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Heterocyclic Compounds

Organic Chemistry
Series One
Volume 4

Consultant Editor
D H Hey FRS
Volume Editor
K Schofield

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Volume 4

Heterocyclic Compounds

Edited by **K. Schofield**
University of Exeter

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Publisher's Note

The MTP International Review of Science is an important new venture in scientific publishing, which we present in association with MTP Medical and Technical Publishing Co. Ltd. and University Park Press, Baltimore. The basic concept of the Review is to provide regular authoritative reviews of entire disciplines. We are starting with chemistry because the problems of literature survey are probably more acute in this subject than in any other. As a matter of policy, the authorship of the MTP Review of Chemistry is international and distinguished; the subject coverage is extensive, systematic and critical; and most important of all, new issues of the Review will be published every two years.

In the MTP Review of Chemistry (Series One), Inorganic, Physical and Organic Chemistry are comprehensively reviewed in 33 text volumes and 3 index volumes, details of which are shown opposite. In general, the reviews cover the period 1967 to 1971. In 1974, it is planned to issue the MTP Review of Chemistry (Series Two), consisting of a similar set of volumes covering the period 1971 to 1973. Series Three is planned for 1976, and so on.

The MTP Review of Chemistry has been conceived within a carefully organised editorial framework. The over-all plan was drawn up, and the volume editors were appointed, by three consultant editors. In turn, each volume editor planned the coverage of his field and appointed authors to write on subjects which were within the area of their own research experience. No geographical restriction was imposed. Hence, the 300 or so contributions to the MTP Review of Chemistry come from many countries of the world and provide an authoritative account of progress in chemistry.

To facilitate rapid production, individual volumes do not have an index. Instead, each chapter has been prefaced with a detailed list of contents, and an index to the 10 volumes of the MTP Review of Organic Chemistry (Series One) will appear, as a separate volume, after publication of the final volume. Similar arrangements will apply to the MTP Review of subsequent series.

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INDEX VOLUME

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INDEX VOLUME

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INDEX VOLUME

Organic Chemistry
Series One

Consultant Editor
D. H. Hey, F.R.S.

Consultant Editor's Note

The subject of Organic Chemistry is in a rapidly changing state. At the one extreme it is becoming more and more closely involved with biology and living processes and at the other it is deriving a new impetus from the extending implications of modern theoretical developments. At the same time the study of the subject at the practical level is being subjected to the introduction of new techniques and advancements in instrumentation at an unprecedented level. One consequence of these changes is an enormous increase in the rate of accumulation of new knowledge. The need for authoritative documentation at regular intervals on a world-wide basis is therefore self-evident.

The ten volumes in Organic Chemistry in this First Series of biennial reviews in the MTP International Review of Science attempt to place on record the published achievements of the years 1970 and 1971 together with some earlier material found desirable to assist the initiation of the new venture. In order to do this on an international basis Volume Editors and Authors have been drawn from many parts of the world.

There are many alternative ways in which the subject of Organic Chemistry can be subdivided into areas for more or less self-contained reviews. No single system can avoid some overlapping and many such systems can leave gaps unfilled. In the present series the subject matter in eight volumes is defined mainly on a structural basis on conventional lines. In addition, one volume has been specially devoted to methods of structure determination, which include developments in new techniques and instrumental methods. A further separate volume has been devoted to Free Radical Reactions, which is justified by the rapidly expanding interest in this field. If there prove to be any major omissions it is hoped that these can be remedied in the Second Series.

It is my pleasure to thank the Volume Editors who have made the publication of these volumes possible.

London

D. H. Hey

Preface

Heterocyclic systems form a majority of the several thousand ring-systems known to organic chemistry. Even an extended review cannot deal with more than a fraction of them. In this volume the major families are dealt with, though many minor systems receive incidental mention.

Most of the work reviewed relates to the chemistry of heteroaromatic systems, and of these a fairly uniform kind of treatment is given. This treatment is less appropriate to such a diverse group as the Oxygen Heterocycles (Chapter 7), and inapplicable to Reduced Heterocycles (Chapter 10). The Macromolecular Heterocyclic Compounds (Chapter 11) include individual compounds of the greatest importance, and the study of this family is now a major activity in the field.

Despite the limitation imposed by the unavoidable need to be selective, it is hoped that this review mirrors accurately the important interests and achievements of those working at present on Heterocyclic Organic Chemistry.

Exeter

K. Schofield

Contents

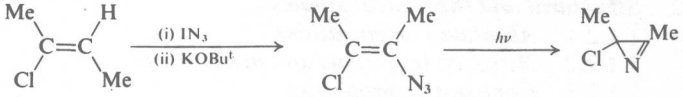
1
Small (3- and 4-Membered) and Medium (Especially 7-Membered) Rings

D. R. MARSHALL
University College of North Wales, Bangor

1.1 THREE-MEMBERED RINGS

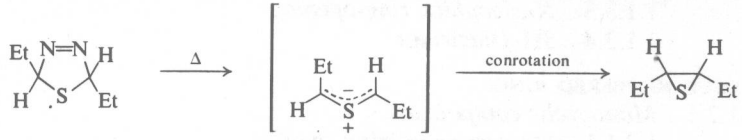
1.1.1 Ring synthesis

Established methods of ring synthesis[1] are generally used, but new methods have been found, especially for nitrogen compounds. Thus nitrenes will add to multiple bonds, and generation of nitrenes by oxidation of *N*-aminophthalimide and related compounds (e.g. by lead tetra-acetate) in the presence of olefins gave aziridines[2]. With acetylenes the nitrenes gave 2*H*-azirines[3], a reaction discussed in Section 1.1.2.4. If the nitrene function is generated within the olefin by decomposition of a vinyl azide, cyclisation takes place and the unsaturation is retained. The azide group can be introduced by

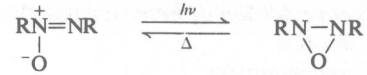


addition of iodine azide, as in the preparation of a 2-chloro-2*H*-azirine[4].

A novel thi-irane synthesis also utilises elimination of nitrogen, but to give an ylid which underwent conrotatory cyclisation (Section 1.1.3.1). As the ylid largely retained its configuration, the *trans*-diethylthiadiazoline



giving a product containing 93% of *cis*-diethylthi-irane, cyclisation may have been rapid and not significantly reversible[5]. Azoxyalkanes, which can be



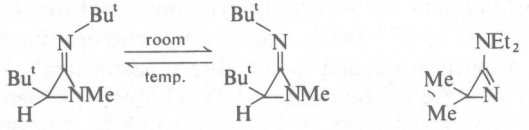
classed as ylids, have been cyclised to oxadiaziridines, in which the ring contains no carbon. The compounds readily reverted to the azoxyalkanes[6].

1.1.1.1 α-Lactams and related compounds

α-Lactones, the classic three-membered cyclic intermediates in reactions, are unstable, but α-lactams have been found to be more stable. It is well known that the presence of substituents favours ring closure, and it also

stabilises the ring. α-Lactams can be obtained by treatment of α-bromoamides with base, and 1,3-di-t-butylaziridin-2-one is quite stable at room temperature, decomposes slowly at 140 °C, and is attacked very slowly by nucleophiles[7]. This synthesis may provide a useful route to amino acids, for the lactams are alkylated at oxygen to imino-ethers by triethyloxonium fluoborate and the ethers are hydrolysed by bicarbonate to amino acids[8].

Cyclisation of α-bromoamidines with base gives aziridine imines analogous



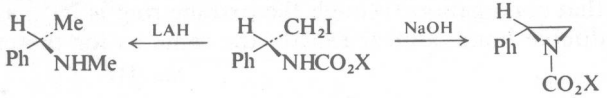
(1) (2)

to α-lactams ('α-lactamidines'?), e.g. (1)[9], while a vinyl azide route gave the isomeric aminoazirine structure (2)[10].

1.1.2 Structural and theoretical studies

1.1.2.1 Absolute configurations

Spectroscopic methods are generally used to determine relative stereochemistry of reactants and products, but the absolute stereochemistry of enantiomers may not be known. This has been determined for 2-phenylaziridine[11]. Iodine isocyanate (another useful reagent for introduction of nitrogen functions) added to styrene gave a racemic product, converted by addition of menthol to diastereomeric urethanes, which were separated. Cyclisation



S(−) (X = menthyl) R(−)

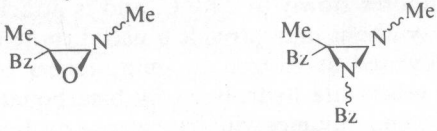
with base gave the aziridines, while reduction gave *N*-methyl-α-phenylethylamines related to known enantiomers.

1.1.2.2 Nitrogen inversions and invertomers

Though nitrogen usually inverts rapidly, in small rings inversion may be so slow as to allow separation of stable invertomers. The inductive and electrostatic effects of an electronegative atom next to the inverting nitrogen appear to be required. The first stable invertomers were *N*-chloroaziridines[12, 13], and others such as *N*-chloro-*trans*-2-phenyl-3-benzoylaziridine[14] have since been separated. *N*-alkoxyaziridines also show slow inversion[15].

The adjacent heteroatom may be in the ring, as in oxaziridines and diaziridines. Thus invertomers of 2,3-dimethyl-3-benzyloxaziridine and 1,3-dimethyl-2,3-dibenzyldiaziridine have been isolated, as well as various others[16]. In the pair of diaziridines the two inverting groups are always

trans to one another, though it is thought that the two nitrogen atoms do not invert synchronously.

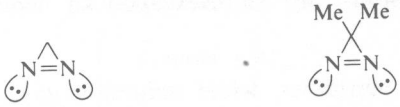


The inversion barriers for several oxaziridines and diaziridines lie in the region of 110–135 kJ mol^{-1} (with, reasonably, entropy barriers near zero), well above the minimum needed to stabilise invertomers[16]. For many other compounds barriers are in the range 40–80 kJ mol^{-1}, which is too small to allow separation of invertomers, but large enough to produce n.m.r. coalescence temperatures up to *c.* 125 °C[17]. Similar inversion rates are found in dialkyldiaziridinones, for which the high i.r. carbonyl frequencies (up to 1880 cm^{-1}) suggest little amide conjugation and hence pyramidal nitrogen[18]. (A similar effect is found in the four-membered 1,2-diazetidinones[19].) How-

ever, hetero-substituents such as chlorine on carbon may lower inversion barriers through double bond–no bond resonance[17].

1.1.2.3 *Conjugative properties*

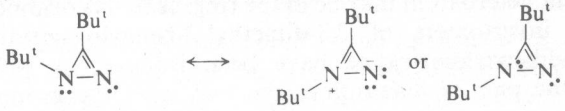
In small heterocyclic rings distortion has effects very similar to those found in cyclopropane. This extends to conjugative effects, for a ^{19}F n.m.r. study has shown that conjugation through the oxirane ring is 26% as effective as through a double bond, almost exactly the same as for the cyclopropane



ring[20]. A related observation is that in diazirine and 3,3-dimethyldiazirine the unshared electron pairs are only *c.* 50% localised[21].

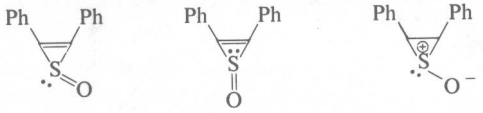
1.1.2.4 *Aromatic and anti-aromatic properties*

The effects of ring strain and electron numbers on resonance are of considerable interest. The amidines (1) and (2) (Section 1.1.1.1) would, but for the ring structure, be strong bases forming stable cations. Unfortunately their p*K* values are not known, but (2) immediately dimerises in acid, contradicting cation stability[10]. The behaviour of the unknown 1*H*-diazirine ring would be



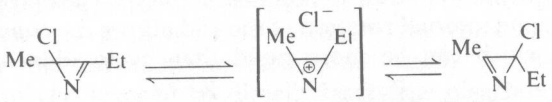
interesting, as it might show some amidine-like stability, or the instability of a 4-π-electron anti-aromatic system. Its synthesis might be eased by t-butyl substituents (cf. lactams).

Dual possibilities also exist for 2,3-diphenylthi-irene 1-oxide[22], which might be predominantly olefinic, or anti-aromatic or aromatic. In fact it is



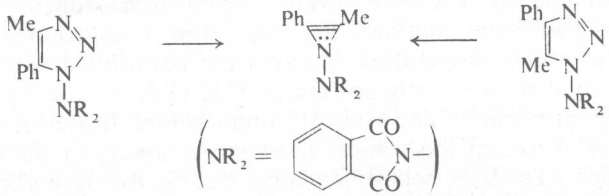
more stable than the corresponding sulphone and its spectroscopic properties indicate conjugation, showing that it adopts the third, most stable, structure. Its stability contrasts with the thermal instability of saturated thi-irane *S*-oxides and aziridine *N*-oxides, which readily cleave to olefins[23, 24].

Dialkyl-2-chloro-2*H*-azirines do not appear to ionise extensively to aromatic azapropenium ions, but the ethyl methyl derivative isomerises via



a polar transition state which may be markedly delocalised[4].

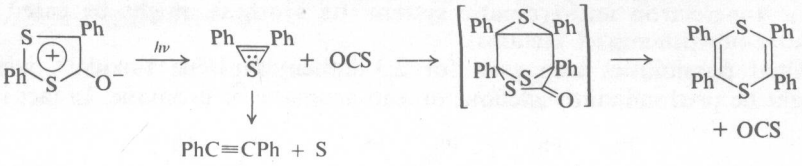
Anti-aromatic properties[25] are expected for 1*H*-azirines, the lower vinylogues of pyrroles. They are isoelectronic with cyclopropyl anions, for which an anti-aromatic energy of *c.* 400 kJ mol^{-1} (depending on the conformation assumed) is calculated[26]. Attempted preparations have failed, and typically give 2*H*-azirines instead, this behaviour being explained by anti-aromatic instability[3]. The intermediacy of a 1*H*-azirine has been demonstrated, however, by pyrolising two isomeric phthalimidotriazoles. Loss of



nitrogen led to nitrenes, which underwent cyclisations and rearrangements, but identical product mixtures were obtained from both triazoles, showing a common intermediate. This was clearly unstable, and was most probably the 1*H*-azirine[27].

Oxirenes and thi-irenes should be similarly anti-aromatic. Oxirenes have been identified in photolyses of α-diazoketones and alkyl diazoacetates[28], and have been postulated as reaction intermediates, e.g. in the photolysis of ^{14}C labelled ketene, when carbon scrambling is observed[29]. Thi-irenes have

also been postulated as intermediates, as in the photolysis of a mesoionic

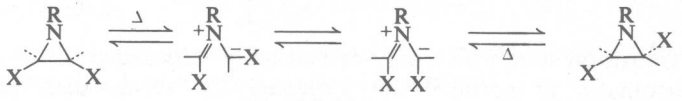


dithiolium oxide[30].

1.1.3 Ring-modifying processes

1.1.3.1 Ylid formation and cyclo-addition

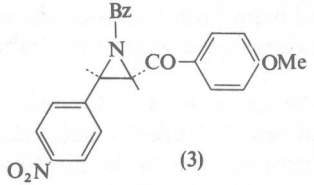
Aziridines undergo thermolytic or photolytic C—C bond cleavage to give dipolar ylids, thermolysis being conrotatory and photolysis disrotatory, in accordance with the Woodward–Hoffmann rules[31]. Cleavage is first order and reversible, and internal rotation of the ylid allows *cis–trans* equilibration of aziridines, which can be more rapid than cyclo-addition with added



(X = CO_2Me)

dipolarophile[32]. Recyclisation (over a few seconds) of these ylids when produced by flash photolysis showed activation entropies of -134 J $mol^{-1}K^{-1}$ (to *cis*-aziridine) and -88 J $mol^{-1}K^{-1}$ (to *trans*-aziridine), showing the transition states to be cyclic[33]. Analogous behaviour is shown by oxiranes such as *cis*- and *trans*-dicyanostilbene oxides[34], while the stereochemistry of the cycloadducts from 2-cyano-*trans*-stilbene oxide and dimethyl fumarate show that here too thermolysis is conrotatory[35].

Whereas at room temperature oxiranes are photolysed to ketones and carbenes, in rigid glasses of ethanol, etc. at 77 K ylids are also formed, giving rise to photochromism[36]. The ylids are immobilised, however, and cannot isomerise. On warming the colours fade, more rapidly in the presence of dipolarophiles. Aziridines behave similarly, but the nitrogen ylids are more stable, even, with suitable substituents, in solution at room temperature.



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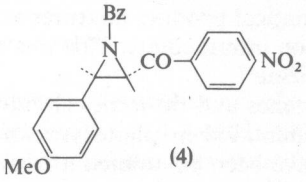

(4)

Thus ylids from (3) (blue) and (4) (red) then have half lives of minutes and hours, respectively. These ylids gave adducts with dipolarophiles, or were reconverted to the parent aziridines by irradiation with visible light.

Dipolarophiles may be electrophilic olefins, carbonyl groups, azo groups, nitroso groups, or imines[37].