heating of the solutions, complex mixtures result from fragmentation, hydrolysis, or intermolecular coupling,[59,76,260] unless intramolecular coupling can take place. When R^1, R^2 and R^3 = Ph, coupling is regiospecific at the 3-phenyl group, yielding **410**.[366] For $R^2 = CO_2Et$, coupling occurs on an activated 2-phenyl group to give **411**, but when R^2 = COMe, only coupling at the acyl group is observed, forming **412**, regardless of the nature of R^1.[59,119]



4.5.2.2. Alkylation

2*H*-Pyrroles and 3*H*-pyrroles also alkylate on the ring nitrogen to give salts. For the 2*H*-pyrroles, these salts have sometimes been isolated as products from direct alkylation of 1*H*-pyrroles,[156,159,160] but generally they have been formed

from the free bases. Alkylating agents, that have normally been used, are methyl iodide,[8,22,36,89,157,369,370] dimethyl sulfate,[330] ethyl iodide and benzyl bromide,[369,370] and the triflate $CF_3SO_3CH_2SiMe_3$.[88] The action of triethyloxonium fluoroborate on the 3-hydroxy-2*H*-pyrroles **49** leads to *N*- and not *O*-alkylation.[24] The diaryl diesters **205** are less nucleophilic, forming salts **413** only with difficulty with fragmentation occurring, in certain cases, under the reaction conditions to produce the 1*H*-pyrroles **414**.[89] Compounds **205** also react with DMAD to give, via rearrangement, the adducts **415**, and not products that might be expected from cycloaddition.[89] Many other reactions between 2*H*-pyrroles and either DMAD or methyl propynoate have been carried out.[343] The first step is generally attack of the ring nitrogen atom on the alkyne, followed by further reaction. 3*H*-Pyrroles are less nucleophilic than the 2*H*-compounds, and few salts have been prepared.[13,131] Often, rearrangement to the 2*H*-salt occurs under the reaction conditions.[13,28]



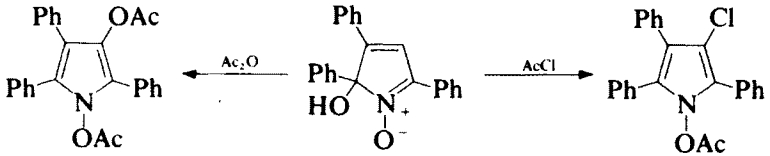
4-Hydroxy-1-azafulvenes are alkylated at the ring nitrogen atom by dimethyl sulfate in the presence of base, whereas the 6-hydroxy analogs give 6-methoxy derivatives with diazomethane.[49]

The azohydrazone **65** alkylates at ring nitrogen with dimethyl sulfate, yielding **168**,[120] while the 3*H*-pyrrol-3-one **416** reacts at the carbonyl group, giving the salt **417**.[50]

4.5.2.3. Acylation

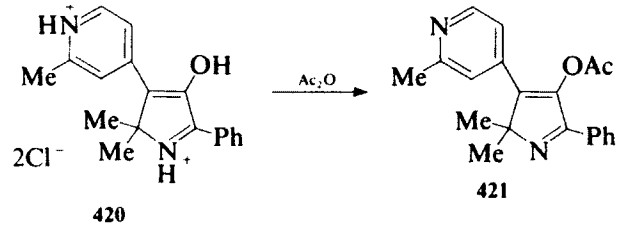
On heating with acetic anhydride, the *N*-oxide **263** is converted into the 1*H*-pyrrole **418**.[305] The mechanism probably involves a [3,3]-sigmatropic

rearrangement of an acetoxy group from C_2 to C_4. With acetyl chloride the product is **419**, together with the furan analog. Both **418** and **419** are light-sensitive, the former being photochromic.[305]

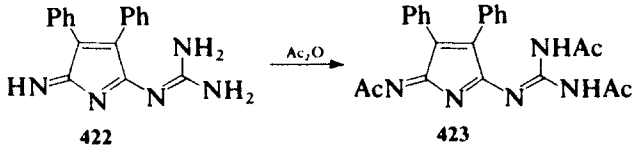


418 **263** **419**

Side-chain acylation is observed in the conversion of the salt **420** into the acetate **421**[115] and in the acetylation of a number of 2*H*-pyrrol-2-imines to amides (e.g., **422** into **423**).[281]



420 **421**



422 **423**

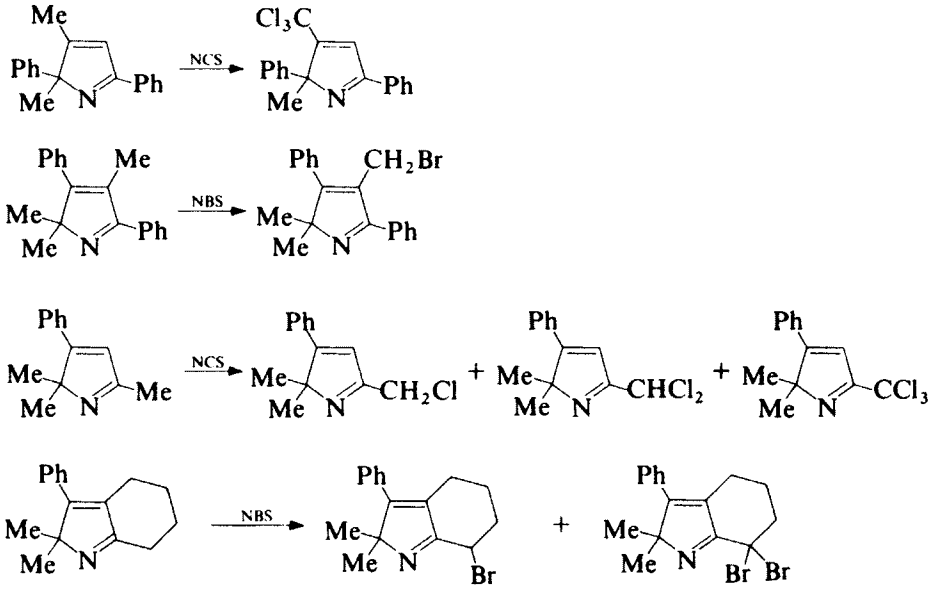
4.5.2.4. Halogenation

Allylic protons in 2*H*-pyrroles may be substituted photochemically by halogen atoms using *N*-bromo- or *N*-chlorosuccinimide at room temperature in carbon tetrachloride.[343] Examples of such reactions are shown in Scheme 7. Where more than one product was formed, the relative amounts depended on the molar ratio of reagents and the reaction time. Brominated derivatives were thermally more labile than the analogous chloro-compounds.

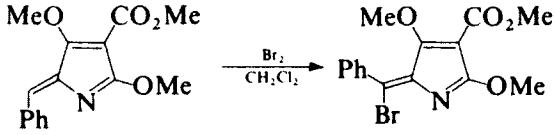
The 1-azafulvene **424** brominates at C_6 with inversion of configuration to give **425**.[49]

4.5.2.5. Complex Formation

Reaction between pentamethyl-2*H*-pyrrole **70** and $Fe_2(CO)_9$ yields the π-complex **426**.[371]

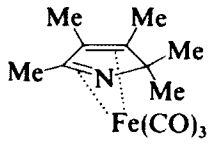


Scheme 7



424 425

Charge-transfer complexes (1 : 1) between 2*H*-pyrrole *N*-oxides and both DDQ and TCNE, but not TCNQ, have been reported.[124] They are stronger than similar complexes with other azomethine *N*-oxides. On the other hand, electron-rich 1-azafulvenes react with TCNQ to form 1 : 1 complexes of the azafulvenium cation and the TCNQ radical anion, for example, **427** from **34**.[54]



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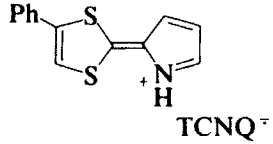

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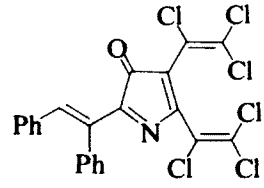


428

4.5.2.6. Other Electrophiles

The phosphorylide **302** reacts with benzaldehyde to yield the derivative **428**.[313]

4.5.3. Nucleophilic Reactions

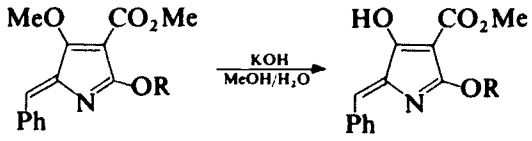
The electrophilic nature of the ring systems **1**–**6** renders them susceptible to attack by a wide range of nucleophiles at a variety of sites. Nucleophilic displacements may take place at sp^2 or sp^3 carbon atoms, both within and outside the ring. Likewise, nucleophilic addition may occur at the C=N carbon atom, or at more remote unsaturated sites. Attack may be followed by ring opening or rearrangement.

4.5.3.1. Oxygen Nucleophiles

4.5.3.1.1. At Ring Atoms with Displacement

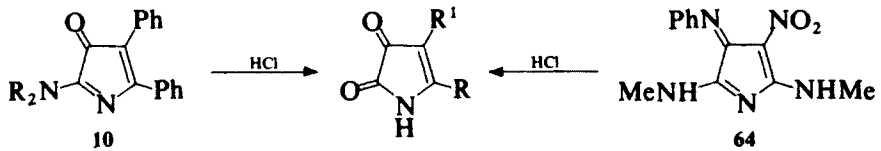
Alkoxy, amino, imino, and halogeno groups have all been displaced under basic or acidic conditions. When the ring atom being attacked is sp^2-hybridized, a carbonyl group is usually the product, although this may sometimes exist in the enol form.

4-Alkoxy groups in 2*H*-pyrroles,[115] 5-methoxy groups in 3*H*-pyrroles,[148,151] and 2-alkoxy groups in 1-azafulvenes[91] have been cleaved in the presence of hydrochloric acid, while the dialkoxy compound **429** (R = Me, Et) is converted selectively in base into **430**.[49]



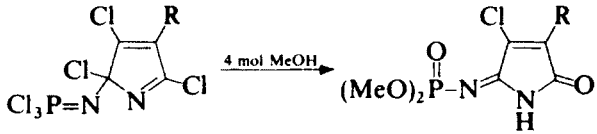
429 **430**

2-Amino-5-alkoxy-3*H*-pyrroles[148,151] and 5-amino-2*H*-pyrrol-2-imines[281,351] are also hydrolyzed by hydrochloric acid; the products are respectively succinimides and maleimides. Compounds **10**[57,60] and **64**[97] are likewise converted into the corresponding diones **431**; in the latter case, the 5-methylamino group is unaffected. Compound **416** is prepared similarly from a pyrroliminium salt.[50]



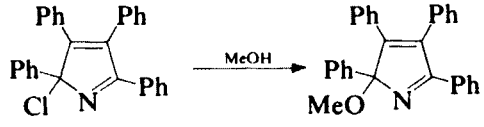
10 **431** **64**

Pentachloro-2*H*-pyrrole **12**[25,184,186] and its analog **234**[278] are both readily hydrolyzed by water with displacement of 2- and 5-substituents to yield 3,4-dichloromaleimide. With methanol, however, **234** and **236** are converted into **432**.[277] Treatment of the 5-chloro compound **84** with silver acetate in aqueous



234 R = Cl
236 R = Ph

432

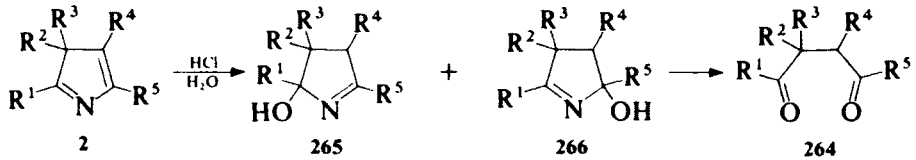


433 434

acidic THF gave the corresponding lactam in high yield,[167] while displacement of the 2-chloro group in **433** yielded the methoxy compound **434**.[69,190,195]

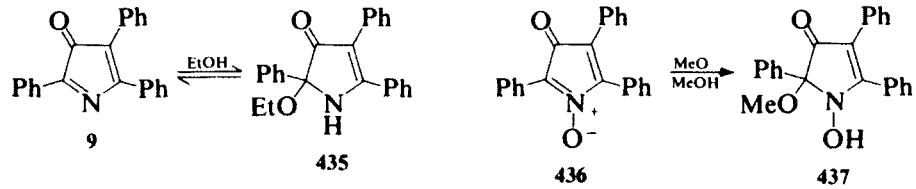
4.5.3.1.2. At Ring Atoms with Addition

3*H*-Pyrroles **2**, when dissolved in dilute hydrochloric acid, are rapidly hydrated to give the isomeric hydroxypyrrolines **265** and **266** and, on longer standing, give the diketones **264**.[13,28] The mechanism probably involves protonation at nitrogen, followed by addition of water. The hydrolysis of 2-hydroxy-2*H*-pyrrole **106** to the 1,4-diketone **108**, under more compelling conditions, may follow a similar pathway.[189]



2 265 266 264

Addition of ethanol to the 3*H*-pyrrol-3-one **9** to give **435**,[57] and of methoxide to its *N*-oxide **436** to form **437**,[292] occurs at the C=N bond.

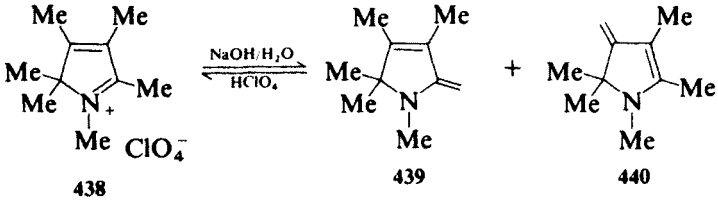


9 435 436 437

4.5.3.1.3. At Ring Substituents with Displacement

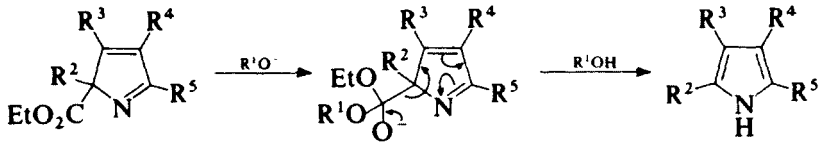
When dissolved in methanol-d_4, with or without added base, the 5-methyl protons of 2*H*-pyrroles have been observed to exchange.[63,65] Similar behavior is to be found with 2-methylpyridines, for similar reasons. Deprotonation in alkyl side chains has frequently been reported in 2*H*-pyrrole salts in the presence

of base,[8,34,36,156,157,159] the salt **438**, for example, giving a mixture of the pyrrolines **439** and **440**.[34] The reaction is readily reversed by acid, but if another electrophile is present, addition may occur at the exocyclic double bond at C_5. In this way, alkylation at the C_5 methyl group of a salt has been achieved,[157] as well as coupling reactions to give useful dyes.[369,370] However, an attempt to alkylate the 5-methyl group of a 2*H*-pyrrole, after treatment with strong base, was unsuccessful.[343]



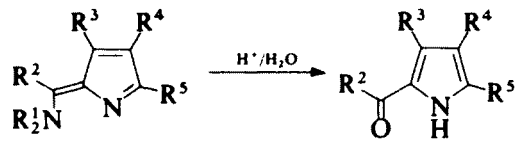
438 **439** **440**

2*H*-Pyrrole-2-carboxylic esters **441** readily lose an ester group under hydrolytic conditions, yielding 1*H*-pyrroles **442**.[176,268,295,297] The reaction is particularly facile with the salts **413**.[89] Loss of other 2-substituents by fragmentation has been observed under both basic[320] and acidic[168,169] conditions.



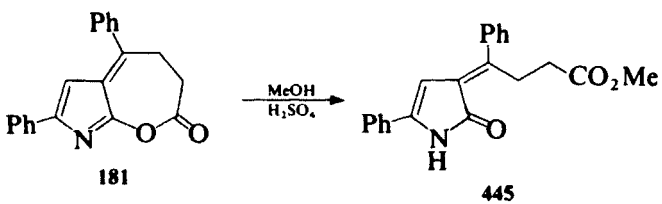
441 **442**

6-Dialkylamino-1-azafulvenes **443**, or their salts, which are also intermediates in the Vilsmeier–Haack formylation of 1*H*-pyrroles, are readily hydrolyzed to yield carbonyl compounds **444**.[48,74,92,94,237,238]



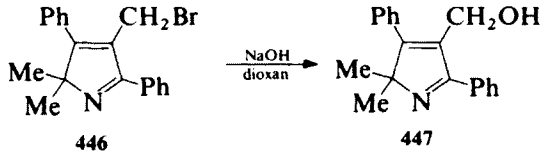
443 **444**

Basic hydrolysis of the benzoate **110** yields the 2-hydroxy-2*H*-pyrrole **106**,[197] while the 2-azafulvene **181** is converted into the ester **445** in acidic methanol.[247]



181 **445**

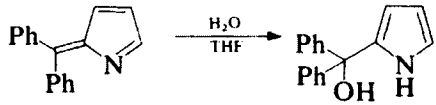
The bromide **446** has been hydrolyzed successfully to **447**,[343] and the 6-bromo group in the 1-azafulvene **425** has been replaced by a hydroxyl group by use of methanolic potassium hydroxide.[49]



446 **447**

4.5.3.1.4. At Ring Substituents with Addition

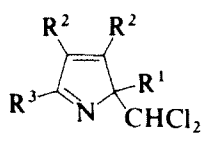
Both the 1-azafulvene **7** and its fluoroborate salt readily add water to form the alcohol **448**.[41] Addition of water to the transient ketene **193**, and to its 2-aza analog, leads to the isolation of 1*H*-pyrrole-2- and -3-carboxylic acids, respectively.[352]



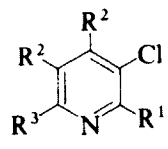
7 **448**

4.5.3.1.5. At Ring Substituents with Rearrangement

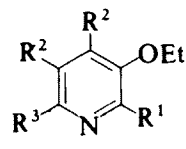
Reports by Plancher and co-workers that **88** (R^1, R^3 = Me) in ethanol could be converted into **89** (R^2 = H) with ethanolic sodium ethoxide,[172] and into **89** (R^2 = Me) under aqueous conditions or into **449** (R^2 = Me) with ethanolic sodium ethoxide,[173] were later shown to be incorrect.[179-182] In the reactions with sodium ethoxide in ethanol, Jones and Rees[182] isolated **450** from **88** (R^1, R^3 = Me; R^2 = H), **451** from **88** (R^1, R^3 = Ph; R^2 = Me), and both **450** and **451** from **88** (R^1, R^2, R^3 = Me). This was explained in terms of the possible intermediacy of 1-azabicyclo[3.1.0]hexenes **452** and **453**.[179,182] In a study of the same reaction, Nicoletti and Forcellese also obtained **450** from **88** (R^1, R^3 = Me; R^2 = H or Me).[180,181] However, in addition they isolated **454** and **455** from **456**; i.e., from **88** R^1 = Me, R^2 = H, but no analogous azabicyclohexene from **88** (R^1, R^2, R^3 = Me).[65,180,181] Although compound **454** was converted into a mixture of **456** and **457** with hydrochloric acid, it was concluded that the azabicycles were not necessarily intermediates in the formation of **450**. The isolation of **455** from **456** also led to the conclusion that **452** (R^2 = H) was unlikely to be an intermediate in the formation of **454**.[65]



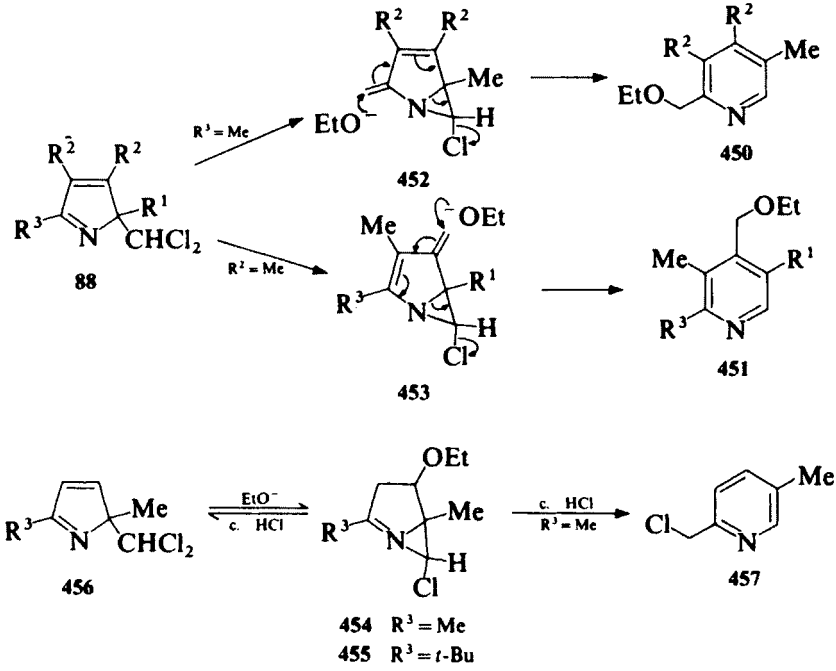
88



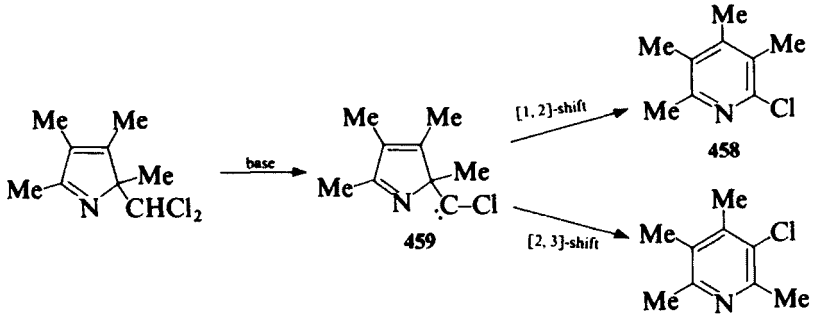
89



449



Pyridines **89** *are* products from 2*H*-pyrroles **88** in reactions with sodium methoxide in toluene at high temperatures, or with butyllithium at low temperatures. The coformation of the 2-chloropyridine **458** from **88** (R^1, R^2, R^3 = Me) (Scheme 8) suggests the intermediacy of the carbene **459**.[177,178] Under very strongly basic conditions, the dichloromethyl proton in compounds **88** exchanges with deuterium.[178]

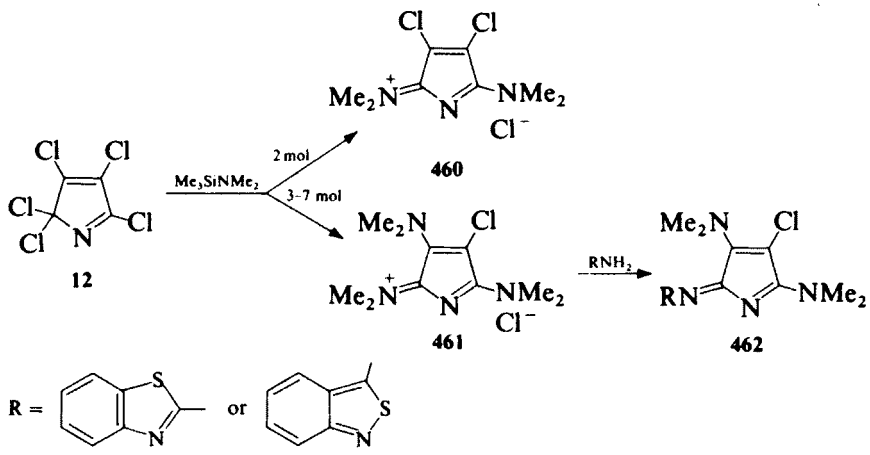


Scheme 8

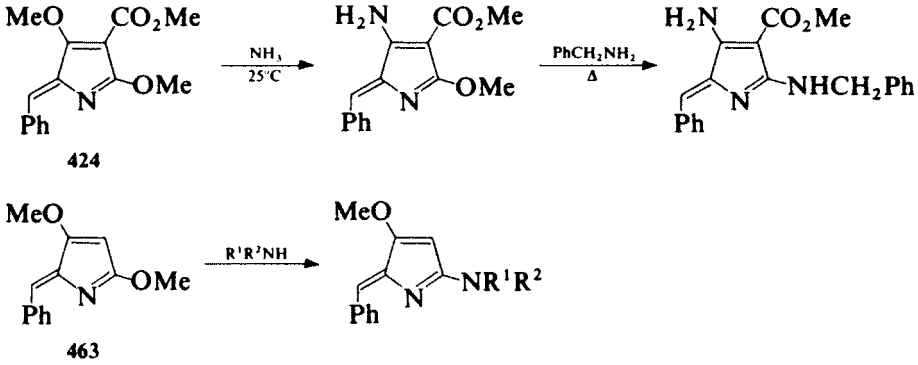
4.5.3.2. Nitrogen Nucleophiles

Pentachloro-2*H*-pyrrole **12** gives products **460** or **461** with Me_3SiNMe_2, depending on the molar ratio of the reactants. The tri-substituted compound

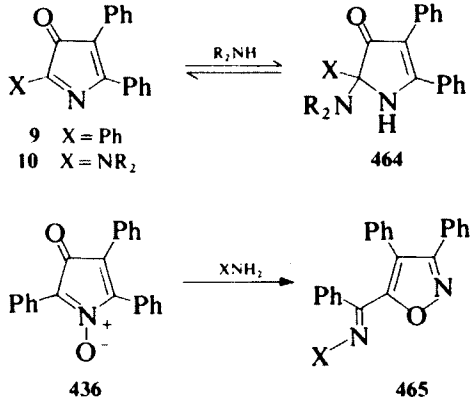
461 reacts further with heterocyclic amines to yield products **462**.[50] Analogs of **12** also react with aniline with displacement of the 2- and 5-chlorine atoms.[277] It has been claimed that 2,2-dimethoxy-2*H*-pyrrole reacts with aromatic 1,3-diamines with displacement of both methoxy groups.[372]



6-Dimethylamino-1-azafulvenes **162** react with secondary amines with direct displacement of the dimethylamino group.[373] With dimethoxy compounds, the site of attack depends on the other substituents present. Thus, in **424** (and **425**) both methoxy groups may be displaced sequentially, with that at C_4 being the most reactive, whereas for **463** it is the 2-methoxy group that is displaced.[49] The 1-chloro group in the 2-azafulvene **354** is readily substituted by pyrrolidine.[52]

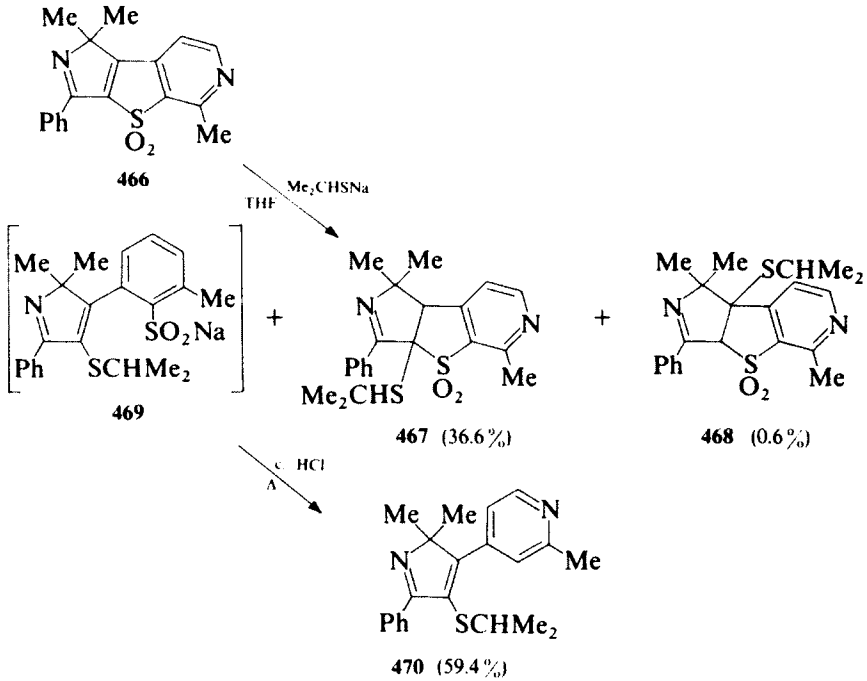


Secondary amines react reversibly with the 3*H*-pyrrol-3-ones **9** and **10** in solution, giving amino adducts **464**,[57] whereas, in contrast, hydroxylamine, semicarbazide, and 2,4-dinitrophenylhydrazine attack the *N*-oxide **436** at C_2, with subsequent ring opening and formation of the isoxazoles **465**.[374]

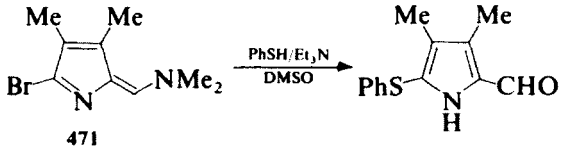


4.5.3.3. Sulfur Nucleophiles

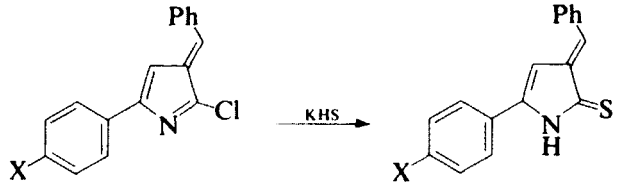
Attack at both C_3 and C_4 of the 2*H*-pyrrole sulfone **466** is observed with sodium 2-propanethiolate, yielding the adducts **467** and **468**, together with the sulfinate **469**, which was converted without isolation into **470**.[115]



Treatment of 2-bromo-1-azafulvene **471** with thiophenol gave **472**, resulting from attack at C_2 and C_6.[373] The 6-bromo-1-azafulvene **425** reacts with sodium sulfide, yielding the 6,6′-sulfide,[49] while the thiolactam **473** is the product from 2-azafulvene **474** and potassium hydrogensulfide.[375]

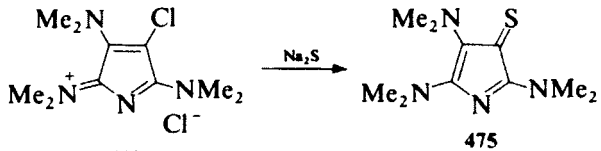


471 472



474 473

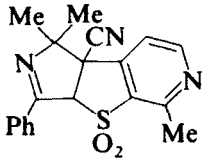
The only reported example of a 3*H*-pyrrol-3-thione **475** was prepared from the salt **461**.[50]



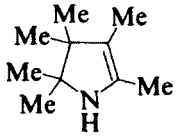
461 475

4.5.3.4. Carbon Nucleophiles

In contrast to the addition of 2-propanethiolate to **466**, cyanide ion adds regiospecifically at C_3 of the 2*H*-pyrrole ring of **466** to give **476**.[115] Methylmagnesium iodide adds at both C_3 and C_5 of the 2*H*-pyrrole salt **438**, yielding the products **477** and **478**.[34]



476



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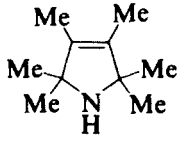
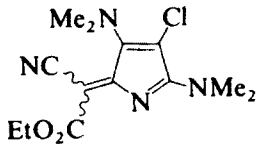


478

Carbanions add regioselectively at C_6 of 1-azafulvenes, forming 2-substituted-methyl 1*H*-pyrroles. Thus, phenyllithium gives 2-trityl-1*H*-pyrrole with **7**,[41] while a range of alkyl- and phenyllithiums add likewise to the 1-azafulvene **158**, formed in situ from the salt **157**.[235] The anion of phenyl methyl sulfoxide also adds to **158**, providing a useful new synthetic approach to 4-substituted indoles.[236]

The 1-azafulvene **479** is formed from the salt **461** and ethyl cyanoacetate in the presence of base,[50] while **480** is the product from a similar reaction with a 5-amino-2*H*-pyrrol-2-one.[281]



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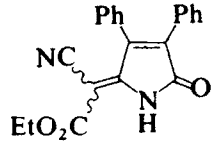
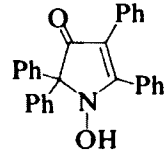


480

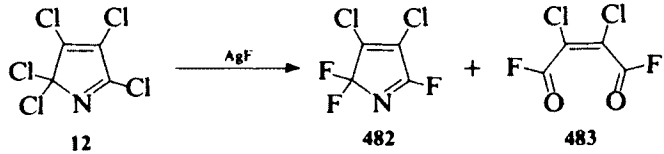


481

Both 2-diazo-[56] and 3-diazopyrroles[58] couple readily with 2-naphthalenol, yielding the corresponding azo-compounds. Phenylmagnesium bromide adds at C_2 of the pyrrolone *N*-oxide **436** in a fashion similar to methoxide ion, forming the adduct **481**.[292]

4.5.3.5. Halide Ions

The lability of the 2- and 5-chloro groups in the pentachloro-2*H*-pyrrole **12** is again demonstrated by the formation of **482** together with **483** with silver fluoride.[185] The 2-chloro-2*H*-pyrrole **433** is readily formed from the hydroxy analog **106** with PCl_5[190] or $SOCl_2$.[69,195]



12 **482** **483**

4.5.3.6. Hydride Ion

2,5-Dimethylpyridine was isolated in high yield from the action of sodium hydride on the 2*H*-pyrrole **88** (R^1, R^3 = Me; R^2 = H) in refluxing toluene. The product could arise from attack of hydride ion on an azabicyclohexene intermediate **452**.[179,182]

4.5.4. Oxidizing Agents

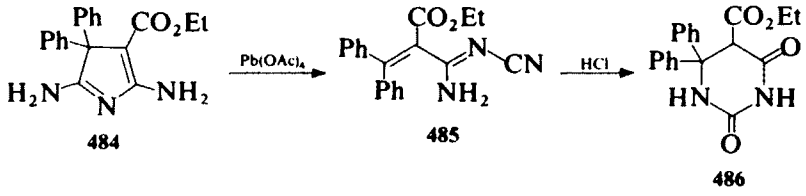
Of the few reported oxidation reactions, most have involved destruction of the pyrrole ring and have been used for structure determination. Oxidation of the side chain, however, has been preparatively useful in some instances.

Ozonolysis of 2,2,3,4,5-pentamethyl-2*H*-pyrrole **70** gave 2,3-butanedione, but no 3,3-dimethyl-2,4-pentanedione, thereby eliminating the 3*H*-isomeric

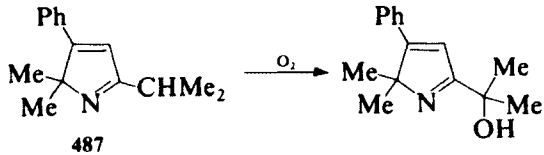
structure.[8,26] Benzonitrile and benzoic acid were the ozonolysis products from the *N*-oxide **436**.[292]

In an early attempt to determine the structure of the 2-hydroxy-2*H*-pyrrole **262**, it was shown by oxidation (CrO_3 in acetic acid) to the diketone **261** and benzimide that no rearrangement of the carbon skeleton had occurred during its preparation from **261**.[194] The 3-hydroxy-3*H*-pyrrole ring of **125** was destroyed by further oxidation with dichromate in acetic acid. Ring cleavage occurred at the C_3–C_4 bond.[201]

Lead tetraacetate oxidation of the diamino compound **484** gave **485**, which cyclized in acid to give the pyrimidine **486**.[376]

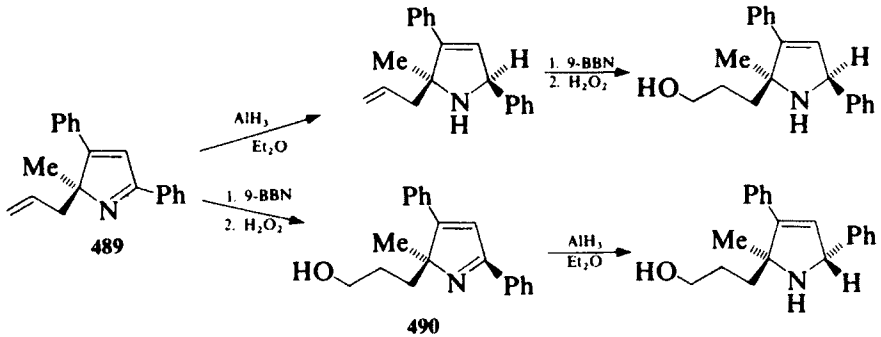


484 **485** **486**



487 **488**

Spontaneous oxidation of the 5-isopropyl-2*H*-pyrrole **487** in air to the alcohol **488** has been reported.[12] It is surprising that, although the alcohol **447** was prepared from the 4-methyl compound with oxygen under basic conditions in dimethyl sulfoxide, a 5-methyl group is not oxidized under the same conditions.[343] The conversion of the 3-methyl *N*-oxide **215** into the aldehyde **216** with selenium dioxide has been referred to in Section 4.4.1.4.1.[90] The terminal alkene group in **489** was oxidized to give **490**, using 9-BBN followed by hydrogen peroxide (see Scheme 9).[80]



489 **490**

Scheme 9

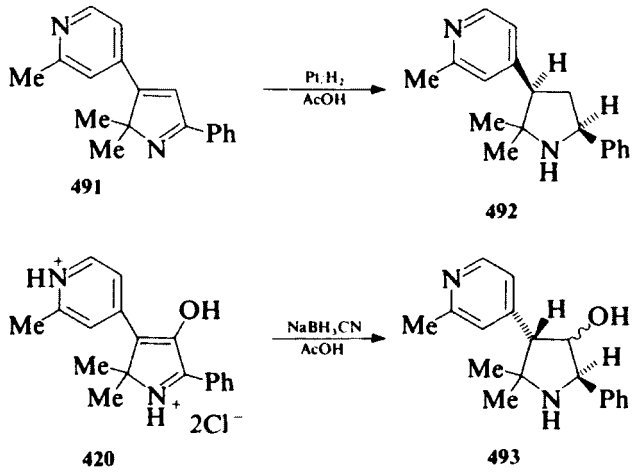
4.5.5. Reducing Agents

It is more convenient to discuss reductions by class of pyrrole rather than by type of reducing agent.

4.5.5.1. 2H- and 3H-Pyrroles

4.5.5.1.1. To Pyrrolines and Pyrrolidines

Simple alkyl- or aryl-substituted 2*H*-pyrroles are reduced to pyrrolidines with both sodium in ethanol,[8,155] and by catalytic hydrogenation over platinum[115,182]. The cis compound **492** was obtained from **491**, whereas sodium cyanoborohydride reduced the salt **420** to the trans derivative **493**.[115]



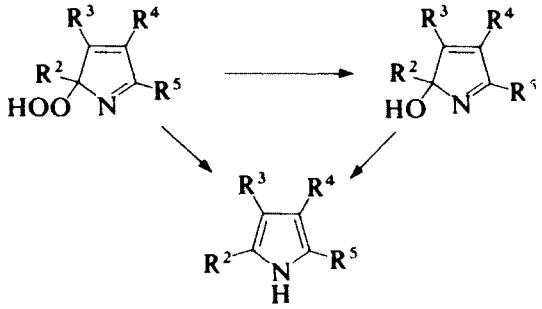
420 493

Brief hydrogenation over palladium[100] and reduction with tin and hydrochloric acid[115] have been reported to convert 2*H*-pyrroles into the 3,4-dihydro compounds.

Generally, metal hydrides add across the C=N bond of both 2*H*-pyrroles and their salts to give the 1,5-dihydro derivatives. In this reductive procedure, sodium borohydride,[36,78,330] sodium cyanoborohydride,[115] and aluminum hydride[80] have all been employed. In the latter case, stereoselectivity could be achieved in the reduction, as shown in Scheme 9.

4.5.5.1.2. To Other 2*H*-Pyrroles

2-Hydroperoxy-2*H*-pyrroles have been reduced to the 2-hydroxy compounds (Scheme 10) by triphenylphosphine,[204] dimethyl sulfide,[240] or, most commonly, potassium iodide in acetic acid.[69,195,202] The latter reagent also reduces compound **128** to the corresponding 2-hydroxy *N*-oxide **494**.[205]

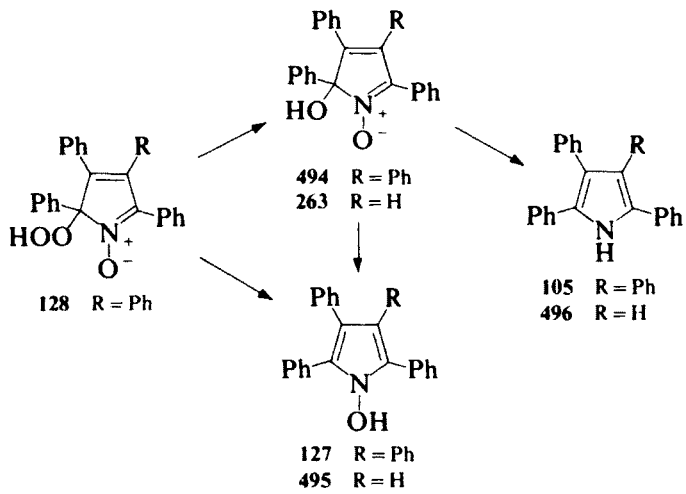


Scheme 10

4.5.5.1.3. To 1*H*-Pyrroles

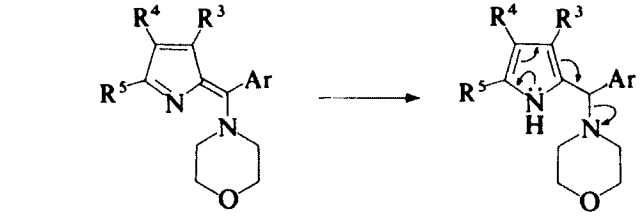
2-Hydroperoxy compounds may also be converted directly into 1*H*-pyrroles (Scheme 10). This has been achieved simply by heating,[69,195] but also with zinc in acetic acid,[21] sodium borohydride,[204] or hydroxylamine.[69,195] The latter reagent reduces **128** to the *N*-hydroxy compound **127**.[205] 2-Hydroxy-2*H*-pyrroles have likewise been reduced to the 1*H*-compounds (Scheme 10) by hydroxylamine[69] and by zinc in acetic acid.[189,194,200] The 3-hydroxy-3*H*-pyrroles **125** were similarly reduced by the latter reagent.[201] In the *N*-oxide series, **494** was reduced to **127** by hydroxylamine,[205] and, analogously, **263** was converted into **495** with sodium–potassium alloy in ether,[304] while the reduction of **263** to **496** was achieved with zinc and acetic acid.[304]

The 2,2′-bipyrrole **115** could be converted back to **114** with 1,4-benzenediol.[121]



4.5.5.2. *1-Azafulvenes*

6-Aryl- and 6-dialkylamino-1-azafulvenes are readily reduced at the C_5–C_6 double bond to give 2-benzyl- and 2-aminomethyl-1*H*-pyrroles, respectively. For the 6-dialkylamino compounds, catalytic hydrogenation using platinum[249] or palladium–barium sulfate[74,373] have been used. The latter reagent also cleaves a C_2–Br bond.[74] A 6-phenyl compound was reduced by hydrogen over Raney nickel,[45] while 6-aryl-6-dialkylamino-1-azafulvenium salts **497**, readily available from 1*H*-pyrroles and aromatic amides by the Vilsmeier-Haack reaction, are reduced in two stages to 2-benzylpyrroles **498** by a variety of reducing agents, the best of which is sodium cyanoborohydride and lithium boroshydride.[239,240]



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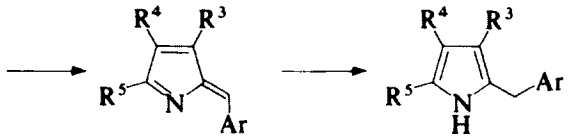
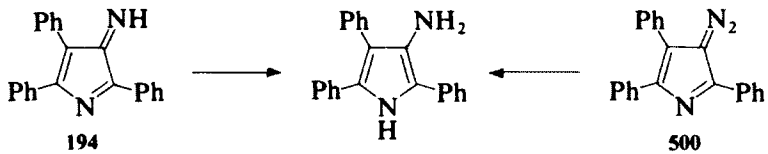


498

Lithium aluminum hydride converts the 1-azafulvene **191** into the corresponding 2-hexafluoroisopropyl-1*H*-pyrrole, which has useful anti-inflammatory properties.[252]

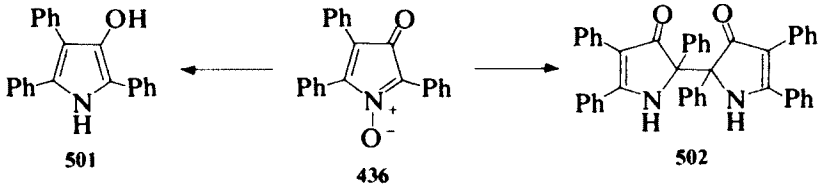
4.5.5.3. *Systems with an Exocyclic C=X Bond*

The imine **194** is reportedly reduced by aluminum amalgam to pyrrolamine **499**;[255] the same product is also formed from the diazo-compound **500** with chloramine, or with zinc in acetic acid or ammonium chloride.[258]



194 **499** **500**

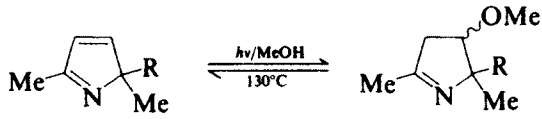
Reduction of the *N*-oxide **436** with lithium aluminum hydride yields the hydroxypyrrole **501**;[374,377] however, contrary to the earlier report,[374] the bipyrrole **502** is formed by the action of sodium borohydride, and not **501**.[377]



501 **436** **502**

4.5.6. Carbenes and Photoinduced Additions

Photochemical addition of methanol to the 2*H*-pyrroles **503** (R = propyl or allyl) gave mixed diastereomers of **504** in very high yields.[63] The reaction, which does not occur in the dark, even with acid catalysis, is reversed on heating. The 2*H*-pyrrol-2-one **182** copolymerises with methyl methacrylate photochemically to form a polymer, containing cyclopropane and isocyanate groups, which may be readily cross-linked with diamines.[378]

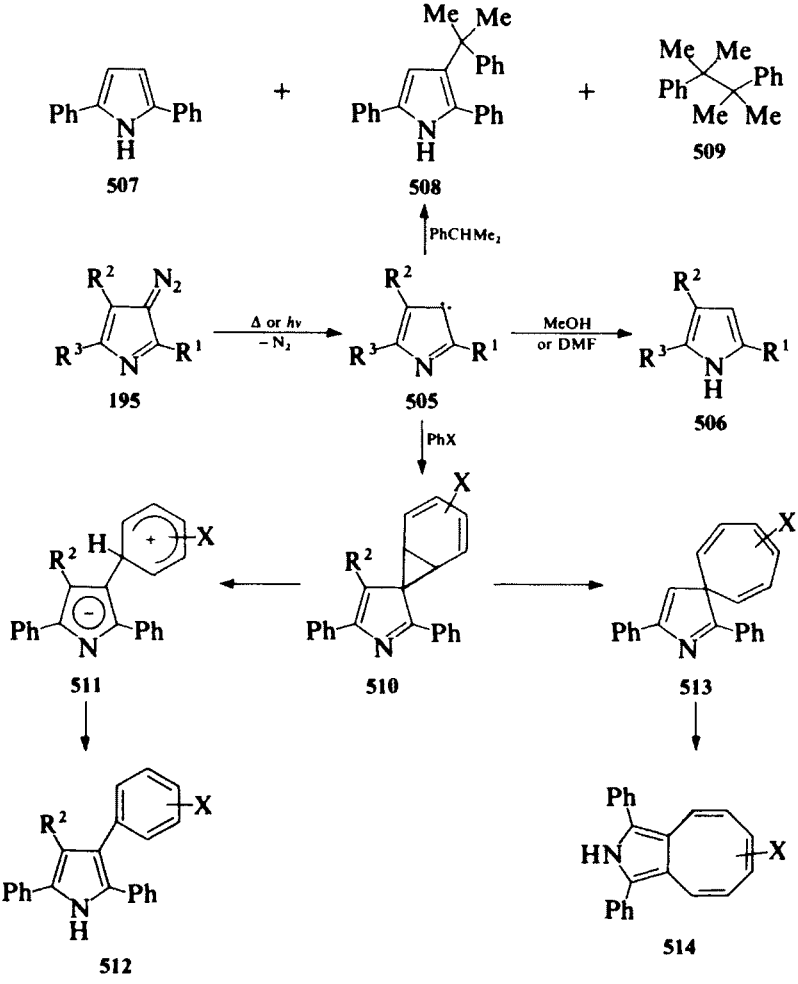


503 **504**

Thermal or photochemical decomposition of 3-diazopyrroles **195** gives a carbene **505**, which may react further with the solvent to form a variety of products. In methanol[379] or dimethyl formamide,[59] hydrogen abstraction occurs to yield the 1*H*-pyrroles,[59] while in isopropylbenzene, **195** (R^1, R^3 = Ph; R^2 = H) gives a mixture of **507**, **508**, and **509**.[98] In benzene[98,379,380] or substituted benzenes,[98,380] an adduct **510** is formed, the fate of which depends on the nature of X. For electron-releasing X, the pathway **511** → **512** is followed, while for electron-withdrawing X, the route is **513** → **514**. For X = H, results are conflicting.[98,379]

4.5.7. Cycloadditions

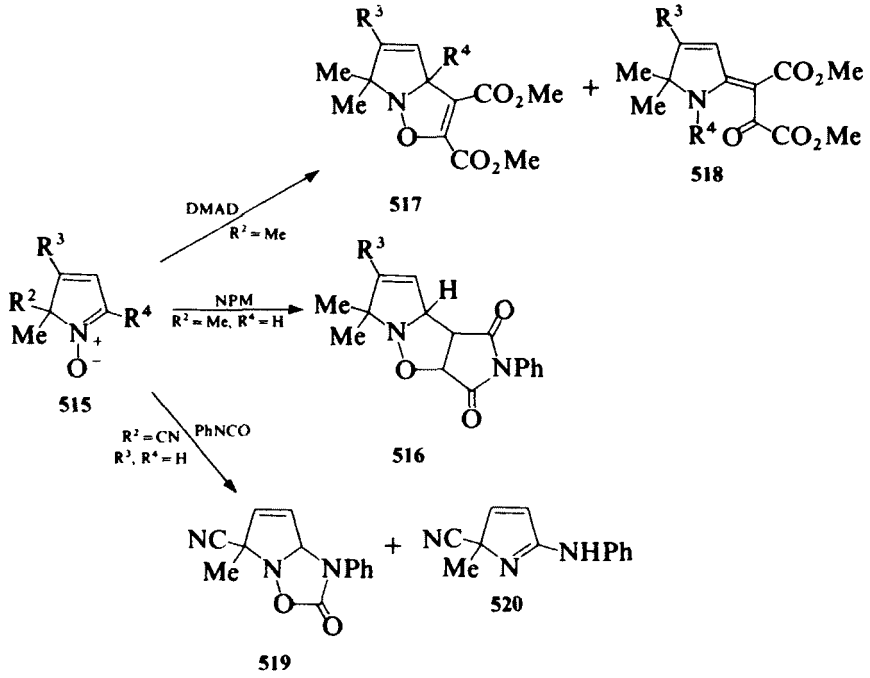
For convenience, cycloadditions are classified according to the number of π-electrons formally involved in the process of ring formation from the two fragments. Processes may be concerted or may take place stepwise.



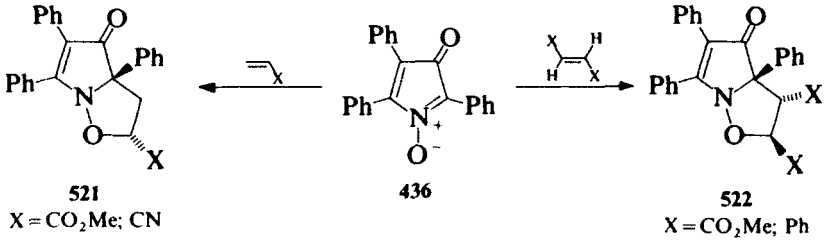
4.5.7.1. [4+2](1,3-Dipolar)Cycloadditions

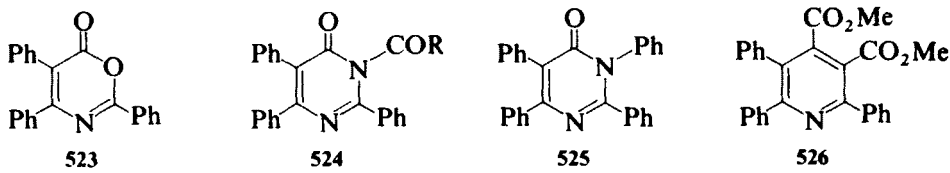
4.5.7.1.1. *N*-Oxides

2*H*-Pyrrole *N*-oxides **515** react with *N*-phenyl maleimide (NPM) to give quantitative yields of **516** (R^3 = H, Ph) and with DMAD to form two products **517** and **518** (R^3 = H, Ph). The latter was formed by rearrangement of **517**; for R^4 = H, it was the only product.[90] The equilibrium between the oxazine **367** and the *N*-oxide **365** (**515**; R^2 = CN; R^3, R^4 = H) was demonstrated by the formation of **519** and **520** with phenylisocyanate. The 1 : 1 adduct **519** was not converted into **520** in boiling chlorobenzene; base catalysis was necessary.[354-356]



The *N*-oxide **436** also reacts in a similar fashion with a number of dipolarophiles, including ketones, nitriles, phenyl isocyanate and alkenes,[374] and alkynes.[374–381] Simple 1:1 adducts **521** and **522** of fixed regio- and stereochemistry are formed only with alkenes.[374] The initial adducts with other dipolarophiles undergoing further rearrangement. Thus, the products from ketones, nitriles, and phenylisocyanate are, respectively, **523**, **524**, and **525**,[374] while alkynes may give complex mixtures, including **526** from DMAD.[374,381]

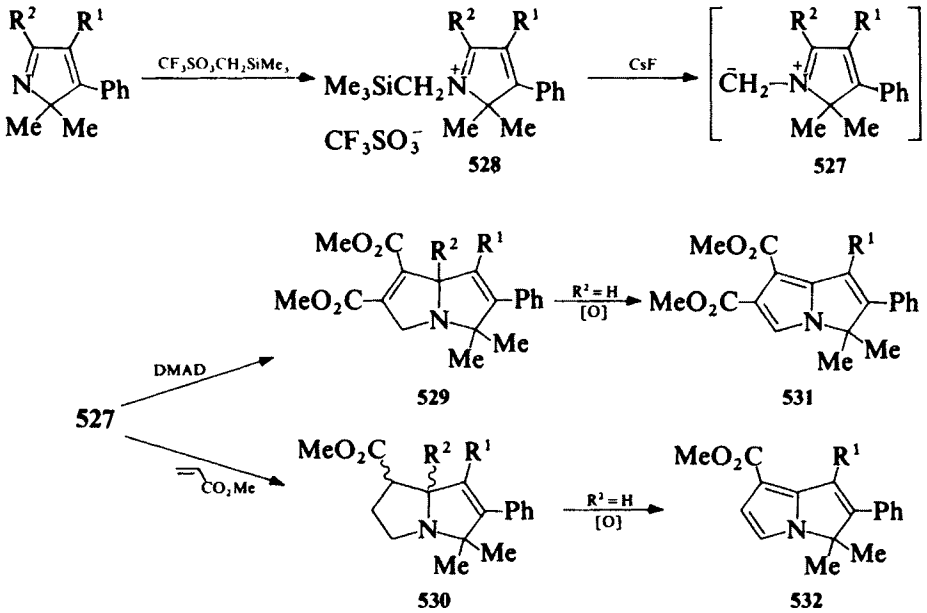




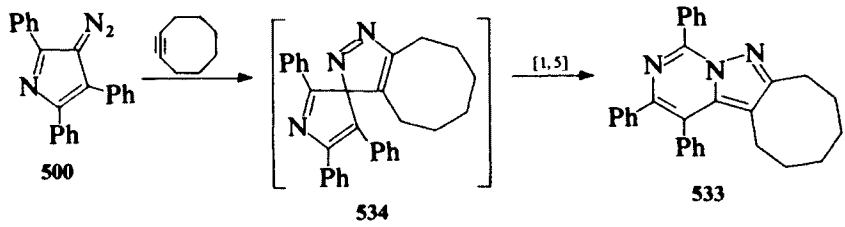
The dimerization of **252** to **253**[294] demonstrates that *N*-oxides of this type may also react as dipolarophiles. The 3*H*-pyrrol-3-one **302** also behaves as a dipolarophile in its further reaction with cyclopropenones **299** and **300**.[313]

4.5.7.1.2. Other 1,3-Dipoles

A useful new synthesis of the pyrrolizine ring system involves addition of DMAD or (regiospecifically) methylacrylate to the *N*-ylide **527**, generated in situ from the salt **528**.[88] For R^2 = H, further oxidation of **529** and **530** occurs to give the products **531** and **532**.



Reaction between cyclooctyne and diazo-3*H*-pyrrole **500** yields **533**, resulting from the [1,5]-sigmatropic rearrangement of the intermediate **534**. This contrasts with the behavior of diazocyclopentadienes, which give spiro-3*H*-pyrazoles as products.[382]

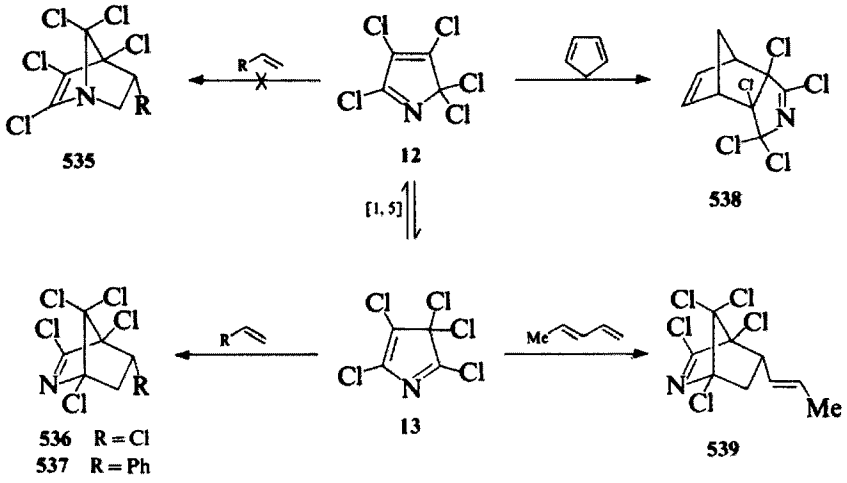


4.5.7.2. [4+2](Diels–Alder)Cycloadditions

As 2*H*- and 3*H*-pyrroles are azacyclopentadienes, and 3*H*-pyrrol-3-ones are azacyclopentadienones, they can reasonably be expected to take part in Diels–Alder reactions. A number of these cycloadditions have been reported.

4.5.7.2.1. 2,2,3,4,5-Pentachloro-2*H*-pyrrole

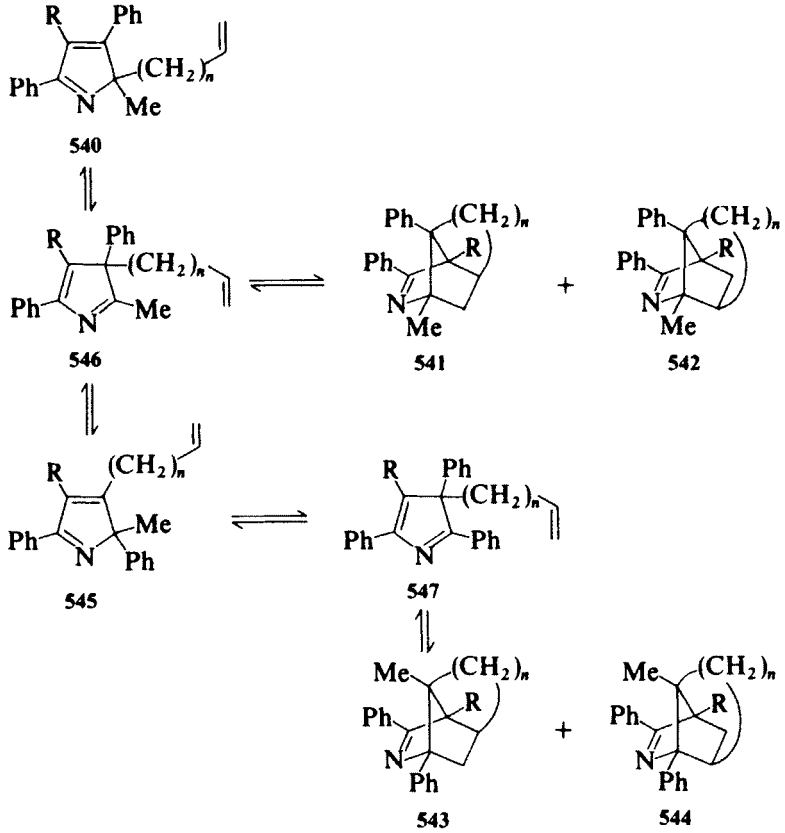
The reaction between pentachloro-2*H*-pyrrole **12** and norbornadiene, cyclopentadiene, ehtene, and certain mono- and 1,1-disubstituted ethenes was observed to yield 1 : 1 adducts, some of which were patented as insecticides.[384–386] Initially, the adducts were assigned structures with a bridgehead nitrogen atom, such as **535**,[25,383] but later X-ray-crystallographic studies on two adducts showed their structures to be **536**[387] and **537**,[70] derived from the 3*H*-pyrrole **13** via a [1,5]-chlorine shift. Simple calculations, based on bond enthalpies, show that adducts derived from 3*H*-pyrroles should be about 88 kJ mol^{-1} more stable than those from isomeric 2*H*-pyrroles.[359] Subsequent work has shown that pentachloropyrrole reacts in the form **12** as a dienophile at the C_3–C_4 double bond with cyclopentadiene to give **538**, in the form **13** as an azadiene with cyclopentene, cyclohexene, and 1,3-pentadiene to give **539**, and in both forms (**12** and **13**) with cyclohexadiene to give two isomeric products.[114] The carbon–chlorine bond in the imidoyl chloride function of adducts derived from **13** is particularly resistant to hydrolysis.[359,388]



4.5.7.2.2. Intramolecular Cyclizations

2*H*-Pyrroles bearing a 3-butenyl or a 4-pentenyl substituent at C_2, C_3, or C_4 undergo in a series of [1,5]-sigmatropic rearrangements at temperatures in the range 165–245°C to an interconverting mixture of isomeric 2*H*- and 3*H*-pyrroles, the latter cyclizing reversibly to tricyclic adducts.[101,340] For example,

structures **540** (R = H, Me; n = 2, 3) form mixtures of adducts **541–544**, the relative proportions depending on R, n, the temperature, and the duration of the reaction. The rate is increased by addition of a Lewis acid or a cation–radical, and no products are observed from the cyclization of isomeric 1*H*- or 2*H*-pyrroles. From determinations of free energies of activation, and from MO calculations on model compounds, it was concluded that the energy barriers to cyclization of 2*H*-pyrroles, for example, **540** and **545**, were higher than the barriers to rearrangement to the 3*H*-pyrroles **546** and **547**, which were higher again than barriers to formation of adducts **541–544**. The rate determining step was thus the conversion of a 2*H*- into a 3*H*-pyrrole.[101]

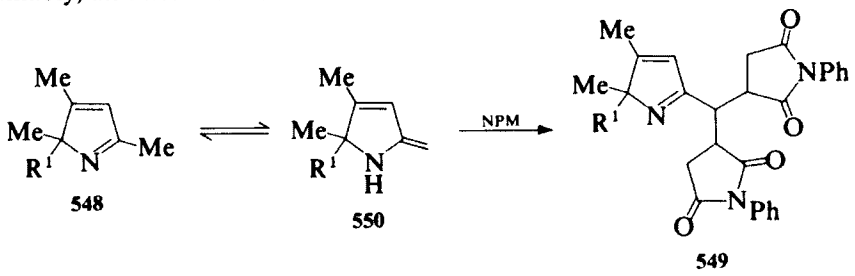


X-Ray crystallographic studies on four tricyclic adducts revealed pyramidalization of the imine carbon atom by 1.2–4.9° by bending toward the endo face, which is consistent with ab initio (STO-3G) calculations.[389]

4.5.7.2.3. Other 2*H*-Pyrroles

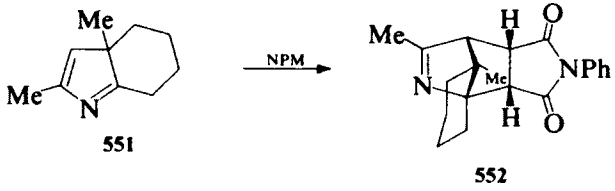
The reluctance of 2*H*-pyrroles to react as azadienes in Diels–Alder reactions is further demonstrated by their reactions with dienophiles at temperatures sufficiently low to prevent significant rearrangement to the 3*H*-isomers. The

formation of the rearranged 1 : 1 adduct **415** from the 2,2-diester **205**[89] and from other 2*H*-pyrroles[343] with DMAD or methyl propynoate were mentioned in Section 4.5.2.2. In addition, compounds **548** (R^1 = Me, Ph) react with excess NPM to yield the 1:2 adducts **549** rather than Diels–Alder products. Presumably, an intermediate enamine **550** is involved.[390]



4.5.7.2.4. 3*H*-Pyrroles

In contrast to the reactions of **548**, and consistent with the discussion in Section 4.5.7.2.2, a number of alkyl and aryl 3*H*-pyrroles **2**, or their mixtures with exocyclic isomers **267** and **268**, cleanly give, on heating with NPM in benzene; high yields of Diels–Alder adducts. An example is the conversion of **551** into **552**; the structure of the latter has been confirmed by X-Ray crystallography.[390]

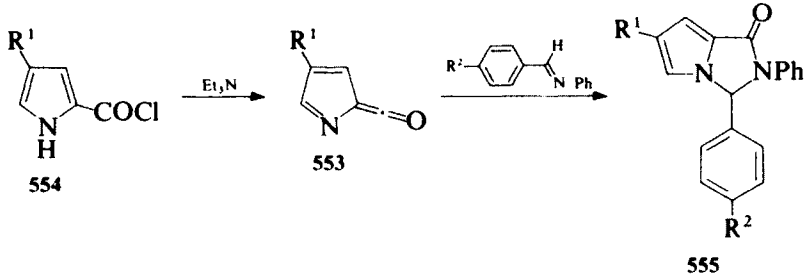


4.5.7.2.5. 3*H*-Pyrrol-3-ones

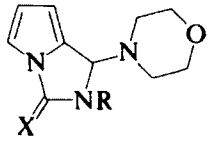
Compound **9** reacts with DMAD, presumably with extrusion of carbon monoxide in analogy with tetracyclone, to form the pyridine **526**.[57] The 3*H*-pyrrol-3-one **302** reacts similarly.[313]

4.5.7.3. [6+2]Cycloadditions

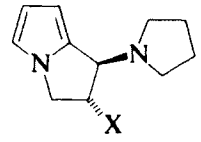
Ketenes **553** (R^1 = H, NO_2), generated from 1*H*-pyrrole-2-carbonyl chlorides **554** with triethylamine, add to benzylidene anilines to form the adducts **555** (R^2 = H, OMe).[391] Similarly, 6-dialkylamino-1-azafulvenes, formed in situ by thermolysis of dimers, react with isocyanates and isothiocyanates to give products of the general structure **556** (X = O, S) in a two step sequence via dipolar intermediates.[250] The trans-adducts in **557**, which eliminate the secondary amine on heating, are formed with electron-deficient alkenes (X = CO_2R,



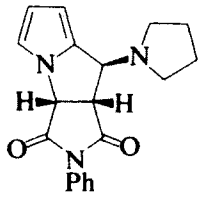
554 553 555



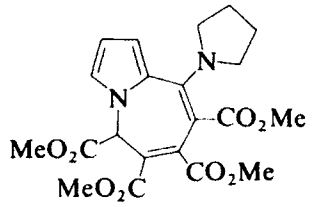
556



557



558



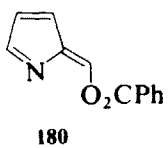
559

COMe), while NPM gives the endo-adduct **558**.[365] Then 2 mol of DMAD react to yield **559**.[366]

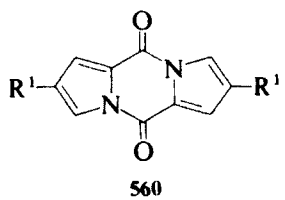
4.5.7.4. [6+6]Cyloadditions

The spontaneous dimerization of 6-dialkylamino-1-azafulvenes to structures such as **159** and **185** has already been mentioned (see Section 4.4.1.10),[234,248,250,365,392] and the dimer **159** has been dilithiated and reacted with a range of electrophiles to give, on workup, excellent yields of 5-substituted-1*H*-pyrrole-2-aldehydes (see Section 3.4.3.4.3).[393] It is possible that the 1-azafulvene **180** (m.p. 178°C)[246] may also be a dimer.

The ketenes **553** dimerize to **560** in the absence of other reactive species.[73,391]



180



560

4.6. REFERENCE TABLES TO PREPARATIONS AND PHYSICAL PROPERTIES

In Tables 4.34–4.55, known compounds are listed in the following order: 2*H*-pyrroles, 3*H*-pyrroles, 1-azafulvenes, 2-azafulvenes, 2*H*-pyrroles with an exocyclic C=X bond, and 3*H*-pyrroles with an exocyclic C=X bond. *N*-oxides and salts, where they are known, follow tables for the respective bases.

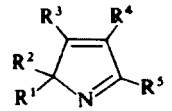
Compounds are listed in the order of increasing numbers of alkyl and alkenyl groups: aryl; haloalkyl; ester, acyl, and nitrile; *O*-linked; *N*-linked; *S*-linked; and halogen groups.

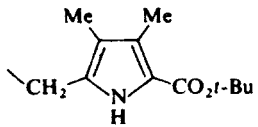
Data include cross-reference to the section describing the preparative method, yields, melting or boiling point, and literature references. The latter are followed by lowercase letters (in Tables 4.34–4.54) indicating that the paper includes information according to the key:

a. UV spectra
b. IR spectra
c. ^{1}H NMR spectra
d. ^{13}C NMR spectra
e. ^{19}F NMR spectra
f. NMR coupling constants
g. Mass spectra
h. X-Ray diffraction
i. MO calculations
j. Optical rotation
k. pK_a measurements
l. Dipole moments
m. Refractive index
n. Picrate derivatives

For 1- and 2-azafulvenes, the geometry of the C_6 substituents has in most cases not been determined. As a general rule, the most bulky of the two groups in 1-azafulvenes tends to be syn to the ring nitrogen atom, unless the latter can form an intramolecular hydrogen bond with a (smaller) OH or NHR group at C_6.

TABLE 4.34. 2*H*-PYRROLES BEARING ONLY ALKYL OR ARYL GROUPS



Substituent								
R^1	R^2	R^3	R^4	R^5	Preparation (Sect. No.)	Yield (%)	Melting or Boiling Point [°C (mm)]	Ref.
$PhCH_2$	$PhCH_2$	H	H	H	4.4.2.1.1	89	78–79	78bcdfg, 242
Me		H	H	H	4.4.1.4.1	22		78cf, 242
Me	*n*-Pr	H	H	Me	4.4.1.1.1			63bcf
Me	$CH_2CH{=}CH_2$	H	H	Me	4.4.1.1.1	28	50(11)	7abcfm, 63bcf
Me	$(CH_2)_3CN$	H	H	Me	4.4.1.1.1	10	100(0.2)	72an
Me	$MeCHCH{=}CH_2$	H	H	Me	4.4.1.3	18		7abcm
Me	*cis*-$CH_2CH{=}CHMe$	H	H	Me	4.4.1.3	12		7abcm
Me	*trans*-$CH_2CH{=}CHMe$	H	H	Me	4.4.1.3	10		7abcm
Et	$MeCHCH{=}CH_2$	H	H	Me	4.4.1.3	5		7abcm
Me	$MeCHCH{=}CH_2$	H	H	Et	4.4.1.3			7abcm
Et	*cis*-$CH_2CH{=}CHMe$	H	H	Me	4.4.1.3	4		7abcm
Et	*trans*-$CH_2CH{=}CHMe$	H	H	Me	4.4.1.3	7		7abc
Me	*cis*-$CH_2CH{=}CHMe$	H	H	Et	4.4.1.3			7abc
Me	*trans*-$CH_2CH{=}CHMe$	H	H	Et	4.4.1.3	4		7abcm
Me	$PhCH_2$	H	H	Me	4.4.1.1.1	10	116(13)	79bcn
Me	PhCHMe	H	H	Me	4.4.1.3	12	113–114(9)	264abcjm

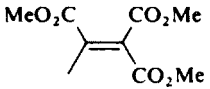
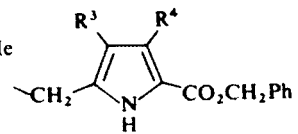
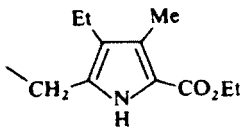
Me		H	H	Me	4.4.1.1.2	15	82–84	100bcdf
Me	Me	Me	H	H	4.4.1.1.1			161n
Me	Me	H	Me	Me	4.4.1.1.1		36–45(14)	8an
					4.4.1.4.2	88	74(85)	272m, 273, 370
Me	Me	Me	H	Me	4.4.1.1.1		30–36(14)	8an
					4.5.1.2.2	50	45(24)	11k, 13abcdmn
Me	Et	Me	H	Me	4.4.1.1.1		54–56(12)	8an
					4.5.1.2.2	40	65(40)	13abcdm
Me	Me	Et	H	Me	4.4.1.1.1		70–72(11)	8an
Me	$CH{=}C{=}CMe_2$	Me	H	Me	4.4.1.1.3	5.8	50–51(0.15)	64abcfg
$(CH_2)_4$		Me	H	Me	4.5.1.2.2	60	85(25)	13abcdmn
Me	Et	Me	Me	H	4.4.1.1.1		74–78(14)	8an
Me	Me	Et	Me	H	4.4.1.1.1		75–95(22)	8an
Me	$(CH_2)_3CN$	Me	Me	H	4.4.1.1.1	6	120(0.2)	72bn
Me	$CH{=}C{=}CMe_2$	Me	Me	H	4.4.1.1.3	8.6	103–104(17)	64abcfg
$PhCH_2$	$PhCH_2$	Me	Me	H	4.4.1.2.3	60	Oil	78bcfg
Me		CH_2CO_2Me	$(CH_2)_2CO_2Me$	H	4.4.1.2.3	45		167
Me	Me	Me	Me	Me	4.4.1.1.1		160; 88–90(75)	155, 160n
					4.4.1.1.1	32–63	51–53(12); 84–85(53)	8amn, 26abc, 34b
Me	Et	Me	Me	Me	4.4.1.1.1	47, 64	98–100(72)	8an, 26abc
Me	Et	CD_3	Me	Me	4.5.1.2.2			131
Me	Me	Et	Me	Me	4.4.1.1.1		85–90(40)	8an
Me	Me	Me	Me	Et	4.4.1.1.1			8
Me	$(CH_2)_3CN$	Me	Me	Me	4.4.1.1.1	14	100(1)	72abn
Me	$CH{=}C{=}CMe_2$	Me	Me	Me	4.4.1.1.3	9	53–54(0.2)	64abcg

TABLE 4.34. (*Contd.*)

Substituent								
R^1	R^2	R^3	R^4	R^5	Preparation (Sect. No.)	Yield (%)	Melting or Boiling Point [°C (mm)]	Ref.
Me		Me	Me	Me	4.4.1.1.1		85	72an
Me	$(CH_2)_4$		Me	Me	4.4.1.1.1			166
					4.5.1.2.2			13abcd
Me	Et	Me	Et	Me	4.4.1.1.1		95–100(32)	8an
$PhCH_2$	$PhCH_2$	Me	Me	Me	4.4.1.1.1	47		34abn
Me	$PhCH_2$	Me	Me	$PhCH_2$	4.4.1.1.1	47	155(0.03)	34abn
Me	Me	H	H	Ph	4.4.3.6	40–74	55–60(0.01)	10d, 324abcfg, 349
					4.4.5.2	37	19–20; 55(3)	9abcdfg, 348d
Me	Me	H	Ph	H	4.4.5.2	80	16.5–17.5; 65(4)	9abcdfg, 348d
					4.4.5.2	74		349
Me	*trans*-$CH_2CH{=}CHMe$	Ph	H	H	4.4.5.1	28		341, 344bcdfg
Me	Ph	Me	H	Me	4.5.1.2.2	60		13abcd
Me	Me	Ph	H	Me	4.4.1.4.2	38	110(0.1)	272, 370
Me	Me	Ph	H	*i*-Pr	4.4.5.1	61		12abcdg
Me	Me	Ph	H	Me_2COH	4.5.4		85–88	12abcdg
Me	Me	Me	H	Ph	4.5.1.2.2	80		11k, 13abcd
					4.4.3.6	20	75–85(0.01)	10abcdfg
Me	Me	Ph	Et	H	4.4.5.1	41		341, 344bcg
Me	$CH_2CH{=}CH_2$	Ph	Et	H	4.4.5.1	35		80bcg
Me	*trans*-$CH_2CH{=}CHMe$	Ph	Et	H	4.4.5.1	51		341, 344bcdg
Me	Me	H	Ph	Ph	4.4.1.4.2	43	65–67	40bcd
Ph	$CH_2CH{=}CH_2$	Ph	H	Me	4.4.5.1			83

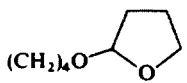
Me	Ph	Me	H	Ph	4.4.5.1	57	70–71	12abcdfg, 339abcg
					4.5.1.2.2	65	70	13abcd
Me	Ph	$(CH_2)_2CH{=}CH_2$	H	Ph	4.4.5.1	23	Oil	101bcg
Ph	$(CH_2)_2CH{=}CH_2$	Me	H	Ph	4.4.5.1	33	95–95.5	101bcg
Ph	$(CH_2)_3CH{=}CH_2$	Me	H	Ph	4.4.5.1	2	Oil	101cf
Me	Me	Ph	H	Ph	4.4.5.1	75	59–61	12abcdg, 81abcg
Me	$CH_2CH{=}CH_2$	Ph	H	Ph	4.4.5.1	87		80bcg, 83c
Me	$(CH_2)_3OH$	Ph	H	Ph	4.5.4	56		80bc
Me	$(CH_2)_2CH{=}CH_2$	Ph	H	Ph	4.4.5.1	88		80bcg
Me	$(CH_2)_4OH$	Ph	H	Ph	4.4.5.1	16		80bcg
Me		Ph	H	Ph	4.4.5.1	51		80bcg
Me	$(CH_2)_3CH{=}CH_2$	Ph	H	Ph	4.4.5.1	74	Oil	101bcg
Me	$PhCH_2$	Ph	H	Ph	4.4.5.1	53		344bcg
$(CH_2)_5$		Ph	H	Ph	4.4.5.1	65	112–114	12abcdg, 81abcg
Me	Me	4-Pyridyl	H	Ph	4.4.1.4.2	98	115	271bcg
$(CH_2)_5$		4-Pyridyl	H	Ph	4.4.1.4.1	71	110–112	271bcg
Me	Me	4-(2-Methyl)pyridyl	H	Ph	4.4.3.6	59	113–114	115bcg
Me	Me	Ph	H	3-Pyridyl	4.4.1.4.2	67	93–94	274bn
Me	Me	4-Pyridyl	H	$4\text{-}ClC_6H_4$	4.4.1.4.2	90	126	271bcg
Me	Me	4-Pyridyl	H	$4\text{-}MeOC_6H_4$	4.4.1.4.2	89	115	271bcg
Me	Me	Ph	Ph	H	4.4.5.1	33		341, 344bcg
Ph	Ph	H	Ph	Me	4.4.1.4.3	100	113–115.5	282b
Me	Me	Ph	Me	Et	4.4.5.1	20	Oil	12abcdg
Me	Me	Ph	$(CH_2)_5$		4.4.5.1	69	74–76	12abcdg
Ph	$(CH_2)_2CH{=}CH_2$	Me	Me	Ph	4.4.5.1	3	Oil	101bc
Ph	$(CH_2)_3CH{=}CH_2$	Me	Me	Ph	4.4.5.1	2	Oil	101c
Me	Ph	Me	$(CH_2)_2CH{=}CH_2$	Ph	4.4.5.1	2	Oil	101cdg
Me	Me	Ph	Me	Ph	4.4.5.1	80	95–96	12abcg, 81abcg
Me	Me	Ph	CH_2OH	Ph	4.5.4	20–53	186–188	343bcdg
Me	$CH_2CH{=}CH_2$	Ph	Me	Ph	4.4.5.1			83

TABLE 4.34. (*Contd.*)

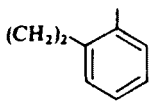
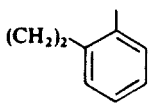
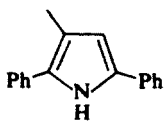
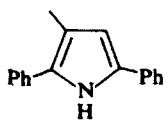
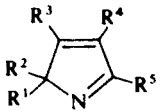
Substituent								
R^1	R^2	R^3	R^4	R^5	Preparation (Sect. No.)	Yield (%)	Melting or Boiling Point [°C (mm)]	Ref.
Me	$(CH_2)_2CH{=}CH_2$	Ph	Me	Ph	4.4.5.1	66	Oil	101bcg
Me	$(CH_2)_3CH{=}CH_2$	Ph	Me	Ph	4.4.5.1	67	Oil	101bcg
Me	$PhCH_2$	Ph	Me	Ph	4.4.5.1	60	Oil	344bcg
Me	Me	Ph	$(CH_2)_2CH{=}CH_2$	Ph	4.4.5.1	75	81–82	101bcg
Me	Me	Ph	$(CH_2)_3CH{=}CH_2$	Ph	4.4.5.1	68	82–84	101bcg
Me	Me	Ph			4.4.5.1	37	64–66	12abcdg
Me	$(CH_2)_3CH{=}CH_2$	Ph			4.4.5.1	31		101cdg
Ph			H	Ph	4.4.1.1.5	27	170	200abc

TABLE 4.35. 2*H*-PYRROLES BEARING ONLY HALOALKYL WITH ALKYL OR ARYL GROUPS



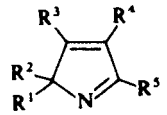
Substituent					Preparation (Sect. No.)	Yield (%)	Melting or Boiling Point [°C (mm)]	Ref.
R^1	R^2	R^3	R^4	R^5				
Me	$CHCl_2$	H	H	Me	4.4.1.1.3	11, 7, 6	93(10)	14abc, 66abcf, 172n, 174
Me	$CHCl_2$	H	H	*t*-Bu	4.4.1.1.3	9	62–65; 80(5)	65abcf
					4.4.1.1.3	40–100		175
Me	CCl_2HgCl	H	H	*t*-Bu	4.4.1.1.3	27	131–132	133bcfh
Me	CCl_2HgPh	H	H	*t*-Bu	4.4.1.1.3	5	108–109	133bcfh, 175bcfh
Me	$CHCl_2$	Me	Me	Me	4.4.1.1.3	12–44	86–88	14abc, 66abcf, 173n, 174
Me	Me	Ph	H	CH_2Cl	4.5.2.4	12	Oil	343c
Me	Me	Ph	H	$CHCl_2$	4.5.2.4	24–35	130–132	343bcdg
Me	Me	Ph	H	CCl_3	4.5.2.4	6–84	57–59	343bcdg
Me	Me	Ph	H	$CHBr_2$	4.5.2.4	10	140–142	343cdg
Me	Ph	CCl_3	H	Ph	4.5.2.4	19		343c
Me	Ph	CH_2Br	H	Ph	4.5.2.4	6		343c
Me	Me	Ph	$-(CH_2)_3CCl_2-$		4.5.2.4	18	119–121	343cg

TABLE 4.35. (*Contd.*)

Substituent					Preparation (Sect. No.)	Yield (%)	Melting or Boiling Point [°C (mm)]	Ref.
R^1	R^2	R^3	R^4	R^5				
Me	Me	Ph	$-(CH_2)_3CHBr-$		4.5.2.4	21		343c
Me	Me	Ph	$-(CH_2)_3CBr_2-$		4.5.2.4	22	105–107	343bcg
Me	Me	Ph	CH_2Br	Ph	4.5.2.4	72	125–127	343bcdg
Ph	$CHCl_2$	Me	Me	Ph	4.4.1.1.3	8	127	66abc
CF_3	CF_3	H	H	*t*-Bu	4.4.3.6	81	28; 41(12)	67bcef
CF_3	CF_3	H	H	Ph	4.4.3.6	61	73	67bce
CF_3	CF_3	H	Ph	*t*-Bu	4.4.3.6	15	38(0.05)	67bce
CF_3	CF_3	H	Ph	Ph	4.4.3.6	14.5	150	67bce
CF_3	CF_3	H	Ph	4-MeC_6H_4	4.4.3.6	—[a]		67bce
CF_3	CF_3	H	Ph	4-FC_6H_4	4.4.3.6	15	112	67bce
CF_3	CF_3	H	Ph	4-ClC_6H_4	4.4.3.6	—[a]		67bce
CF_3	CF_3	Ph	H	*t*-Bu	4.4.3.6	31	50(0.05)	67bce
CF_3	CF_3	Ph	H	Ph	4.4.3.6	11.5	82	67bce
CF_3	CF_3	Ph	H	4-MeC_6H_4	4.4.3.6	—[a]		67bce
CF_3	CF_3	Ph	H	4-FC_6H_4	4.4.3.6	13	71	67bce
CF_3	CF_3	Ph	H	4-ClC_6H_4	4.4.3.6	—[a]		67bce
CF_3	CF_3	Ph	Ph	*t*-Bu	4.4.3.6	15, 43	143	67bce, 314b
CF_3	CF_3	Ph	Ph	Ph	4.4.3.6	39	123	67bce

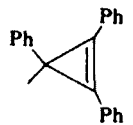
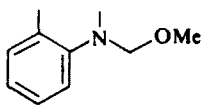
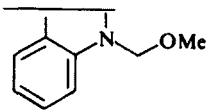
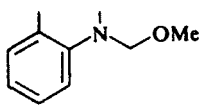
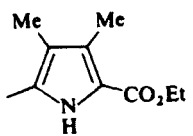
[a] Inseparable mixture with regioisomer.

TABLE 4.36. 2*H*-PYRROLES BEARING ESTER, ACYL, OR NITRILE AND OTHER GROUPS



Substituent					Preparation (Sect. No.)	Yield (%)	Melting or Boiling Point [°C (mm)]	Ref.
R^1	R^2	R^3	R^4	R^5				
Me	Me	H	H	CO_2Et	4.4.2.1.3	43	86–88(2)	15abcfg
$(CH_2)_5$		H	H	CO_2Me	4.4.2.1.3	36	Oil	15bcdfg
CF_3	CF_3	H	CO_2Me	H	4.4.3.6	85	40(0.15)	68bce
Me	Me	H	SR[a]	CO_2Me	4.4.1.4.1	33	Oil	269bcg
CO_2Et	Me	Me	H	Me	4.5.1.1.3	35	Oil	28abcdg, 154bcdf
CO_2Et	Me	Me	H	*t*-Bu	4.5.1.1.3	38	Oil	28abcdg
Me	Me	CO_2Et	H	NMePh	4.4.3.6	16	100–110(0.01)	328, 329abcg
CF_3	$(CH_2)_2COMe$	H	CO_2Me	*i*-Pr	4.4.3.6	51	98(0.2)	320c
CF_3	$(CH_2)_2COMe$	CO_2Me	H	*i*-Pr	4.4.3.6			
CF_3	CF_3	H	CO_2Me	*t*-Bu	4.4.3.6			315b, 316bc
CF_3	CF_3	CO_2Me	H	*t*-Bu	4.4.3.6			
					4.4.3.6	80	57; 98(12)	315b, 316bc
CO_2Et	Me	Me	Me	Me	4.5.1.1.3	32	Oil	28abcdg
Me	CH_2CO_2Et	Me	CO_2Et	Me	4.4.5.4	65	Oil	36acg
Me	OH	NH_2	CO_2Et	Me	4.4.1.1.5	50	187	105bcdh
Me	OH	NH_2	COMe	Me	4.4.1.1.5	50	165	105bcd
Me	Ph	H	H	CO_2Et	4.4.2.1.3			284cf
CO_2Et	Me	Me	H	Ph	4.5.1.1.3	30	Oil	28abcdg
Me	Me	H	CO_2Me	Ph	4.4.3.6	2	Oil	19bcg
Me	Me	CO_2Me	H	Ph	4.4.3.6	57	Oil	19bcg

Table 4.36. (*Contd.*)

Substituent					Preparation (Sect. No.)	Yield (%)	Melting or Boiling Point [°C (mm)]	Ref.
R^1	R^2	R^3	R^4	R^5				
Me		CO_2Me	H	Ph	4.4.3.6	30	159–160	323abc
Me	Me	Ph	CO_2Me	H	4.4.5.1	5	59–61	17abcdg, 346abc
CF_3	CF_3	H	CO_2Me	Ph	4.4.3.6			315b, 316bc
CF_3	CF_3	CO_2Me	H	Ph	4.4.3.6			
					4.4.3.6		15	315b, 316bc
CO_2Me	$CH_2CH{=}CH_2$	H			4.4.1.1.1 4.4.1.3	13, 62	87–89	164abcdgh
CO_2Me	$CH_2CMe{=}CH_2$	H			4.4.1.1.1 4.4.1.3	11, 50	Gum	164abcdg
CO_2Me	$CH_2CH{=}CMe_2$	H			4.4.1.1.1 4.4.1.3	56	Gum	164abcdg
CO_2Et	$CHCl_2$	Me	Me		4.4.1.1.3	32	134.5–136	176ab

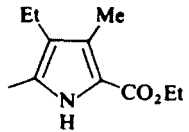
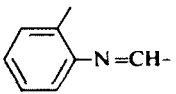
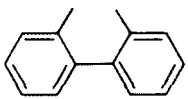
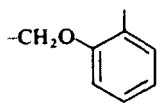
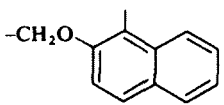
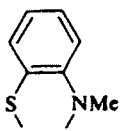
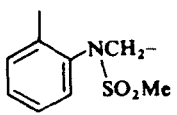
CO_2Et	$CHCl_2$	Me	Et		4.4.1.1.3	22	102.5–104	176abc
		CO_2Me	CH_2CO_2Me	OEt	4.4.1.1.2	13	116	92bc
Ph	OH	NH_2	CO_2Et	Me	4.4.1.1.5	15	173	105bcd
Ph	Ph	H	H	CO_2Et	4.4.2.1.3	82	94	284bcf
		H	H	CO_2Et	4.4.2.1.3	88	105–106	284b
CO_2Me	Ph	H			4.4.3.6.4	7.5	88–90	333bcg
CO_2Me	Ph	H			4.4.3.6.4	10		333bcg
Me	Me	CO_2Et	Ph	Ph	4.4.3.6	35	102.3–103.3	17d, 19abcg
Me	Me	Ph	CO_2Et	Ph	4.4.3.6	12	101–103	19abcg
CF_3	CF_3	CO_2Me	CO_2Me	H	4.4.3.6	80	65(0.01)	68bce
Me	Me	CO_2Me	CO_2Me	NMePh	4.4.3.6	43	83.1–83.5	17d, 328, 329abcg
$(CH_2)_5$		CO_2Me	CO_2Me	SCH_2Ph	4.4.3.6	52	100(0.001)	322
CF_3	$(CH_2)_2COMe$	CO_2Me	CO_2Me	$CHMe_2$	4.4.3.6	82	112(0.01)	320bc
CF_3	CF_3	CO_2Me	CO_2Me	*t*-Bu	4.4.3.6	68	61	314b, 316bc

Table 4.36. (*Contd.*)

Substituent					Preparation (Sect. No.)	Yield (%)	Melting or Boiling Point [°C (mm)]	Ref.
R^1	R^2	R^3	R^4	R^5				
$CHBr_2$	OH	CO_2Et	Me	CO_2Et	4.4.1.1.4	30	152	187
CBr_3	OH	CO_2Et	Me	CO_2Et	4.4.1.1.4	6	125	188bc
CO_2Et	OH	Me	CO_2Et	$CHBr_2$	4.4.1.1.4	12	131	188bc
CO_2Et	OH	Me	CO_2Et	CBr_3	4.4.1.1.4	6	145	188bc
		CO_2Me	CO_2Me	SMe	4.4.3.7	30	245	334abc, 335abc
CO_2Et	CO_2Et	$3\text{-}ClC_6H_4$	H	Me	4.4.2.2.1	74	79–80	295abc, 297, 298
CO_2Et	CO_2Et	$3\text{-}BrC_6H_4$	H	Me	4.4.2.2.1	52	77.5–78	296, 297, 298
Me	Me	CO_2Me	CO_2Me	Ph	4.4.3.6	55, 69	61–61.5	17d, 18abcg, 330bcd
Me	$CH_2CH{=}CH_2$	CO_2Me	CO_2Me	Ph	4.4.3.6	55	58–60	325bcg
Me	$(CH_2)_3CH{=}CH_2$	CO_2Me	CO_2Me	Ph	4.4.3.6	78	Oil	326abcg
Me	$(CH_2)_2CH{=}CHCO_2Me$	CO_2Me	CO_2Me	Ph	4.4.3.6	93	Oil	326abcg
		CO_2Et	Me	CO_2Et	4.4.1.1.2	81	121–122.5	168abc
Me	Me	Ph	CO_2Me	CO_2Me	4.4.5.1	28	103.5–105	17abcdg, 346abcd
Me	Me	Ph	CO_2Et	CO_2Et	4.4.5.1	20	92.5–93	17abcdg, 346abc
CF_3	CF_3	CO_2Me	CO_2Me	Ph	4.4.3.6	25–70	97–98	314b, 316bc, 317b, 319b
CF_3	CF_3	CO_2Me	CO_2Me	$4\text{-}MeC_6H_4$	4.4.3.6	23–78	58; 62.5–63	108bce, 316bc, 317b, 319b

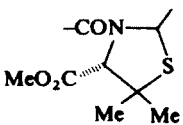
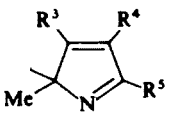
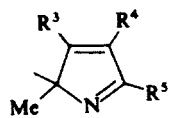
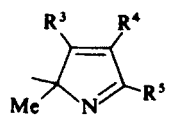
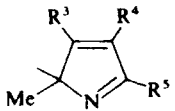
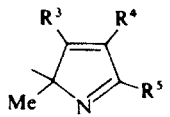
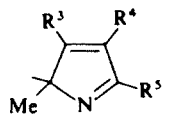
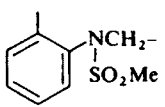
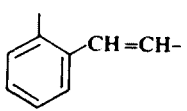
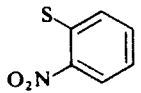
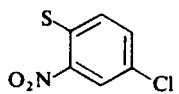
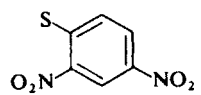
CO_2Et	CO_2Et	Ph	H	Ph	4.4.1.4.1	63	97	102d, 268bc
					4.4.2.2.1	46		268bc
CO_2Et	CO_2Et	Ph	H	$4\text{-}MeC_6H_4$	4.4.1.4.1	10	101	102bcd
CO_2Et	CO_2Et	Ph	H	$4\text{-}ClC_6H_4$	4.4.1.4.1	65	90	102d, 268bc
CO_2Et	CO_2Et	Ph	H	$3\text{-}NO_2C_6H_4$	4.4.1.4.1	82	144	102d, 268bc
CO_2Et	CO_2Et	Ph	H	$4\text{-}NO_2C_6H_4$	4.4.1.4.1	60	119–121	102d, 268bc
CO_2Et	CO_2Et	$4\text{-}MeC_6H_4$	H	Ph	4.4.1.4.1	72	112–113	102d, 268bc
CO_2Et	CO_2Et	$4\text{-}MeOC_6H_4$	H	Ph	4.4.1.4.1	58	104	102d, 268bc
CO_2Et	CO_2Et	$4\text{-}ClC_6H_4$	H	Ph	4.4.1.4.1	78	133	102d, 134h, 268bc
CO_2Et	CO_2Et	$3\text{-}NO_2C_6H_4$	H	Ph	4.4.1.4.1	80	130	102d, 268bc
CO_2Et	CO_2Et	$4\text{-}NO_2C_6H_4$	H	Ph	4.4.1.4.1	63	122	102d, 268bc
CO_2Et	CO_2Et	$4\text{-}ClC_6H_4$	H	$4\text{-}ClC_6H_4$	4.4.1.4.1	75	123	102d, 268bc
$4\text{-}ClC_6H_4$	$CH_2CH{=}CMe_2$	CO_2Me	CO_2Me	Ph	4.4.3.6			321c
		CO_2Me	CO_2Me	Ph	4.4.3.6			331
Me		COMe	Ph	Ph	4.4.1.1.5	High	130–142 dec.	121bc
Me		COMe	Ph	$4\text{-}MeOC_6H_4$	4.4.1.1.5	High	150–155 dec.	121bc
Me		COMe	$4\text{-}MeOC_6H_4$	Ph	4.4.1.1.5	High	130–155 dec.	121bc

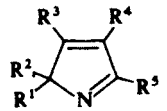
Table 4.36. (*Contd.*)

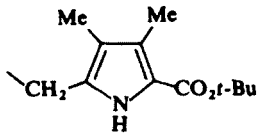
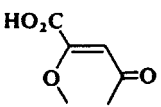
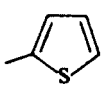
Substituent					Preparation (Sect. No.)	Yield (%)	Melting or Boiling Point [°C (mm)]	Ref.
R^1	R^2	R^3	R^4	R^5				
Me		COMe	4-$MeOC_6H_4$	4-$MeOC_6H_4$	4.4.1.1.5	High	150–155 dec.	121bc
Me		COEt	4-$MeOC_6H_4$	4-$MeOC_6H_4$	4.4.1.1.5	High	140–145 dec.	121bc
Me		COPh	4-$MeOC_6H_4$	4-$MeOC_6H_4$	4.4.1.1.5	High	185–190	121b
		COMe	Me	CO_2Et	4.4.1.1.2	77	93–95	169abc
CN	Me	H	H	NHPh	4.5.7.1.1	11	148–150	354, 355bcf
Me	Me	CN	H	Ph	4.4.3.6	55, 80	50.6–51.5	16abcdg
Me			CN	H	4.4.5.2	25	148–149.5	350bcf

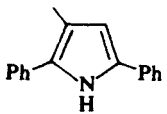
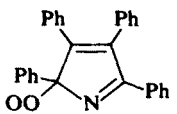
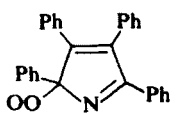
CN	CO_2Et	3,4-$Me_2C_6H_3$	H	4-$MeOC_6H_4$	4.4.3.5	8	157–159	103bcd
CN	CO_2Et	4-$MeOC_6H_4$	H	3,4-$Me_2C_6H_3$	4.4.3.5	15	145–146	103bcd
CN	$(CH_2)_2CO_2Et$	OEt	CO_2Et	Me	4.4.1.2.1	14	Oil	243abcd
CN	Me	CO_2Me	CO_2Me		4.4.3.6	65	104–105	332c
CN	Me	CO_2Me	CO_2Me		4.4.3.6	80	165–166	332c
CN	Me	CO_2Me	CO_2Me		4.4.3.6	30	144–146	332c
CN	CN	H	H	Ph	4.4.2.1.3	14	145–146	285bc
CF_3	CF_3	CN	CN	Ph	4.4.3.6	43	59	109bc, 110bce

[a] R = $(CH_2)_2NHCO_2CH_2(4\text{-}NO_2C_6H_4)$.

TABLE 4.37. 2*H*-PYRROLES BEARING ONLY *O*-LINKED SUBSTITUENTS AND ALKYL OR ARYL GROUPS

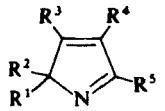


Substituent					Preparation (Sect. No.)	Yield (%)	Melting or Boiling Point [°C (mm)]	Ref.
R^1	R^2	R^3	R^4	R^5				
H	H	Me	Me	OMe	4.4.1.2.1		65(12)	20aik, 46acik
OOH	*t*-Bu	H	H	*t*-Bu	4.4.1.1.6	60	138–139	21abc
Me		H	H	OEt	4.4.1.2.1	72		78bcfg
OH	*t*-Bu	*t*-Bu	H	*t*-Bu	4.5.5.1.2	66	137	21bc
OOH	*t*-Bu	*t*-Bu	H	*t*-Bu	4.4.1.1.6	78	142–143	21abc
Me	Me	OMe	H	Me	4.4.2.1.1	55	55–56(8)	22abm, 276
	CH=CHCOCH=CH	Ph	H	OEt	4.4.2.2.2	57	125	104bcdg
OH	$(CH_2)_4$		H	Ph	4.5.5.1.2	100	154–155 dec.	204ab
OOH	$(CH_2)_4$		H	Ph	4.4.1.1.6	100	126–128 dec.	204abc
OOH	$(CH_2)_4$		H	4-MeC_6H_4	4.4.1.1.6	100		204
OOH	$(CH_2)_4$		H	4-ClC_6H_4	4.4.1.1.6	100		204
OOH	$(CH_2)_4$		H	4-BrC_6H_4	4.4.1.1.6	100		204
Me	Me				4.4.3.6	7.4	> 210	327bc

OH	Ph	H	H	Ph	4.5.5.1.2	50	169–174 dec.	69ab
OOH	Ph	H	H	Ph	4.4.1.1.6	50	168–173 dec.	69ab
Me	Me	4-(2-Methyl)pyridyl	OMe	Ph	See ref.	54	82.5–84	115bcg
Me	Me	4-(2-Methyl)pyridyl	OAc	Ph	4.5.2.3	52	122.5–124	115bcg
OH	Ph	Ph	H	Ph	4.4.3.1.1	70–80	180–182	189a, 191, 192, 303
OH	Ph		H	Ph	4.4.1.1.5	33	178	200abc
OH	Ph	Ph	Ph	Ph	4.4.1.1.5		171–173; 178–181	189,190ab
					4.4.1.1.7	60		209
							178–181; 180–182	190ab, 193ab
					4.4.3.1.1	95	204–205	69ab, 202ab
					4.5.5.1.2	90	204–205	69ab, 195, 196, 202ab
					4.5.3.1.3	72	168–170	197
OMe	Ph	Ph	Ph	Ph	4.5.3.1.1	56, 60	122–124	69ab, 190abc, 195ab
					4.4.1.1.7	80	124	208c
OEt	Ph	Ph	Ph	Ph	4.4.1.1.7	35	89	208c
O_2CPh	Ph	Ph	Ph	Ph	4.4.1.1.5	53	251–252	197bc
OOH	Ph	Ph	Ph	Ph	4.4.1.1.6	89–90	170–172 dec.	69ab, 195, 202ab
	Ph	Ph	Ph	Ph	4.4.1.1.5[a]		230–232 dec.	195, 196
	Ph	Ph	Ph	Ph	4.4.1.1.5[a]		193–194	196
OH	4-MeC_6H_4	4-MeC_6H_4	4-MeC_6H_4	4-MeC_6H_4	4.4.1.1.7	40	223	206abc
OH	4-$MeOC_6H_4$	4-$MeOC_6H_4$	4-$MeOC_6H_4$	4-$MeOC_6H_4$	4.4.1.1.7	81	209	207abc

[a] Two compounds are diastereomers.

TABLE 4.38. 2*H*-PYRROLES BEARING ONLY *N*-LINKED SUBSTITUENTS AND ALKYL OR ARYL GROUPS



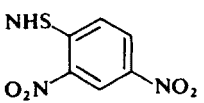
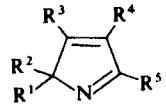
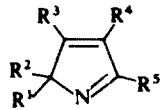
Substituent					Preparation		Melting or Boiling Point	
R^1	R^2	R^3	R^4	R^5	(Sect. No.)	Yield (%)	[°C (mm)]	Ref.
Me	Me	NEt_2	H	Me	4.4.2.1.1	60	49–50(0.5)	22abm, 276
CF_3	CF_3	NEt_2	Me	*t*-Bu	4.4.3.6	11	109(12)	111bce
CF_3	CF_3	Me	NEt_2	*t*-Bu	4.4.3.6	8	105(12)	111bce
	CONMeCONMeCONH	NMe_2	H	NMe_2	4.4.3.5			106cdfh
	CH=CHCOCH=CH	Ph	H		4.4.2.2.2	48	220	104bcdg
	CH=CHCOCH=CH	Ph	H		4.4.2.2.2			302
	CH=CHCOCH=CH	Ph	H	NMePh	4.4.2.2.2	62	206	301abcdg
Me	Me	Ph	Ph	NH_2	4.4.5.1	76	169–170	12abcdg, 81abcg
	$(CH_2)_5$	Ph	Ph	NH_2	4.4.5.1	70	270–271	12abcdg, 81abcg
		Ph	Ph	Ph	4.4.1.1.5	18	172–174	135h

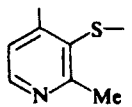
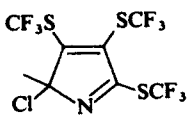
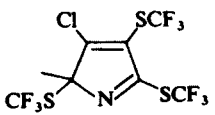
TABLE 4.39. 2*H*-PYRROLES BEARING BOTH *O*- AND *N*-LINKED SUBSTITUENTS AND ALKYL OR ARYL GROUPS



Substituent					Preparation		Melting or Boiling point	
R^1	R^2	R^3	R^4	R^5	(Sect. No.)	Yield (%)	[°C (mm)]	Ref.
Me	H	OH	Me	NEt_2	4.4.3.4	61	114	23abc, 310
n-Pr	H	OH	Me	NEt_2	4.4.3.4	70	120	23abc, 310
Me	Me	OH	Me	NEt_2	4.4.3.4	86	140–142	24abc
H	H	OH	Ph	NMe_2	4.4.3.4	82	214	23abc, 310
Me	H	OH	Ph	NMe_2	4.4.3.4	66	174	23abc, 310
n-Pr	H	OH	Ph	NMe_2	4.4.3.4	57	180	23abc, 310
i-Bu	H	OH	Ph	NMe_2	4.4.3.4	77	186	23abc, 310
$PhCH_2$	H	OH	Ph	NMe_2	4.4.3.4	64	168	23abc, 310
$(CH_2)_2CO_2Et$	H	OH	Ph	NMe_2	4.4.3.4	40	115	23abc, 310
Me	Ph	OH	Me	NEt_2	4.4.3.4	92	207	24ac

TABLE 4.40. 2*H*-PYRROLES BEARING *S*-LINKED AND HALOGEN SUBSTITUENTS



Substituent					Preparation		Melting or Boiling Point	
R^1	R^2	R^3	R^4	R^5	(Sect. No.)	Yield (%)	[°C (mm)]	Ref.
Me	Me	4-(2-Methyl)pyridyl	*i*-PrS	Ph	4.5.3.3	59	97.5–98.5	115bcg
Me	Me			Ph	See ref.	8.5	154.5–155.5	115bcg
Me	Me			Ph	4.4.3.6	86	242.5–244.5	115bc
Cl		SCF_3	SCF_3	SCF_3	4.4.1.1.4	31	140.5–141	113be
SCF_3		Cl	SCF_3	SCF_3	4.4.1.1.4	20	109–110	113be

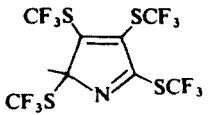
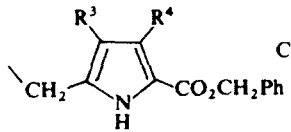
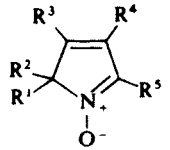
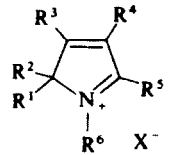
SCF_3		SCF_3	SCF_3	SCF_3	4.4.1.1.4	62	122–123	112be, 137h, 394
Me	Me	H	Cl	Me	4.4.3.6	8	60–70 (0.02)	10abcg
$(CH_2)_5$		4-Pyridyl	Br	Ph	4.4.1.4.1	55	172	271bcg
Me		CH_2CO_2Me	$(CH_2)_2CO_2Me$	Cl	4.4.1.1.2	43		167
Ph	Cl	Ph	Ph	Ph	4.5.3.5			69a, 195a
Cl	$N{=}PCl_3$	Cl	Ph	Cl	4.4.2.1.2	65	95–97	277
Cl	$NHPOCl_2$	Cl	Ph	Cl	4.4.2.1.2	90	194–195	277
Cl	$N{=}PCl_3$	Cl	Cl	Cl	4.4.2.1.2	85	129–132 (0.04)	277, 278b
Cl	$NHPOCl_2$	Cl	Cl	Cl	4.4.2.1.2	100	220–221	277
NHPh	$NHPO(NHPh)_2$	Cl	Cl	NHPh	4.5.3.2	78	181–182 dec.	277
F	F	Cl	Cl	F	4.5.3.5	44	107.5–108.5	185
Cl	Cl	Cl	Cl	Cl	4.4.1.1.4	60–90	92(11)	25abd, 70bd, 114f, 184
					4.4.1.1.4		209(760)	186

TABLE 4.41. 2*H*-PYRROLE *N*-OXIDES



Substituent					Preparation		Melting Point	
R^1	R_2	R_3	R_4	R_5	(Sect. No.)	Yield (%)	(°C)	Ref.
Me	Me	H	H	H	4.4.1.4.1	30	Oil	90cfg
Me	Me	H	Me	*t*-Bu	4.4.1.4.3	90	43–44	37abcfg
Me	Me	H	$CH{=}CH_2$	*t*-Bu	4.4.1.4.3	100		37cf
Me	Me	H	*i*-Pr	*t*-Bu	4.4.1.4.3	90	57–59	37abc
Me	Me	H	*t*-Bu	*t*-Bu	4.4.1.4.3	94	68–69	37abc
Me	Me	H	$PhCH_2$	*t*-Bu	4.4.1.4.3	5	84–86	37abcfg
Me	Me	Ph	H	H	4.4.1.4.1	60	108–109	90cfg
Me	Me	H	Me	Ph	4.4.1.4.3	92	85–86	37abcfg
Me	Me	Me	H	Ph	4.4.1.4.1	15	124	90cfg
Me	Me	Ph	H	*t*-Bu	4.4.1.4.1	89	118–121	38abcg
Me	Me	Ph	H	Ph	4.4.1.4.1	76	76; oil	38abcg, 90cg
Me	Me	CHO	H	Ph	4.4.1.4.1	40	105	90cg
Me	Me	H	H	CN	4.4.1.4.1	76	55–56	39abcg, 270abc
Me	Me	Me	H	CN	4.4.1.4.1	71	93–94	39abcfg, 270
Me	Me	Ph	H	CN	4.4.1.4.1	69	129–131	39abcg, 270
OH	Ph	Ph	H	Ph	4.4.3.1.1		175; 180 dec.	303, 304, 305
OMe	Ph	Ph	H	Ph	4.5.3.1.1	High	172	304, 305
OH	Ph	Ph	Ph	Ph	4.5.5.1.2		216–218 dec.	205
OOH	Ph	Ph	Ph	Ph	4.4.1.1.6		208–210 dec.	205b
Me	Me	Br	H	*t*-Bu	4.4.1.4.1	50	160–162	38abcg
Me	Me	Br	D	*t*-Bu	4.4.1.4.1	56		38b
Me	Me	Br	Ph	Ph	4.4.1.4.1	77	150–152	40abcg
Me	Me	Br	4-$MeOC_6H_4$	4-$MeOC_6H_4$	4.4.1.4.1	83	162–163	40abcg
Me	Me	Br	Br	Ph	4.4.1.4.1	26	118–119	38abcg, 270

TABLE 4.42. 2*H*-PYRROLE SALTS



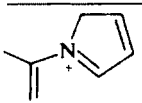
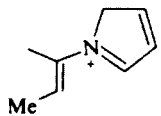
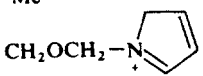
Substituent							Preparation		Melting Point	
R^6	R^1	R^2	R^3	R^4	R^5	X	(Sect. No.)	Yield (%)	(°C)	Ref.
	H	H	H	H	H	FSO_3	4.4.1.1.8			213cdf
	H	H	H	H	H	BF_4	4.4.1.1.8			213cf
	H	H	H	H	H	FSO_3	4.4.1.1.8			213cf
t-Bu	H	H	H	H	H	BF_4	4.4.1.1.8	100	123 dec.	85c
t-Bu	H	H	*t*-Bu	H	H	BF_4	4.4.1.1.8	100	173–174 dec.	85cdf
H	H	H	*t*-Bu	H	*t*-Bu	BF_4	4.4.1.1.8	100	164–166 dec.	85cdf
H	H	*t*-Bu	H	H	*t*-Bu	BF_4	4.4.1.1.8	100	143–145 dec.	85cdf
H	H	*t*-Bu	*t*-Bu	H	*t*-Bu	BF_4	4.4.1.1.8	100	107–109 dec.	85cdf
Me	Me	Me	H	Me	Me	I	4.5.2.2	60		369, 370
Et	Me	Me	H	Me	Me	I	4.5.2.2			369, 370
$PhCH_2$	Me	Me	H	Me	Me	Br	4.5.2.2			369, 370
Me	Me	Me	Me	Me	Me	$AuCl_4$	4.5.2.2		100–101	156, 157, 159
						Cl	4.5.2.2		125	160n
						ClO_4	4.5.2.2		191–192	34ab, 131
						FSO_3	4.4.1.1.1			166
						I	4.5.2.2		173–174	8an
Me	Me	Me	Me	Me	*i*-Pr	$AuCl_4$	4.5.3.1.3		99.5–100.5	157
Me	$(CH_2)_5$		Me	$(CH_2)_4$		ClO_4	4.4.1.4.4	80	170–171	35ab
Me	$(CH_2)_5$		*t*-Bu	$(CH_2)_4$		ClO_4	4.4.1.4.4	70	181–182	35ab

TABLE 4.42. (*Contd.*)

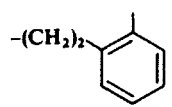
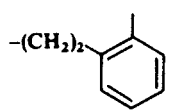
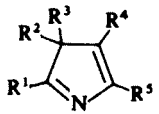
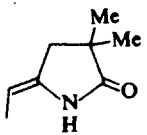
Substituent							Preparation		Melting Point	
R^6	R^1	R^2	R^3	R^4	R^5	X	(Sect. No.)	Yield (%)	(°C)	Ref.
Me	$PhCH_2$	$PhCH_2$	Me	Me	Me	I	4.5.2.2			34a
Me	$PhCH_2$	Me	Me	Me	$PhCH_2$	I	4.5.2.2			34a
Me	Me	Me	Ph	H	Me	I	4.5.2.2			369, 370
Me	$(CH_2)_5$		Ph	$(CH_2)_4$		ClO_4	4.4.1.4.4	75	239–240	35ab
Me	Me	Me	Ph	H	Ph	CF_3SO_3	4.5.2.2	25		88bc
Me	Me	CH_2CO_2Et	Me	CO_2Et	Me	I	4.5.2.2	100	142–144	36ac
Me	Me	Me	CO_2Me	CO_2Me	Ph	$MeSO_4$	4.5.2.2			330
H	CO_2Et	CO_2Et	Ph	H	Ph	BF_4	4.5.2.1	90	140–142	89bcd
Me	CO_2Et	CO_2Et	Ph	H	Ph	I	4.5.2.2	55	187–188	89bcd
						PF_6	4.5.2.2	80	176	89bcd
Me	CO_2Et	CO_2Et	$4\text{-}MeOC_6H_4$	H	Ph	I	4.5.2.2	45	159 dec.	89bcd
Me	Me	Me	OMe	H	Me	I	4.5.2.2		145–146	22
H	OH	Ph	Ph	Ph	Ph	Cl	4.5.2.1	80	238–240	195a
						Cl	4.5.2.1	97, 22	189–191 dec.	190ab, 361
						ClO_4	4.4.1.1.7	100		209
Me	OH	Ph	Ph	Ph	Ph	ClO_4	4.4.1.1.7	100	150 dec.	210abc
H	OH	$4\text{-}MeC_6H_4$	$4\text{-}MeC_6H_4$	$4\text{-}MeC_6H_4$	$4\text{-}MeC_6H_4$	ClO_4	4.4.1.1.7			206b
		Me	SMe	Ph	Ph	I	4.4.1.2.1	100	130–131	245abc
		Ph	SMe	Ph	Ph	I	4.4.1.2.1	100	181–182	245abc
H	H	H	OH	Ph	NMe_2	Cl	4.5.2.1		163	23ab
H	Me	H	OH	Ph	NMe_2	Cl	4.5.2.1		156	23ab
H	$PhCH_2$	H	OH	Ph	NMe_2	Cl	4.5.2.1		120	23
H	$(CH_2)_2CO_2CH_2Ph$	H	OH	Ph	NMe_2	Cl	4.5.2.1		169	23

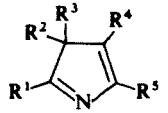
TABLE 4.43. 3*H*-PYRROLES BEARING ONLY ALKYL OR ARYL SUBSTITUENTS



Substituent					Preparation		Melting or Boiling Point	
R^1	R^2	R^3	R^4	R^5	(Sect. No.)	Yield (%)	[°C (mm)]	Ref.
Me	Me	Me	H	Me	4.4.3.1.2	46		11k, 13abcdfmn, 154bcdf
Et	Me	Me	H	Me	4.4.3.1.2	15[a]		13abcdf, 154
	Me	Me	H	Me	4.4.1.4.3	70		275acf
$(CH_2)_4$		Me	H	Me	4.4.3.1.2	—[a]		13abcdf
Me	Me	Et	Me	H	4.4.1.1.1	Low		26abcf
Me	Me	Me	Me	Me	4.4.1.1.1	45		26abc
Me	Me	Et	Me	Me	4.4.1.1.1	19		26abcf
Me	CD_3	Et	Me	Me	4.4.1.1.1			26c
Me	$(CH_2)_4$		Me	Me	4.4.1.1.1			166
Me	$(CH_2)_5$		Me	Me	4.4.1.1.2	73		166
Me	Me	Me	$(CH_2)_3$		4.4.3.1.2	—[a]		13abcd
H	Me	Me	H	Ph	4.4.3.1.2	88		13abcd
Ph	Me	Me	H	H	4.4.3.4	9		71bcfgm
Ph	Me	Me	H	Me	4.4.3.1.2	92	38(0.05)	11k, 13abcdfm, 154
Ph	$(CH_2)_5$		H	Me	4.4.3.1.2	68		13abcdm
Me	Me	Me	H	Ph	4.4.3.1.2	—[a]		13abcd
Me	Ph	Me	H	Ph	4.4.3.1.2	85		13abcdm
1-Isoquinolinyl	Ph	Ph	H	Ph	4.4.4	26	196–198	27ac, 336
1-Isoquinolinyl	Ph	4-$MeOC_6H_4$	H	Ph	4.4.4		204.5–205.8	336
1-Phthalazinyl	Ph	Ph	H	Ph	4.4.4	30	237–238	337bc

[a] Inseparable mixture with isomer(s) having an exocyclic C=C bond.

TABLE 4.44. 3*H*-PYRROLES BEARING ESTER, NITRILE, AND HETERO-LINKED SUBSTITUENTS



Substituent					Preparation		Melting Point	
R^1	R^2	R^3	R^4	R^5	(Sect. No.)	Yield (%)	(°C)	Ref.
H	H	CO_2Me	Me	H	4.4.3.7			141
Me	Me	CO_2Et	H	Me	4.4.3.1.2	12	Oil	28abcdf, 132bcdf
t-Bu	Me	CO_2Et	H	Me	4.4.3.1.2	7	Oil	28abcdf
Me	Me	CO_2Et	H	*t*-Bu	4.4.3.1.2	65[a]	Oil	28abcd
Me	Me	Me	Me	CO_2Et	4.4.3.5	12	Oil	312abcd
Me	Me	CO_2Et	Me	Me	4.4.3.1.2	47	Oil	28abcdf
Me	Me	CO_2Et	$(CH_2)_4$		4.4.3.1.2	20	Oil	28abcd
Me	$(CH_2)_4$		Me	CO_2CH_2Ph	4.4.1.1.1			166
Ph	Me	CO_2Et	H	Me	4.4.3.1.2	33	Oil	28abcd, 132
Ph	Me	CO_2Et	H	*t*-Bu	4.4.3.1.2	64	Oil	28abcd
Me	Me	CO_2Et	H	Ph	4.4.3.1.2	47[a]	Oil	28abcd, 132c
$(CH_2)_4$		CO_2Et	H	Ph	4.4.3.1.2	36	Oil	28abcd
Ph	Me	Me	Me	CO_2Et	4.4.3.5	5	Oil	312abcd
Me	Me	Me	Ph	CO_2Et	4.4.3.5	4	65–66	312abcd
Me	Me	CO_2Et	Me	Ph	4.4.3.1.2	32	Oil	28abcd
Ph	Me	CO_2Et	H	Ph	4.4.3.1.2	55	70–71	28abcdf, 132
CO_2Et	Me	CO_2Et	H	Ph	4.4.3.1.2	11	Oil	28abcd
NH_2	Ph	Ph	CO_2Me	H	4.4.2.1.2	Low	272	82bcg, 107df
NH_2	$PhCH_2$	$PhCH_2$	CO_2Et	OMe	4.4.2.1.2	32	256–257	30bc, 148bc
NH_2	$PhCH_2$	$PhCH_2$	CO_2Et	NH_2	4.4.2.1.2	32	240	30b
NH_2	$PhCH_2$	$PhCH_2$	CO_2Et	$NHCH_2Ph$	4.4.2.1.2	80	218–220	30abc, 148bc
NH_2	Me	Ph	CO_2Et	NH_2	4.4.2.1.2	20	237	30b
NH_2	Et	Ph	CO_2Et	NH_2	4.4.2.1.2	25	220	30b

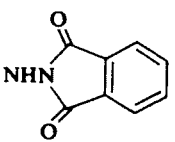
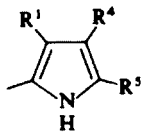
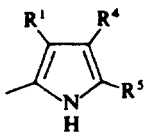
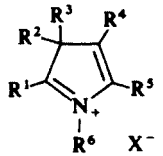
NH_2	Ph	Ph	CO_2Et	NH_2	4.4.2.1.2	65	268–270	30b, 148b
NH_2	$PhCH_2$	$PhCH_2$	CO_2Et	Br	4.4.2.1.2		224–225	152bc
NH_2	Ph	Ph	CO_2Et	Br	4.4.2.1.2	34	250	152bc
NMe_2	Et	Ph	CO_2Me	CO_2Me	4.4.5.1			17d, 138h
t-Bu	H	CH_2CO_2Me	–CONMe	CONMe–	4.4.3.4	14	144–146	84abcf
Ph	Me	CN	H	Me	4.4.3.1.2	15	Oil	28abcdf
Ph	Me	CN	H	*t*-Bu	4.4.3.1.2	50	67–68	28abcd
Ph	Me	CN	H	Ph	4.4.3.1.2	45	93–94	28abcdh
NH_2	$PhCH_2$	$PhCH_2$	CN	OMe	4.4.2.1.2	54	234	151bc
NH_2	Me	Ph	CN	OMe	4.4.2.1.2	45	231	151bc
NH_2	Et	Ph	CN	OMe	4.4.2.1.2	50	229	151bc
NH_2	Ph	Ph	CN	OMe	4.4.2.1.2	32	251	151bc
NH_2	$PhCH_2$	$PhCH_2$	CN	$NHPO(OMe)_2$	4.4.2.1.2	48	238–239	151bc
NH_2	Me	Ph	CN	$NHPO(OMe)_2$	4.4.2.1.2	38	242–243	151bc
NH_2	Et	Ph	CN	$NHPO(OMe)_2$	4.4.2.1.2	45	240–241	151bc
NH_2	Ph	Ph	CN	$NHPO(OMe)_2$	4.4.2.1.2	25	270–271	151bc
$N{=}PPh_3$	$PhCH_2$	$PhCH_2$	CN		4.4.2.1.2	40	272	279bcg
$(CH_2)_4$			NH_2	CN	4.4.3.3	86	252 dec.	31abcd
Me	Ph		NH_2	CN	4.4.3.3	92	233 dec.	31abcd
NH_2	Me	Et	CN	Cl	4.4.2.1.2	50	160–161	150
NH_2	Me	*i*-Bu	CN	Cl	4.4.2.1.2	83	177–178	150
NH_2	Me	*n*-Bu	CN	Cl	4.4.2.1.2	45	162–163	150
NH_2	Me	$PhCH_2$	CN	Cl	4.4.2.1.2	73	170–171	150
NH_2	Et	Et	CN	Cl	4.4.2.1.2	80	186–187	150

TABLE 4.44. (*Contd.*)

Substituent					Preparation		Melting Point	
R^1	R^2	R^3	R^4	R^5	(Sect. No.)	Yield (%)	(°C)	Ref.
NH_2	Et	*i*-Pr	CN	Cl	4.4.2.1.2	80	191–192	150
NH_2	*n*-Pr	*n*-Pr	CN	Cl	4.4.2.1.2	75	193–194	150
NH_2	*n*-Bu	*n*-Bu	CN	Cl	4.4.2.1.2	79	182–184	150
NH_2	Me	Ph	CN	Cl	4.4.2.1.2	91	198–199	149
NH_2	Me	4-EtC_6H_4	CN	Cl	4.4.2.1.2	86	179–180	149
NH_2	Me	4-BrC_6H_4	CN	Cl	4.4.2.1.2	94	205–206	149
NH_2	Et	Ph	CN	Cl	4.4.2.1.2	91	213–214	149
NH_2	Et	Ph	CN	Br	4.4.2.1.2	35	240–241	152b
NH_2	Ph	Ph	CN	Cl	4.4.2.1.2	78	264–266	149
$N(n\text{-}Bu)_2$	H	H	H	$N(n\text{-}Bu)_2$	4.4.2.1.2			29ab
$NMe(n\text{-}C_{18}H_{37})$	H	H	H	$NMe(n\text{-}C_{18}H_{37})$	4.4.2.1.2			29ab
Ph	OH		Ph	Ph	4.4.1.1.5	4	160	201abcg
4-MeC_6H_4	OH		Ph	Ph	4.4.1.1.5	6	164	201abcg

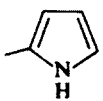
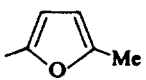
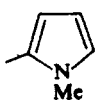
[a] Inseparable mixture with isomer having exocyclic C=C bond.

TABLE 4.45. 3*H*-PYRROLE SALTS



Substituent										
R^6	R^1	R^2	R^3	R^4	R^5	X	Preparation (Sect. No.)	Yield (%)	Melting Point (°C)	Ref.
Me	Me	Me	Me	H	Me	I	4.5.2.2			13abcd
H	Me	Me	Me	Me	Me	FSO_3	4.4.1.1.1			166
Me	Me	Me	Me	Me	Me	ClO_4	4.5.2.2			131
H	Ph	Me	Me	H	Me	BF_4	4.5.2.1		100	13abcd
H	NH_2	Me	Et	CN	Cl	Cl	4.4.2.1.2	95	150–151	150
H	NH_2	Me	*s*-Bu	CN	Cl	Cl	4.4.2.1.2	91	175–176	150
H	NH_2	Me	*n*-Bu	CN	Cl	Cl	4.4.2.1.2	65	175–176	150
H	NH_2	Me	$PhCH_2$	CN	Cl	Cl	4.4.2.1.2	97	175–177	150
H	NH_2	Et	Et	CN	Cl	Cl	4.4.2.1.2	63	181–182	150
H	NH_2	Et	*i*-Pr	CN	Cl	Cl	4.4.2.1.2	70	187–188	150
H	NH_2	*n*-Pr	*n*-Pr	CN	Cl	Cl	4.4.2.1.2	48	189–190	150
H	NH_2	*n*-Bu	*n*-Bu	CN	Cl	Cl	4.4.2.1.2	68	178–180	150
H	NH_2	Me	Ph	CN	Cl	Cl	4.4.2.1.2		179–180	149
H	NH_2	Me	4-EtC_6H_4	CN	Cl	Cl	4.4.2.1.2		171–172	149
H	NH_2	Me	4-BrC_6H_4	CN	Cl	Cl	4.4.2.1.2		192–193	149
H	NH_2	Et	Ph	CN	Cl	Cl	4.4.2.1.2		204–206	149
H	NH_2	Ph	Ph	CN	Cl	Cl	4.4.2.1.2		260–262	149
H	Br	H	Ph	Ph	NH_2	Br	4.4.2.1.2	89	180–190 dec.	280b
H	Br	H	4-$MeOC_6H_4$	4-$MeOC_6H_4$	NH_2	Br	4.4.2.1.2	100	140–145 dec.	280b
H	Br	H	4-ClC_6H_4	4-ClC_6H_4	NH_2	Br	4.4.2.1.2	63	178 dec.	280

TABLE 4.46. 1-AZAFULVENES BEARING ONLY ALKYL OR ARYL GROUPS

Substituent					Preparation		Melting Point	
R^1	R^2	R^3	R^4	R^5	(Sect. No.)	Yield (%)	(°C)	Ref.
$-CH_2-$		H	H	H	4.4.5.4			353bc
$-O-$		H	H	H	4.4.1.2.4			73b
$4\text{-}Me_2NC_6H_4CH{=}CH-$	Me	H	H	$CHPh_2$	4.4.1.1.9		> 300 dec.	229
	H	H	H	H	4.4.1.1.9			232
	H	Me	H	Me	4.4.1.1.9			232acf
	H	Me	H	Me	4.4.1.1.9		50	232acf

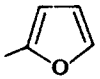
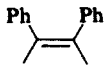
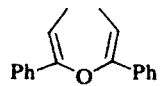
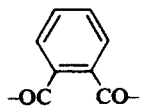
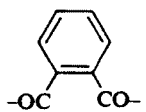
		H	Me	Et	Me	4.4.1.1.9		185	226
		H	Me	Et	Me	4.4.1.1.9			232acf
Ph		Ph	H	H	H	4.4.1.2.4	80	107–109	41acfl
			Ph	H	Ph	4.4.1.1.12		Oil	42ab
			Ph	H	Ph	4.4.1.1.11	69	173	42a
Ph		Ph	Ph	H	Ph	4.4.1.1.12			42a
CF_3		CF_3	H	4-FC_6H_4	4-FC_6H_4	4.4.1.2.4			252

TABLE 4.47. 1-AZAFULVENES BEARING ESTER OR ACYL SUBSTITUENTS

Substituent					Preparation		Melting Point	
R^1	R^2	R^3	R^4	R^5	(Sect. No.)	Yield (%)	(°C)	Ref.
Ph	Ph	Me	CO_2Et	Me	4.4.1.2.4		178	251
		Me	CO_2Et	Me	4.4.1.1.9	70	126	228
		Me	COPh	Me	4.4.1.1.9	33	235	228
CO_2Me	CH_2CO_2Me	Me	Me	OEt	4.4.1.1.2			91ac
OH	Et	CO_2Me	H	Ph	4.4.5.3	60	185–187	44abcdf
OH	Ph	CO_2Et	H	Ph	4.4.5.3	79	212	44bcd
NMe_2	H	CO_2Me	CH_2CO_2Me	OEt	4.4.1.2.1	84	114	92bc
NMe_2	H	CO_2Me	CH_2CO_2Me	Cl	4.4.1.2.2	86	148	92bc
Ph	H	OH	CO_2Me	OMe	4.5.3.1.1	60	175	49abc
Ph	H	OH	CO_2Me	OEt	4.5.3.1.1	60	178	49abc
Ph	H	OH	SO_3Me	OMe	4.4.1.2.1	20	168	49abc
Ph	H	OMe	CO_2Me	OMe	4.4.1.2.1	75	67	49abc
Ph	H	OMe	CO_2Me	OEt	4.4.1.2.1	80	56	49abc
Ph	H	NH_2	CO_2Me	OMe	4.5.3.2	90	220	49abc
Ph	H	NH_2	CO_2Me	OEt	4.5.3.2	90	180	49abc

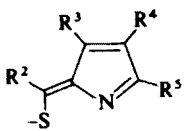
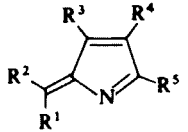
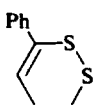
Ph	H	$NHCH_2Ph$	CO_2Me	OMe	4.5.3.2	80	162	49abc
Ph	H		CO_2Me	OMe	4.5.3.2	80	176	49abc
Ph	H	NH_2	CO_2Me	$NHCH_2Ph$	4.5.3.2	20	200	49abc
Ph	H	$NHCH_2Ph$	CO_2Me	$NHCH_2Ph$	4.5.3.2	15	125	49abc
Ph	H		CO_2Me		4.5.3.2	15	145	49abc
OH	Ph	OMe	CO_2Me	OMe	4.5.3.1.3	40	143	49abc
OMe	Ph	OMe	CO_2Me	OMe	4.5.2.2	70	109	49abc
	Ph	OMe	CO_2Me	OMe	4.5.3.3	30	320	49abc
Br	Ph	OMe	CO_2Me	OMe	4.5.2.4	30	105	49abc
Br	Ph	NH_2	CO_2Me	OMe	4.5.3.2	60	176	49abc
Br	Ph	NHMe	CO_2Me	OMe	4.5.3.2	80	157	49abc
Br	Ph	NHMe	CO_2Me	NHMe	4.5.3.2	50	123	49abc
Br	Br	CO_2Et	Me	SO_3H	4.4.1.1.4	38		187
CO_2Me	CN	NMe_2	Cl	NMe_2	4.5.3.4	32		50abc

TABLE 4.48. 1-AZAFULVENES BEARING ONLY HETERO-LINKED SUBSTITUENTS AND ALKYL OR ARYL GROUPS



Substituent					Preparation		Melting point	
R^1	R^2	R^3	R^4	R^5	(Sect. No.)	Yield (%)	(°C)	Ref.
O_2CPh	H	H	H	H	4.4.1.2.1		178	246
	H	H	H	H	4.4.1.1.10		Oil dec.	48
		Me	H	Me	4.4.1.1.11		130–132 dec.	42ac
NMe_2	Ph	H	H	H	4.4.1.1.10	40	114	43ac
NMe_2	4-MeC_6H_4	H	H	H	4.4.1.1.10	55	122	43ac
NMe_2	4-$MeOC_6H_4$	H	H	H	4.4.1.1.10	35	100	43ac
NMe_2	4-ClC_6H_4	H	H	H	4.4.1.1.10	57	108	43ac
NMe_2	4-$NO_2C_6H_4$	H	H	H	4.4.1.1.10	50	122	43c
Ph	H	Me	Me	OEt	4.4.1.1.9	70	89	45ac
4-MeC_6H_4	H	Me	Me	OMe	4.4.1.1.9	38	64	46abcgk
4-$Me_2NC_6H_4$	H	Me	Me	OMe	4.4.1.1.9	48	111–112	46abcgk
		Ph	H	Ph	4.4.1.1.11		135	42a

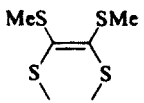
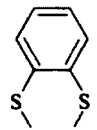
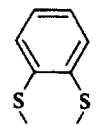
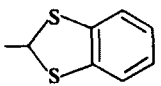
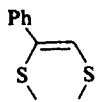
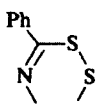
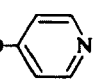
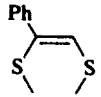
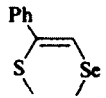
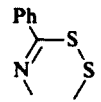
		H	H	H	4.4.1.1.11	82	85–87	47abcf
		H	H	H	4.4.1.1.11	81	75–77	51abcdf
		H	H	H	4.4.1.1.11	31	> 130 dec.	47cf
	H	H	Br	H	4.4.1.1.10		160–165 dec.	48abc
	H	H	I	H	4.4.1.1.10			48
		H	H		4.4.1.1.11	98	147–151 dec.	47cf
		Me	H	Me	4.4.1.1.11			42ai
		Me	H	Me	4.4.1.1.11		119	42ai

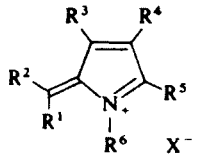
TABLE 4.48. (*Contd.*)

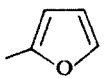
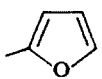
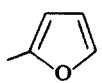
Substituent					Preparation		Melting point	
R^1	R^2	R^3	R^4	R^5	(Sect. No.)	Yield (%)	(°C)	Ref.
NMe_2	H	Me	Me	Cl	4.4.1.1.10	62	132	94
NMe_2	H	Me	Me	Br	4.4.1.1.10	81	121; 125	94c, 237
	H	Me	Me	Br	4.5.3.2	71	121	373
	H	Me	Me	Br	4.5.3.2	74	149	373
NMe_2	H	Et	Me	Br	4.4.1.1.10	50	119	74b
NMe_2	H	$(CH_2)_2CO_2Me$	Me	Br	4.4.1.1.10	75	129	74bc
NMe_2	H	Me	$(CH_2)_2CO_2Me$	Br	4.4.1.1.10	80	138	74bc
Ph	H	Me	Me	OEt	4.4.1.1.9	70	89	45ac
Ph	H	OH	H	OMe	4.5.3.1.3	70	139	49abc
Ph	H	OH	H	OEt	4.5.3.1.3	70	141	49abc
Ph	H	OMe	H	OMe	4.4.1.2.1	80	35	49abc
Ph	H	OMe	H	OEt	4.4.1.2.1	80	33	49abc
Ph	H	OMe	H	$NHCH_2Ph$	4.5.3.2	50	112	49abc
Ph	H	OMe	H		4.5.3.2	60	120	49abc
Ph	H	OMe	H	NHNHCOPh	4.5.3.2	65	224	49abc
Ph	H	OMe	H		4.5.3.2	50	248	49abc

		Ph	H	Ph	4.4.1.1.11		132	42a
		Ph	H	Ph	4.4.1.1.11		130	241a
		Ph	H	Ph	4.4.1.1.11		175	42a
	H	H	Br	Br	4.4.1.1.10		122–124.5	48bc
	H	Br	Br	Br	4.4.1.1.10		175–178	48abc
OEt	Ph	NHCH=CH_2	H	H	4.4.3.2	50[a]		93cdf
Ph	OEt	NHCH=CH_2	H	H	4.4.3.2	10[a]		93cf
OEt	Ph	NHCH=CHMe	Me	H	4.4.3.2	52[a]		93
Ph	OEt	NHCH=CHMe	Me	H	4.4.3.2	10[a]		93

[a] N → $W(CO)_5$ complexes.

TABLE 4.49. 1-AZAFULVENE SALTS



Substituent							Preparation		Melting point	
R^6	R^1	R^2	R^3	R^4	R^5	X	(Sect. No.)	Yield (%)	(°C)	Ref.
H	4-$Me_2NC_6H_4CH{=}CH$–	Me	H	H	H	Br	4.4.1.1.9			229
H	4-$Me_2NC_6H_4CH{=}CH$–	Me	Me	H	Me	Br	4.4.1.1.9			229
H		H	Me	H	Me	Cl	4.4.1.1.9		> 280	226
H		H	Me	Et	Me	Br	4.4.1.1.9		83–84	226
						ClO_4	4.4.1.1.9		217 dec.	226
H	4-$Me_2NC_6H_4$	H	Me	$CH_2CH(CO_2H)_2$	Me	Cl	4.4.1.1.9		190	224
						ClO_4	4.4.1.1.9			224
H	4-$Me_2NC_6H_4CH{=}CH$–	Ph	Me	H	Me	Br	4.4.1.1.9			229
H		H	Me	COMe	Me	ClO_4	4.4.1.1.9		280 dec.	226
H	4-$Me_2NC_6H_4$	H	Me	CO_2Et	Me	ClO_4	4.4.1.1.9		215 dec.	224, 230
H	4-$Me_2NC_6H_4CH{=}CH$	H	Ph	CO_2Et	Me	Br	4.4.1.1.9			229
H	4-$Me_2NC_6H_4CH{=}CH$	Me	Ph	CO_2Et	Me	Br	4.4.1.1.9			229
H	Ph	Ph	H	H	H	BF_4	4.4.1.2.4	70	149–151	41
Me	Ph	Ph	H	H	H	BF_4	4.4.1.2.4	95	142–144	253

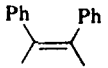
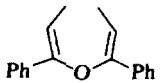
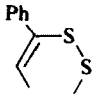
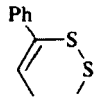
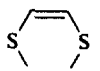
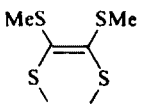
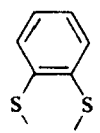
Me	4-MeC_6H_4	Ph	H	H	H	BF_4	4.4.1.2.4	90	158–160	253
Me	4-MeC_6H_4	4-MeC_6H_4	H	H	H	BF_4	4.4.1.2.4	96	180–182	253
H			Ph	H	Ph	ClO_4	4.4.1.1.12	79	222 dec.	42ab
H			Ph	H	Ph	ClO_4	4.4.1.1.11		306 dec.	42a
H	Ph	Ph	Ph	H	Ph	ClO_4	4.4.1.1.12	62	265 dec.	42a
H			Me	H	Me	ClO_4	4.4.1.1.11	88	256 dec.	42ai
H			Ph	H	Ph	ClO_4	4.4.1.1.11	40	220 dec.	42a
H			H	H	H	I	4.4.1.1.11	92		47abcf
H			H	H	H	BF_4	4.4.1.1.11	91	186–188	51abcdf
H			H	H	H	ClO_4	4.4.1.1.11	84	> 230 dec.	47cf

TABLE 4.49. (*Contd.*)

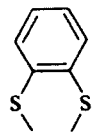
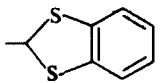
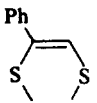
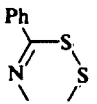
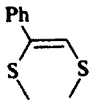
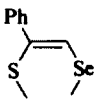
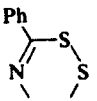
Substituent							Preparation		Melting point	
R^6	R^1	R^2	R^3	R^4	R^5	X	(Sect. No.)	Yield (%)	(°C)	Ref.
H			H	H		BF_4	4.4.1.1.11	51	179–180 dec.	47bcf
H			Me	H	Me	ClO_4	4.4.1.1.11	89	240 dec.	42ai
H			Me	H	Me	ClO_4	4.4.1.1.11	40	245 dec.	42ai
H			Ph	H	Ph	ClO_4	4.4.1.1.11	67	241 dec.	42a, 241
H			Ph	H	Ph	ClO_4	4.4.1.1.11			241
H			Ph	H	Ph	ClO_4	4.4.1.1.11	51	245 dec.	42a

TABLE 4.50. 2-AZAFULVENES

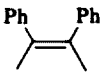
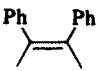
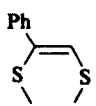
Substitutent					Preparation		Melting Point	
R^1	R^2	R^3	R^4	R^5	(Sect. No.)	Yield (%)	(°C)	Ref.
H		$-CH_2-$	H	H	4.4.5.4			353bc
Ph			H	Ph	4.4.1.1.12		Oil	42
Ph			Ph	Ph	4.4.1.1.12			42
Ph	Ph	Ph	H	Ph	4.4.1.1.12		187	42a
Ph	Ph	Ph	Ph	Ph	4.4.1.1.12	55	208	42a
$-O_2C(CH_2)_2-$		Ph	H	Ph	4.4.1.2.1	48	209 dec.	247
Cl	H	Ph	H	Ph	See ref.			375
Cl	H	Ph	H	$4\text{-}MeC_6H_4$	See ref.			375
Cl	H	Ph	H	$4\text{-}MeOC_6H_4$	See ref.			375
Cl	H	Ph	H	$4\text{-}ClC_6H_4$	See. ref.			375
	$4\text{-}Et_2NC_6H_4$	Ph	CN	Ph	4.5.3.2		188	52abc
Cl	$4\text{-}Et_2NC_6H_4$	Ph	CN	Ph	4.4.5.3		185	52ab
Me			H	Me	4.4.1.1.11			42ai

TABLE 4.50. (*Contd.*)

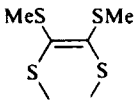
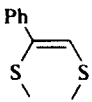
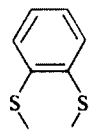
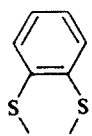
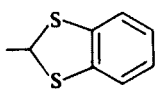
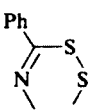
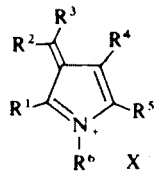
Substitutent					Preparation		Melting Point	
R^1	R^2	R^3	R^4	R^5	(Sect. No.)	Yield (%)	(°C)	Ref.
Me			H	Me	4.4.1.1.11	70	105–109 dec.	47abc
Me			H	Me	4.4.1.1.11			51a
Me			H	Me	4.4.1.1.11			42ai
Me			H	Me	4.4.1.1.11	68	182–185 dec.	47c
Me				Me	4.4.1.1.11	92	204–209 dec.	47c
Me			H	Me	4.4.1.1.11			42i

TABLE 4.51. 2-AZAFULVENE SALTS



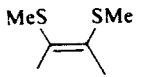
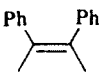
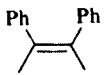
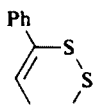
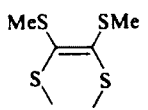
Substitutent							Preparation		Melting Point	
R^6	R^1	R^2	R^3	R^4	R^5	X	(Sect. No.)	Yield (%)	(°C)	Ref.
H	Me			H	Me	BF_4	4.4.1.1.11	76	198–199	51abc
H	Ph			H	Ph	ClO_4	4.4.1.1.12	50	235 dec.	42ab
H	Ph			Ph	Ph	ClO_4	4.4.1.1.12	59	205 dec.	42ab
						Cl	4.4.1.1.9	88	245 dec.	77b
H	Ph	Ph	Ph	H	Ph	ClO_4	4.4.1.1.12	80	226 dec.	42a
H	Ph	Ph	Ph	Ph	Ph	ClO_4	4.4.1.1.12			42
H	Me			H	Me	ClO_4	4.4.1.1.11	45	255 dec.	42ai
H	Me			H	Me	I	4.4.1.1.11	83	214–219 dec.	47abc
H	Me			H	Me	BF_4	4.4.1.1.11	99	256–257	51abcd

TABLE 4.51 (*Contd.*)

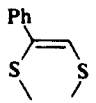
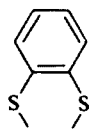
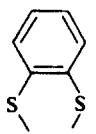
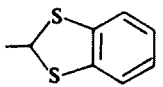
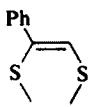
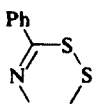
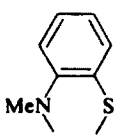
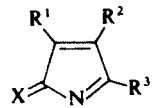
Substitutent										
R^6	R^1	R^2	R^3	R^4	R^5	X	Preparation (Sect. No.)	Yield (%)	Melting Point (°C)	Ref.
H	Me			H	Me	ClO_4	4.4.1.1.11	73	220 dec.	42ai
H	Me			H	Me	ClO_4	4.4.1.1.11	67	225–227	47bc
H	Me				Me	BF_4	4.4.1.1.11	76	223–226 dec.	47bc
H	Ph			H	Ph	ClO_4	4.4.1.1.11			241
H	Me			H	Me	ClO_4	4.4.1.1.11	16	229 dec.	42ai
H	SMe			H	H	Br	4.4.2.3	70	217	95acfm

TABLE 4.52. 2*H*-PYRROLES BEARING AN EXOCYCLIC C=X BOND



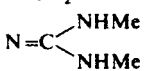
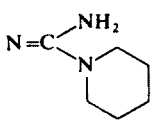
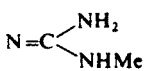
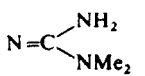
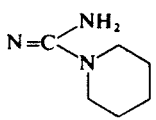
Substituent				Preparation		Melting Point	
X	R^1	R^2	R^3	(Sect. No.)	Yield (%)	(°C)	Ref.
O	H	H	O-(1-Adamantyl)	4.4.1.2.1	98	132–140 dec.	55abcf
O	COMe	Ph	$PhCH_2$	4.4.5.1	66	126 dec.	347bc
O	Ph	Ph		4.5.2.1.1		204–209 dec.	281
O	Ph	Ph		4.5.2.1.1		253–255	281
O	OH	Cl	SCF_3	4.4.1.1.4	14	89–90	75bce
NH	Ph	Ph	$N{=}C(NH_2)_2$	4.4.2.1.2		210 dec.	281
NH	Ph	Ph		4.4.2.1.2		213 dec.	281
NH	Ph	Ph		4.4.2.1.2		244 dec.	281a
NH	Ph	Ph		4.4.2.1.2		226 dec.	281

TABLE 4.52. (*Contd.*)

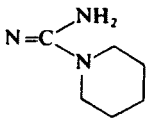
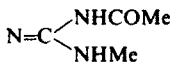
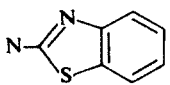
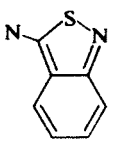
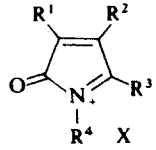
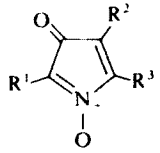
X	Substituent R^1	R^2	R^3	Preparation (Sect. No.)	Yield (%)	Melting Point (°C)	Ref.
NH	Ph	Ph	$N{=}C(NHMe)_2$	4.4.2.1.2		220 dec.	281
NCOMe	Ph	Ph		4.5.2.3		227	281
NCOMe	Ph	Ph		4.5.2.3		211 dec.	281
NCOMe	Ph	Ph	$N{=}C(NHCOMe)_2$	4.5.2.3		185–186	281
NPh	Ph	Ph	NH_2	4.4.5.2		258	351
	NMe_2	Cl	NMe_2	4.5.3.2	53	193	50ac
	NMe_2	Cl	NMe_2	4.5.3.2	53	179	50a
N_2	Ph	H	Ph	4.4.1.2.5		104–104.5	56ab
N_2	Ph	COMe	Ph	4.4.1.2.5		102–103	56ab
N_2	Ph	OAc	Me	4.4.1.2.5		102	262
N_2	Ph	NO_2	Ph	4.4.1.2.5		116–117; 114 dec.	56b, 262
$NPOCl_2$	Cl	Cl	Cl	4.5.3.1.1	80–83	193–194	278b
$NPO(NHPh)_2$	Cl	Cl	NHPh	4.5.3.2	89	177–179	277

TABLE 4.53. SALTS OF 2*H*-PYRROL-2-ONES



Substituent					Preparation	
R^1	R^2	R^3	R^4	X	(Sect. No.)	Ref.
H	H	H	H	$SbCl_6$	4.4.1.4.4	99cf
H	H	H	Me	$SbCl_6$	4.4.1.4.4	99cf

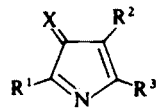
TABLE 4.55. 3*H*-PYRROL-3-ONE *N*-OXIDES

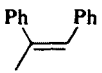
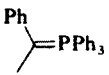


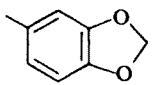
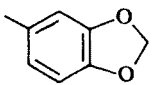
Substituent			Preparation		Melting Point	
R^1	R^2	R^3	(Sect. No.)	Yield (%)	(°C)	Ref.
t-Bu	Ph	Me	4.4.2.1.4			294
Ph	Ph	Me	4.4.2.1.4			294
Ph	Ph	Et	4.4.2.1.4			294
Ph	Ph	*n*-Bu	4.4.2.1.4			294
Ph	Ph	Ph	4.4.2.1.4	—[a]	175–177	292, 374, 377, 381
4-MeC_6H_4	Ph	Ph	4.4.2.1.4			381
4-$MeOC_6H_4$	Ph	Ph	4.4.2.1.4		182	293
4-ClC_6H_4	Ph	Ph	4.4.2.1.4	—[a]	201	292
4-BrC_6H_4	4-ClC_6H_4	Ph	4.4.2.1.4	—[a]	180 dec.	292

[a] Yields for Ref. 292 are 70–75%.

TABLE 4.54. 3*H*-PYRROLES BEARING AN EXOCYCLIC C=X BOND



Substituent				Preparation		Melting Point	
X	R^1	R^2	R^3	(Sect. No.)	Yield (%)	(°C)	Ref.
O				4.5.2.6	65	167–169	313ab
O				4.4.3.5	48	192 dec.	313ab
O	Ph	Ph	Ph	4.4.3.5			57ab, 381
O	NMe_2	Ph	Ph	4.4.3.5	55	157–158	57abc, 60abcg
O	NEt_2	Ph	Ph	4.4.3.5	17	111–112	60abc, 61h
O		Ph	Ph	4.4.3.5	51	155–156	57abc, 60abc
O		Ph	Ph	4.4.3.5	69	157–158	57abc, 60abc
O		Ph	Ph	4.4.3.5	47	156–157	57abc, 60abc
O	NMe_2	Cl	NMe_2	4.5.3.1.1	64	114	50abc
S	NMe_2	NMe_2	NMe_2	4.5.3.3	22	142–145	50abc
NH	Ph	Ph	Ph	4.4.1.2.5		170	255

NPh	NHMe	NO_2	NHMe	4.4.5.3		247–248 dec.	97cgh
N_2	Ph	H	Me	4.4.1.2.5		81–82 dec.	58ab
N_2	Ph	H	Ph	4.4.1.2.5	89.5	122–123 dec.	58ab, 257, 258, 368b, 98bc, 260, 380
N_2	4-ClC_6H_4	H	4-ClC_6H_4	4.4.1.2.5		119–121	259, 261
N_2	Ph	Ph	H	4.4.1.2.5		170 dec.	259, 261
N_2	Ph	Ph	Ph	4.4.1.2.5		158–159 dec.	58ab, 257, 366, 367
N_2	4$(CH_2{=}CH)C_6H_4$	Ph	Ph	4.4.1.2.5		> 125	261
N_2	4-PhC_6H_4	Ph	Ph	4.4.1.2.5		125–130	259, 261
N_2	4-$PhSOC_6H_4$	Ph	Ph	4.4.1.2.5		96–110	261
N_2	4-$MeSO_2C_6H_4$	Ph	Ph	4.4.1.2.5			261
N_2	4-$PhMeNSO_2C_6H_4$	Ph	Ph	4.4.1.2.5		100–110 dec.	259, 261
N_2	4-$MeCONHC_6H_4$	Ph	Ph	4.4.1.2.5		130	261
N_2	4-ClC_6H_4	Ph	Ph	4.4.1.2.5		119–121	259, 261
N_2	Ph			4.4.1.2.5		120	261
N_2	Me	Me	CO_2Et	4.4.1.2.5		79.5–80	58ab
N_2	Ph	COMe	Me	4.4.1.2.5	80	65 dec.	59abc
N_2	3-$MeOC_6H_4$	COMe	Me	4.4.1.2.5	70	73 dec.	119bc
N_2	3-$MeOC_6H_4$	CO_2Et	Me	4.4.1.2.5	70	73 dec.	119bc
N_2	Ph	COMe	Ph	4.4.1.2.5	75	148 dec.	59abc
N_2	Ph	CO_2H	Ph	4.4.1.2.5		189 dec.	76bc
N_2	Ph	CO_2Et	Ph	4.4.1.2.5	90	115	76bc
N_2	Ph	CN	Ph	4.4.1.2.5	85	150	76bc
N_2	Ph	NO_2	Ph	4.4.1.2.5	27	144.5–145 dec.	58ab
NNHPh	Ph	–N=NPh	Ph	4.4.1.1.13	70	240–241 dec.	120abcg

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