COMPREHENSIVE ORGANIC CHEMISTRY

The Synthesis and Reactions of Organic Compounds

SIR DEREK BARTON, F.R.S.

AND

W. DAVID OLLIS, F.R.S.

Volume 4 Heterocyclic Compounds

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Volume 4 Heterocyclic Compounds

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Foreword

During more than a century, the development of organic chemistry has been associated with extensive documentation. Vast numbers of textbooks, monographs, and reviews have been published with the objective of summarizing and correlating the results obtained by many thousands of organic chemists working in academic and industrial research laboratories. However, out of this colossal literature there is but a relatively small number of textbooks and multi-volumed works which have become generally accepted as representing real steps forward in the presentation of our subject.

During the classical era of organic chemistry (1820–1940), textbooks which had a profound influence on the teaching of the subject included, for example, works by Armstrong (1874), van't Hoff (1875), Roscoe–Schorlemmer (1878), Richter (1888), Gattermann (1895), van't Hoff–Werner–Eiloart (1898), Meyer–Jacobson (1902), Schmidt–Rule (1926), Karrer (1928), Freudenberg (1933), Richter–Anschütz (1935), and Gilman (1938). These texts provide an opportunity to comment on the relationship between the history of organic chemistry and its associated publications. The *Treatise on Chemistry* by Roscoe and Schorlemmer consisted of three volumes (5343 pages) published in nine parts over the period 1878–1892: the major component was Volume III (6 parts, 3516 pages) which was devoted to organic chemistry. Another instructive example is the important work *Lehrbuch der Organischen Chemie*, produced by Victor Meyer and Paul Jacobson. The increase in size from the edition (1735 pages) published during 1902–1903 to the edition (5115 pages) published over the period 1913–1924 is striking.

Many have expressed concern about the problems of maintaining effective contact with the expanding literature of organic chemistry, but few have allowed themselves to become involved with attempted solutions. The decision to publish Comprehensive Organic Chemistry was not taken lightly. The absence of a work reflecting the current rapid development of modern organic chemistry has been lamented by many eminent chemists, including the late Sir Robert Robinson (1886–1975) who played an important role in the initiation of this project shortly before his death. Comprehensive Organic Chemistry was conceived, designed, and produced in order to meet this deficiency. We realised that the current rate of growth of organic chemistry demanded speedy publication and, furthermore, that its interaction with other subjects including biochemistry, inorganic chemistry, molecular biology, medicinal chemistry, and pharmacology required the collaboration of many authors. The selection of topics to be included in order to justify the work as being comprehensive has not been easy. We recognize that some areas of organic chemistry have not been given the detailed treatment which can be justified, but we have done our best to meet the expectations of the majority of readers. In particular, we have not made a special section for Theoretical Organic Chemistry. This is not because of any lack of appreciation on our part of the importance of Theory. It is because a correct treatment of Theory cannot be made comprehensible in an abbreviated form. It is also because Theory changes with time more rapidly than the facts of the subject. Theory is better treated in our view in specialist monographs. The same arguments apply equally to the fundamental subject of Stereochemistry. Any comments regarding errors and omissions will be appreciated so that they can be dealt with in future editions.

The contents of each volume have been brought together so as to reflect what are judged to be the truly important facets of modern organic chemistry. The information is presented in a concise and logical manner with mechanistic organic chemistry being adopted to provide a constant and correlative theme. The dominating intention of the Editorial Board has been to ensure the publication of a contribution to the literature of

organic chemistry which will be genuinely useful and stimulating. Emphasis has therefore been given throughout to the properties and reactions of all the important classes of organic compounds, including the remarkable array of different compounds prepared by synthesis as well as natural products created by biosynthesis. Of course, the study of natural products provided the original foundation stones on which modern synthetic organic chemistry now firmly stands.

As a major presentation of modern organic chemistry, Comprehensive Organic Chemistry will be doubly useful because we have provided, in a separate volume, an extensive index. Not only have the contents of the work been indexed in the ordinary way, but we have also added a substantial number of additional references from the original literature. These do not appear in the text itself. Thus, the reader who wishes to obtain additional information about reactions and reagents mentioned in the text will quickly be able to consult the original literature. The Index volume has been prepared by a team from Pergamon Press.

Our debt to the Authors and to the Volume Editors is considerable. We are very grateful to all our colleagues for the efficient way in which they have tried to meet the challenges (and the deadlines!) which have been presented to them. We hope that the Authors have enjoyed their association with this venture. In a lighter vein, we also trust that their feelings are different from the statement 'this task put system into my soul but not much money into my purse' attributed to Henry Edward Armstrong (1848–1937) after he had written his *Introduction to Organic Chemistry* in 1874.

We are delighted to acknowledge the masterly way in which Robert Maxwell, the Publisher, and the staff at Pergamon Press have supported the Volume Editors and the Authors in our endeavour to produce a work which correctly portrays the relevance and achievements of organic chemists and their contributions to knowledge by research.

D. H. R. Barton
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W. D. Ollis
Deputy Chairman

Preface to Volume 4

Organic chemistry is largely comprised of heterocyclic chemistry. As a consequence of the size of the subject, any single volume is bound to omit more systems than it includes. In planning this treatise, the scope of the subject matter, and how best to organize it, were kept very much in mind. The organizational problem was resolved by considering the potential needs of those seeking to use it. Since readers will include those requiring a fresh insight into heterocyclic chemistry, it had to contain details of the more familiar and common systems. Besides such readers, specialists seeking information on more complex and less usual structures of practical importance had also to be included. As a consequence, certain topical areas, such as the chemistry of purine systems (Chapter 17.5) and meso-ionic compounds (Chapter 20.4) are covered in depth. The organizational consequence of such deliberations was very much in the traditional mode, with systems arranged according to the number and type of heteroatoms present and the size and number of rings present. In order to complement other volumes in this treatise, the discussion of fully saturated heterocyclic systems has largely been omitted from Volume 4. For example, cyclic ethers and cyclic amines are mainly dealt with in Chapters 4.4 and 6.1, respectively.

The use of the symbols ly, my, and hy, adopted by some of the authors, refer to low, medium, and high yields, respectively. This symbolism serves as a useful indication of the efficiency of a particular reaction or process.

The limitations on space will inevitably mean that errors of omission have been perpetrated for which I, as editor of this volume, take full responsibility. The contents of individual chapters were arranged by consultation with the authors. It was intended to allow contributors enough freedom, in their presentations, to be able to impart their own individuality and style. This they have achieved, thus making the whole work far more enjoyable to read. I would like to record my thanks to all the contributors for their enthusiastic and efficient help with the preparation of this volume. Without their cooperation the work would still be only a dream, rather than a reality.

London P. G. SAMMES

Contents

PART 16

NITROGEN SYSTEMS: THE AZINES

16.1

Pyridines

D. M. SMITH
University of St. Andrews

The credit for the discovery of pyridine and its simple alkyl derivatives belongs to the nineteenth-century Scottish chemist, Thomas Anderson. At a meeting of the Royal Society of Edinburgh in April 1846, he presented a paper[1] describing the isolation from coal tar of a new organic base, *picoline**, which was isomeric with aniline. In a subsequent paper[2] he showed that picoline was also a component of the foul-smelling basic oil ('odorine') obtained by dry distillation of deer-horn, and in a third paper,[3] dated April 1851, he described the careful fractionation of this bone-oil, which gave two further bases, *pyridine* and *lutidine**.

The structural relationship between pyridine and benzene was first recognized, apparently independently, by Körner in 1869 and Dewar in 1871,[5] and the formulation of pyridine as azabenzene (**1**) was finally established by Ladenburg[6] in 1888. Proof that picoline and lutidine were pyridine derivatives was achieved by oxidation of the alkyl groups to carboxyl and decarboxylation of the resulting acids (*cf.* Ref. 4).

16.1.1 THE PYRIDINE MOLECULE

Pyridine contains a delocalized 6π-electron system, like benzene, and the molecular dimensions of pyridine (see formula **2**) include C—C and C—H bond lengths extremely close to those of benzene (C—C, 139.7 pm; C—H, 108.4 pm). The resemblance to benzene is also obvious in the ultraviolet[8] and infrared[9] spectra of pyridine. Unlike benzene, however, pyridine has a large dipole moment, 2.26 D†; the polarization of the molecule, which may be represented by the canonical structures (**3**), is reflected in the electron densities at the various ring positions, which may be calculated by molecular-orbital methods, and also in the chemical shifts in both ^1H and ^{13}C n.m.r. spectra.

A typical set of calculated π-electron densities[11] (this particular set being based on Extended Hückel Theory) is given in formula (**4**), and illustrates the general result from all such calculations, namely that the electron densities at the ring positions decrease in the order $1 > 3 > 4 \approx 2$.

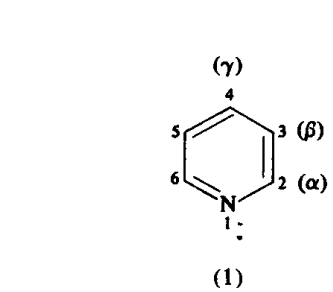
The ^1H[12] and ^{13}C[13] chemical shifts‡ of the various atoms in pyridine are shown in formulae (**5**) and (**6**), respectively: the deshielding effect of the hetero-atom is most pronounced at the 2- and 6-positions, and is also noticeable at the 4-position. Inter-proton coupling constants in simple pyridine derivatives[12] are approximately as follows: $J_{2,3}$, 4.0–6.0; $J_{3,4}$, 6.8–9.2; $J_{2,4}$, 1.0–2.5; $J_{3,5}$, 0.6–1.9; $J_{2,6}$, 0–0.5; $J_{2,5}$, 0–1.8 Hz.

The principal features of the mass spectrum of pyridine itself[14] are intense ions corresponding to $M^{+\cdot}$ and $(M-HCN)^{+\cdot}$. Substituted pyridines may also show $(M-HCN)^{+\cdot}$ ions in their mass spectra, but in the case of alkylpyridines there are competing fragmentation processes which lead to pyridylmethylene (or, more probably, azatropylium) ions (**7**).[14]

* The 'picoline' and 'lutidine' obtained by Anderson were almost certainly mixtures of isomers: for example, Weidel[4] oxidized 'picoline' with potassium permanganate and obtained both pyridine-2- and -3-carboxylic acids

† For a table of dipole moments of simple pyridine derivatives, see Ref. 10a.

‡ Parts per million downfield from tetramethylsilane: carbon tetrachloride solutions.



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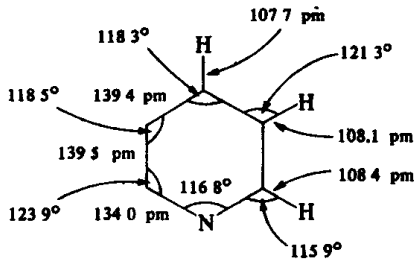

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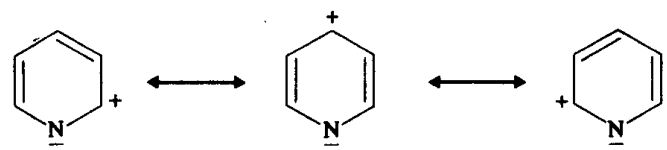

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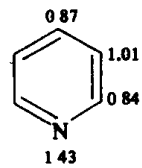

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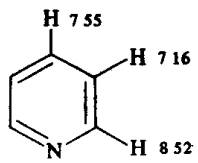

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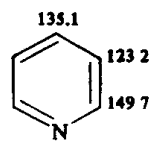

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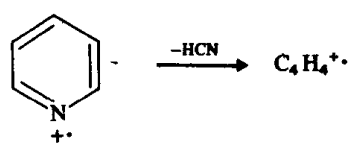
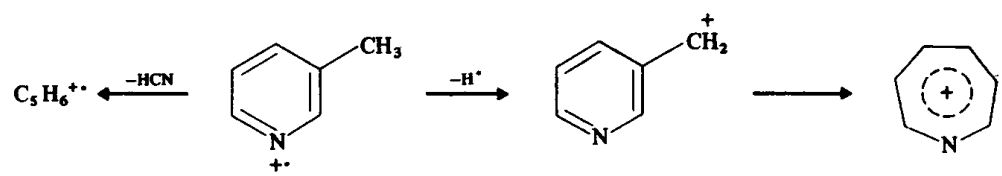


m/e 79 (100%) *m/e* 52 (76%)



m/e 66 (44%) *m/e* 93 (100%) *m/e* 92 (31%) (7)

16.1.2 PYRIDINES AS TERTIARY BASES

16.1.2.1 Protonation

Pyridine and its homologues are weakly basic: pyridine itself has pK_a 5.20 in water at 25 °C, and simple alkylpyridines have pK_a values in the range 5.5–7.5.[15a] Electron-withdrawing substituents in the ring decrease the basicity, especially substituents in the 2- and 6-positions. This is well illustrated in the chlorinated pyridines, the pK_a values of which are as follows: 2-chloro-, 0.72; 3-chloro-, 2.84; 4-chloro-, 3.83; 2,3-dichloro-, −0.85; 2,6-dichloro-, −2.86; pentachloro-, −6.02.

16.1.2.2 Quaternization

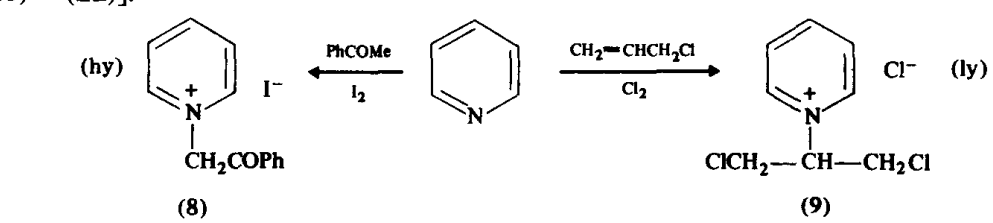
Alkyl (and reactive aryl) halides react with pyridines to form quaternary *N*-alkyl- (or *N*-aryl-) pyridinium salts. Methylation, for example, is normally effected by methyl iodide.

Diazomethane has also been used for the methylation of pyridine, in the presence of fluoroboric acid.[16] The methylation of the most weakly basic pyridine derivatives, *e.g.* pentahalogenopyridines, may be achieved using methyl fluorosulphonate.[17]

Alkylation of pyridines, using alkyl halides, may be accompanied by dehydrohalogenation of the latter to give an alkene. The elimination reaction is of particular importance when the halide is secondary or tertiary, when the alkene produced forms part of a conjugated system, or when the pyridine has a sterically hindered hetero-atom (*e.g.* '*sym*-collidine' — 2,4,6-trimethylpyridine) and can thus undergo *N*-protonation more easily than *N*-alkylation.[18]

In some cases, pyridinium salts may be conveniently prepared by the reaction of pyridine with a reactive methylene compound and iodine[19] (*e.g.* the preparation of **8**) and in others by the reaction of pyridine with an alkene and a halogen[20] (*e.g.* the preparation of **9**).

N-Acylpyridinium salts, formed by the reaction of pyridines with acyl halides or anhydrides, are isolable although highly reactive,[21,22] being rapidly hydrolysed even by atmospheric moisture. They undergo nucleophilic attack at the carbonyl carbon atom extremely readily, and are thus very effective acylating agents. They have been detected as intermediates in the pyridine-catalysed hydrolysis of anhydrides[23] (*i.e.* the acylation of water), and are the presumed intermediates in various other acylations in pyridine solution, such as the conversion of acyl chlorides into anhydrides[22,24] or diacyl sulphides[22] (diacylation of water or hydrogen sulphide), or the *O*-acylation of β-keto-esters[25] [*e.g.* (**10**)→(**11**)].



4-(*N*,*N*-Dialkylamino)pyridines are evidently much better acylation catalysts than pyridine itself, and have been used to bring about the acylation of sterically hindered alcohols.[26] The increased effectiveness of these pyridine derivatives may be due to their enhanced basicity (the dimethylamino-compound has pK_a 9.71) and to the relative stability of their *N*-acyl derivatives: some of these are stable enough to be stored for several months, and have been used for the *N*-acylation of amino-acids in aqueous alkali.[27]

N-Nitropyridinium salts are, in some cases, effective nitrating agents,[28] pyridine perbromide (*N*-bromopyridinium bromide?) and pyridine hydrobromide perbromide ($C_5H_5\overset{+}{N}H\,Br_3^-$) have both found application as brominating agents,[29] and the pyridine–sulphur trioxide adduct ($C_5H_5\overset{+}{N}—SO_3^-$) is a convenient source of sulphur trioxide for the formation of sulphates and sulphonates.[30]

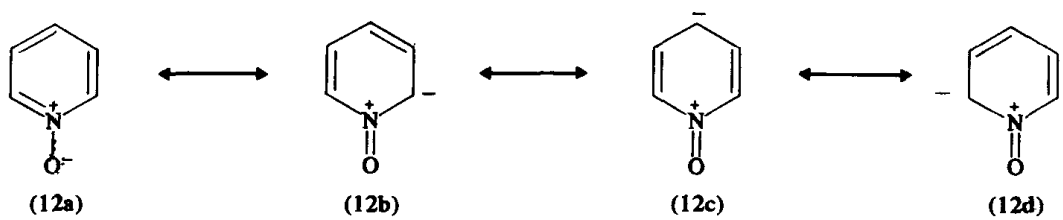
16.1.2.3 *N*-Oxide formation

N-Oxidation of pyridines is normally carried out by reaction with peracids. Peracetic acid, which may be prepared *in situ* from 30% hydrogen peroxide in acetic acid, is the

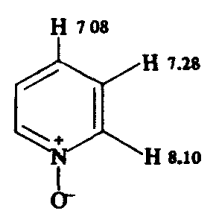
most common reagent,[31] although aromatic peracids (perbenzoic, *m*-chloroperbenzoic, and perphthalic acids, for example) have also been used;[32] the advantage of the latter is that the reactions may be carried out under mild conditions in non-polar solvents such as chloroform. The more weakly basic pyridines require stronger oxidizing agents or reaction conditions: pentahalogenopyridines, for example, are oxidized by peroxytrifluoroacetic acid,[33] or hydrogen peroxide and an organic acid in presence of sulphuric acid.[34]

16.1.2.4 Properties and reactions of pyridine *N*-oxides

The normal representation of pyridine *N*-oxide as (**12a**) takes no account of any back-donation of electrons from the oxygen into the ring (such as may be represented by the canonical forms **12b–d**). That such back-donation is a significant phenomenon is evident from dipole moment measurements[35] and from the ^1H [36] and ^{13}C [13] n.m.r. spectra. The dipole moment of pyridine *N*-oxide itself is 4.24 D, much less than the sum of the dipole moment of pyridine and the $N^+—O^-$ bond moment (*ca.* 6.6 D). The ^1H and ^{13}C chemical shifts for pyridine *N*-oxide, shown in formulae (**13**) and (**14**) respectively, demonstrate that the deshielding effect at the 2- and 4-positions is less in pyridine *N*-oxide than in pyridine itself. Calculated π-electron densities for the various atoms in pyridine *N*-oxide (a typical set[37] is shown in formula **15**) reveal a higher density at the 2- and 4-positions of pyridine *N*-oxide than those of pyridine.



(12a) (12b) (12c) (12d)



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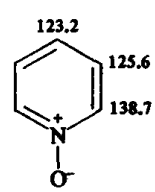

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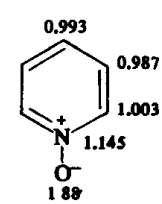

(15)

The main feature of the mass spectra of pyridine *N*-oxides[38] is an intense $(M-16)^+$ ion.

Pyridine *N*-oxides are weaker bases than the corresponding pyridines: pyridine *N*-oxide itself has pK_a 1.90, and the pK_a values of most simple analogues lie within the range −2 to +3.[39a] Alkylation and acylation of the *N*-oxides takes place on oxygen, and the resulting *N*-alkoxy- and *N*-acyloxy-pyridinium salts are useful synthetic intermediates by virtue of the ease with which they undergo nucleophilic addition–elimination (AE_a) reactions (*cf.* Section 16.1.3.2).

Reduction of pyridine *N*-oxides, to regenerate the parent pyridines, has been effected by a wide variety of reducing agents.[39b,40a] The reagent of choice for any particular case depends on the nature of other substituents in the molecule. For example, catalytic hydrogenation over Raney nickel or palladium–charcoal,[41] or reagents such as iron in acetic acid,[42] ferrous oxalate,[43] or sodium borohydride and aluminium chloride[44] are likely to affect reducible groups in the molecule other than the *N*-oxide.

The most frequently used reducing agents are trivalent phosphorus compounds, especially phosphorus trihalides. Phosphorus trichloride in chloroform reduces a wide variety