Tetrahedron Vol. 41, No. 12, pp 2239 to 2329, 1985
Printed in Great Britain

0040-4020/85 $5.00 + .00
Pergamon Press Ltd.

TETRAHEDRON REPORT NUMBER 185

HETEROCYCLIC MESOMERIC BETAINES†

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(*Received* 1 *March* 1984)

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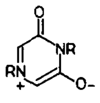
† This Review formed the basis of two Plenary Lectures entitled "Heterocyclic Mesomeric Betaines" given by one of us (W.D.O.) at the Annual Colloquium on Synthetic Organic Chemistry held at the Katholieke Universiteit, Leuven, Belgium (25 February 1983) and the 185th American Chemical Society National Meeting, Seattle, Washington (20–25 March 1983).

I. THE CONCEPTS OF CONJUGATION, CROSS-CONJUGATION, AND PSEUDO-CROSS-CONJUGATION IN HETEROCYCLIC MOLECULES

What are the common structural features and what are the significant differences between the heterocyclic molecules **1**, **2** and **3**?



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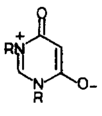

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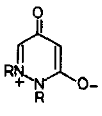

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This question could be answered by just stating that the molecules **1**, **2** and **3** are all heterocyclic mesomeric betaines. This general answer, however, conceals an informative distinction because there are three fundamentally different types of conjugation associated with the π-electron systems of these three molecules. Thus, molecule **1** is a *conjugated* heterocyclic mesomeric betaine, molecule **2** is a *cross-conjugated* heterocyclic mesomeric betaine, and molecule **3** is a *pseudo-cross-conjugated*† heterocyclic mesomeric betaine.

The identification of the type of conjugation associated with the π-electron systems of heterocyclic mesomeric betaines is important so three additional examples are given which are considered to be instructive. Molecule **4** is a *conjugated* heterocyclic mesomeric betaine, molecule **5** is a *cross-conjugated* heterocyclic mesomeric betaine, and molecule **6** is a *pseudo-cross-conjugated* heterocyclic mesomeric betaine.

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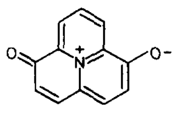
† The need to introduce the new term pseudo-cross-conjugated is discussed in Section IV (p. 2258).



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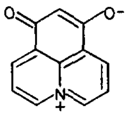

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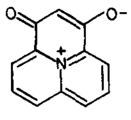

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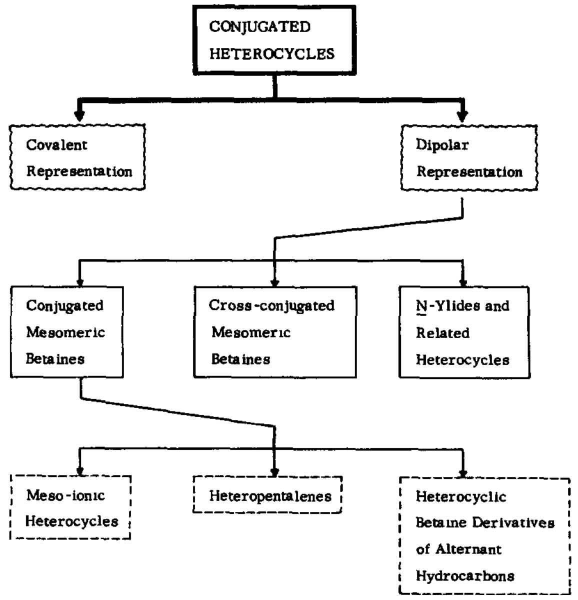
This classification of heterocyclic mesomeric betaines can be usefully developed at a fundamental level by understanding that mesomeric betaines are isoconjugate† with alternant and non-alternant hydrocarbon anions and dianions. These characteristics of the bonding π-electron systems present in the molecules of heterocyclic mesomeric betaines form an excellent basis for their classification: they also provide a satisfying correlation of their chemistry and reactivity. We now present a new system for the classification of heterocyclic mesomeric betaines which is based upon (i) the type of conjugation associated with their π-electron systems and (ii) their relationships as isoconjugates† of either alternant or non-alternant hydrocarbon mono-anions or dianions.

The development of heterocyclic chemistry has been associated with an increased understanding of the need to divide conjugated heterocyclic molecules into two main groups (Scheme 1). One group contains those conjugated heterocycles which are satisfactorily represented by uncharged covalent structures. This group presents no problems and the isoconjugate† relationship of its members to aromatic or anti-aromatic carbocycles is generally accepted. The other group consists of those conjugated heterocycles which cannot be represented, even approximately, by any uncharged covalent structure: the only acceptable representation is a dipolar structure. The dipolar structure is selected from the variety of dipolar structures which, in valence bond terminology, contribute as canonical forms to the mesomeric structure of the molecule. Members of this class of heterocycles are all included in the following definition.

Mesomeric betaines are neutral conjugated molecules which can be represented only by dipolar structures in which both the positive and negative charges are delocalised within the π-electron system.

Mesomeric betaines are of two types (i) acyclic mesomeric betaines and (ii) heterocyclic mesomeric betaines. Acyclic mesomeric betaines are exemplified by 1,3-dipoles[2] and 1,5-dipoles.[3] The classification of heterocyclic mesomeric betaines as a basis for the correlation of the chemistry of heterocyclic mesomeric betaines forms the subject of the present Report.



Scheme 1. The old classification of heterocyclic mesomeric betaines.

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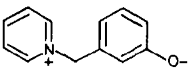
† The term isoconjugate is used as defined by Dewar.[1] Systems are said to be isoconjugate when they have the same number of conjugated similarly connected atoms with the same total number of π-electrons. This definition is in accord with Dewar's teaching[1] that the terms isoconjugate and isoelectronic are not synonymous.



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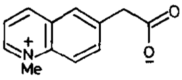

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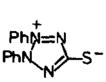
The term heterocyclic mesomeric betaine has an attractive utility because it brings together within one general group a large number of different types of heterocycles which possess a unifying structural feature. This is their dipolar character and this has a dominant influence upon many aspects of their chemistry.

The difficulty which we have experienced[4–6] in persuading chemists to restrict their use of the term *meso-ionic* only to our definition[4] encourages us to mention certain molecules which should not be described as heterocyclic mesomeric betaines. Dipolar molecules which are specifically excluded by the definition given above are exemplified by the *zwitterions* **7** and **8**. This use of existing nomenclature is recommended for such molecules because, although there is charge delocalisation in the zwitterions **7** and **8**, the positive and negative charges are specifically associated with separate, insulated π-electron systems. This feature is best dealt with by adopting existing terminology and describing the examples **7** and **8** as zwitterions. If it is absolutely necessary, **7** and **8** could be described as mesomeric zwitterions, but this should be discouraged.



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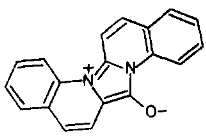

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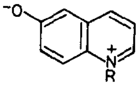

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It is interesting to note that the first 5-membered heterocyclic mesomeric betaine **9** was synthesised by Fischer and Besthorn in 1882.[7a] Subsequently, Besthorn[7b] discovered Besthorn's Red, but the constitution **10** was not proposed for this pigment until 1939.[7c] This proposal was later developed by Brown and Hammick,[7d] who recognised Besthorn's Red as a mesomeric betaine **10**. The first 6-membered heterocyclic mesomeric betaine **11** was synthesised in 1891.[8] Subsequently many heterocyclic mesomeric betaines have been described, but it is only recently that real progress has been made towards their systematic classification. The exception to this statement is the systematic investigation of heterocyclic *N*-oxides by Katritzky[9] and by Ochiai,[10] and the rich chemistry of heterocyclic *N*-ylides.[11,12] The important distinction between conjugated mesomeric betaines and cross-conjugated mesomeric betaines depicted in Scheme 1 was not recognised until 1977.[13]

Three major classes of conjugated mesomeric betaines have recently been the subject of detailed reviews. These are meso-ionic heterocycles,[4–6] the heteropentalenes,[14–19] and conjugated mesomeric betaines isoconjugate with alternant hydrocarbon anions.[20] Katritzky in 1955[21] explicitly emphasised that meso-ionic heterocycles belonged to the general class of mesomeric betaines. This view is correct, but Baker and Ollis[22] advocated the retention of the term meso-ionic and this has been justified by the maintenance of interest in this class of heterocycles. However, it is very important that the term meso-ionic should be applied only to those 5-membered heterocycles which conform to the following definition.[4–6]

A compound may be appropriately called meso-ionic if it is a 5-membered heterocyclic compound which cannot be represented satisfactorily by any one covalent or dipolar structure and possesses a sextet of π-electrons in association with the atoms comprising the 5-membered ring.

This definition is appropriately related to the definition of mesomeric betaines given above. It may also be noted that two types (**A** and **B**) of meso-ionic heterocycles have been recognised and we continue to advocate that the term meso-ionic should be used to describe only those 5-membered heterocycles which belong to type **A** and type **B**.[4–6] Using acceptable combinations of carbon and hydrogen atoms in association with nitrogen, oxygen, and sulphur as heteroatoms, then 144 representatives of type **A** and 84 representatives of type **B** meso-ionic heterocycles can be visualised.[4] A similar analysis has been made of the mesomeric betaines which could exist which are isoconjugates of the bicyclic 10π-pentalenyl dianion.[14] In this case, four general types (**A**, **B**, **C** and **D**) of mesomeric heteropentalenes have been recognised and these four types are each associated with the indicated number of possible heterocyclic members: type **A** (51), type **B** (24), type **C** (96) and type **D** (96). Many of these mesomeric heteropentalenes are unknown and so are targets for synthesis.[14]

Clearly the classification of heterocyclic betaines presented in Scheme 1 has served a useful purpose, but its limitations became apparent when we made an attempt to classify many other heterocyclic mesomeric betaines which were either known or might be expected to exist. The classification which we now wish to propose is presented in Scheme 2. This proposal is based upon the following four definitions which are, of course, conditioned by the definition of mesomeric betaines given above.

Conjugated heterocyclic mesomeric betaines are cyclic mesomeric betaines in which the positive and negative charges are not restricted to separate parts of the π*-electron system of the molecule. The positive and negative charges are in mutual conjugation and both are associated with the common conjugated* π*-electron system of the molecule.*

Conjugated heterocyclic N*-ylides and related dipolar compounds constitute a subdivision of conjugated heterocyclic mesomeric betaines which can be satisfactorily represented by* 1,2*-dipolar structures such as* N*-oxides, in which the negative charge is accommodated at an exocyclic atom or group.*

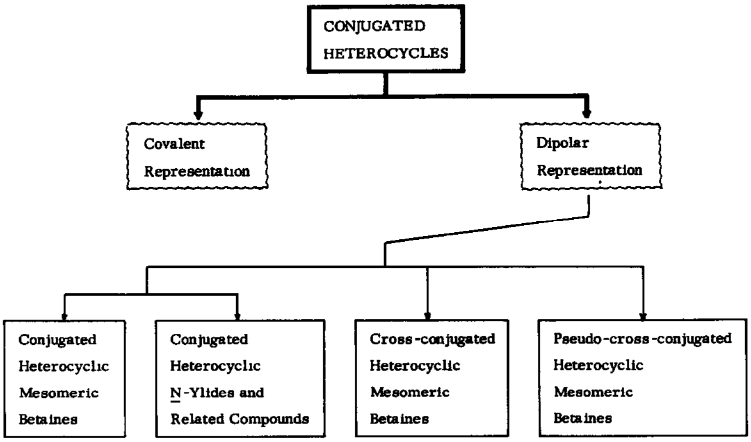
Cross-conjugated heterocyclic mesomeric betaines are cyclic mesomeric betaines in which the positive and negative charges are exclusively restricted to separate parts of the π*-electron system of the molecule.*

Pseudo-cross-conjugated heterocyclic mesomeric betaines are cyclic mesomeric betaines in which the positive and negative charges are effectively but not exclusively restricted to separate parts of the π*-electron system of the molecule.* The need for, and the significance of, this definition becomes apparent when specific examples of pseudo-cross-conjugated mesomeric betaines are discussed later (Section III, 13, 14, 15 and 16; Section IV).

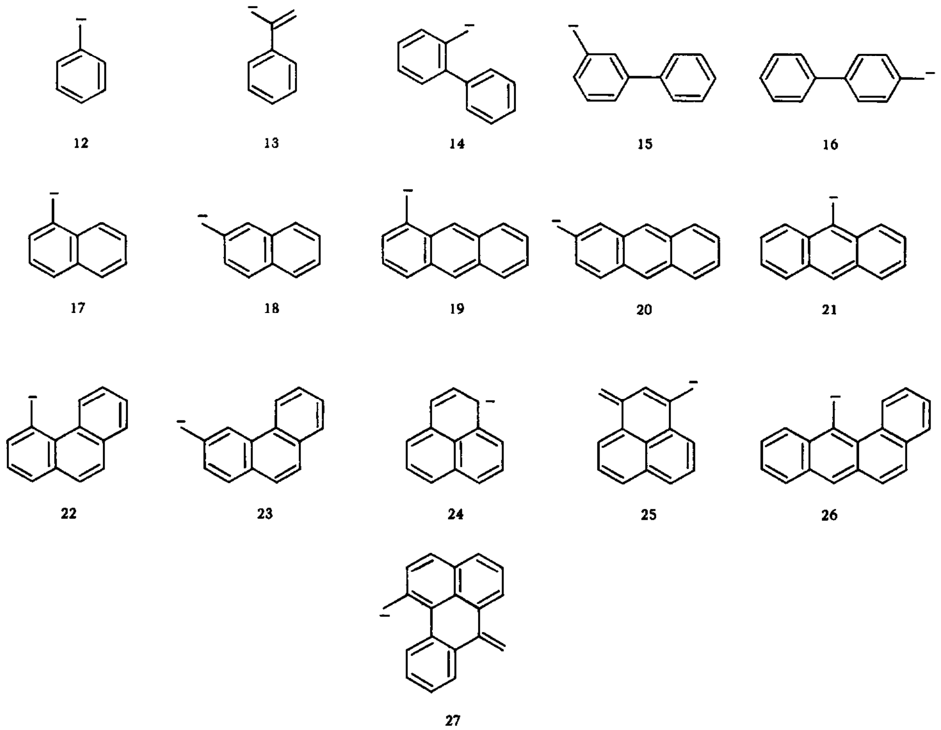
These four major classes of heterocyclic mesomeric betaines (Scheme 2) are then separated into four sub-classes whose members are isoconjugate with one of the four following types:

(i) Odd alternant hydrocarbon anions (Scheme 3);
(ii) Odd non-alternant hydrocarbon anions (Scheme 4);
(iii) Even alternant hydrocarbon dianions (Scheme 5);
(iv) Even non-alternant hydrocarbon dianions (Scheme 6).

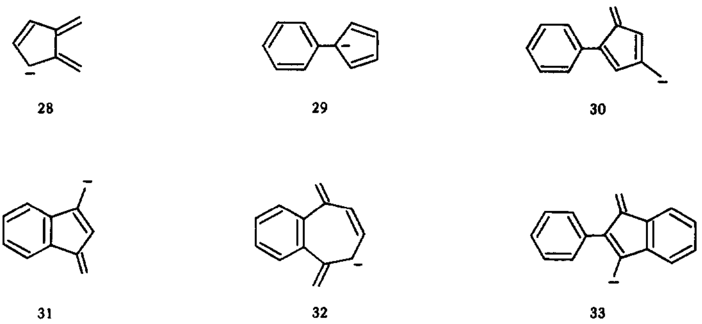
This classification obviously leads to 16 different categories into which all heterocyclic mesomeric betaines isoconjugate with hydrocarbon anions and dianions can be placed. This is a rigorous system of classification which has a sound theoretical foundation. It may be mentioned parenthetically that there is a number of heterocyclic mesomeric betaines which do not belong to the 16 categories designated above. However, these additional heterocyclic mesomeric betaines can be rationally accommodated by recognising that the classification can be easily extended to include, for example, (a) conjugated mesomeric betaines which are isoconjugate with odd non-alternant hydrocarbon trianions and (b) cross-conjugated mesomeric betaines which are isoconjugate with odd non-alternant hydrocarbon trianions. Known examples of these two types are given in Section VII. It is emphasised that this classification of heterocyclic mesomeric betaines is comprehensive. There can be no exceptions.



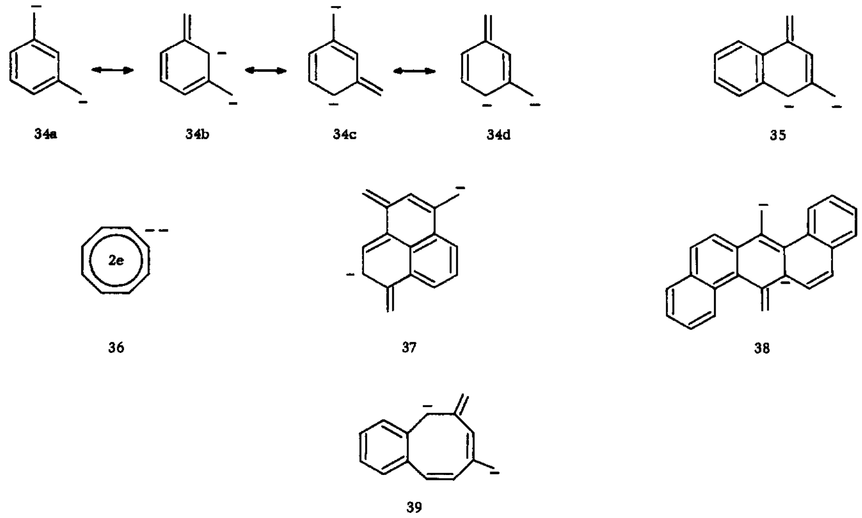
Scheme 2. A new proposal for the classification of heterocyclic mesomeric betaines



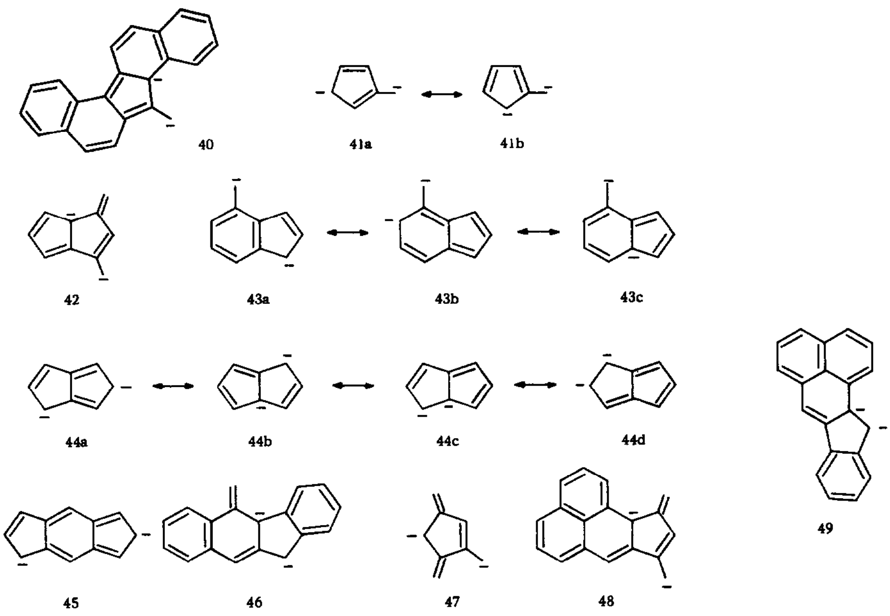
Scheme 3. Odd alternant hydrocarbon anions.



Scheme 4. Odd non-alternant hydrocarbon anions.



Scheme 5. Even alternant hydrocarbon dianions.



Scheme 6. Even non-alternant hydrocarbon dianions.

II. ALTERNANT AND NON-ALTERNANT HYDROCARBONS

The basis of the classification of heterocyclic mesomeric betaines now proposed rests upon the recognition that conjugated hydrocarbons can be classified as odd alternant, odd non-alternant, even alternant, and even non-alternant. This concept was initially introduced by Coulson and Rushbrooke[23] and was developed by Coulson and Longuet-Higgins.[24] The profound implications of this treatment of conjugated systems became widely recognised[25–28] and as a result of Dewar's teachings[1] and his advocacy of the molecular orbital treatment of heteroconjugated systems, we have now adopted this general approach to classify heterocyclic mesomeric betaines.

The terms odd and even refer to the total numbers of atoms which participate in the conjugated systems. Alternant hydrocarbons are defined as conjugated systems in which the skeletal atoms can be divided into two sets, starred and unstarred, in such a way that no atoms of like parity are directly bonded. If the numbers of atoms in the starred and unstarred sets differ then the larger number is starred. Non-alternant hydrocarbons[26] are conjugated systems which are easily recognised because the skeletal atoms cannot be divided into starred and unstarred sets in such a way that atoms of like parity are not directly bonded. Thus, all conjugated systems containing odd-membered rings must be non-alternant.

Two types of alternant hydrocarbons can be recognised: (a) even alternant hydrocarbons associated with m starred atoms and m − 2n unstarred atoms, (b) odd alternant hydrocarbons associated with m starred atoms and m − (2n + 1) unstarred atoms. Even alternant hydrocarbons can be subdivided into two types,[1,14] Kekulé hydrocarbons and non-Kekulé hydrocarbons. Kekulé even alternant hydrocarbons have classical polyene structures. Non-Kekulé even alternant hydrocarbons must be biradicals and examples include 2,2′-biallyl, *m*-quinodimethane and triangulene.

Odd alternant hydrocarbons must be radicals. A typical example is the benzyl radical.

Two types of non-alternant hydrocarbons can be recognised: (a) even non-alternant hydrocarbons and (b) odd non-alternant hydrocarbons. Even non-alternant hydrocarbons can be subdivided into two types, Kekulé hydrocarbons and non-Kekulé hydrocarbons. Kekulé hydrocarbons have classical polyene structures. Typical examples of even non-alternant systems which are Kekulé hydrocarbons include the 5-membered fulvene and pentalene. Non-Kekulé hydrocarbons cannot be represented by classical polyene structures and even non-alternant non-Kekulé hydrocarbons must be diradicals. The 3,4-dimethylene fulvene diradical is an example.

Odd non-alternant hydrocarbons must be radicals. A typical example is the cyclopentadienyl radical.

In summary, four types of non-Kekulé hydrocarbons (i, ii, iii and iv) can be recognised which must be either radicals or diradicals:

(i) Odd alternant hydrocarbon radical;
(ii) Odd non-alternant hydrocarbon radical;
(iii) Even alternant hydrocarbon diradical;
(iv) Even non-alternant hydrocarbon diradical.

Addition of one electron to the singly occupied molecular orbital (SOMO) of types (i) and (ii) gives the corresponding anion. Addition of two electrons to suitable molecular orbitals of the types (iii) and (iv) gives the corresponding dianions. It is obvious that these processes lead to the following four types (a, b, c and d) of hydrocarbon anions and dianions:

(a) Odd alternant hydrocarbon anion;
(b) Odd non-alternant hydrocarbon anion;
(c) Even alternant hydrocarbon dianion;
(d) Even non-alternant hydrocarbon dianion.

A major objective of this Report is the presentation of the case that the majority of all known heterocyclic mesomeric betaines can be classified as the isoconjugates of these four types (a, b, c and d) of hydrocarbon anions and dianions. This classification leads directly to 16 categories (Section III). All known heterocyclic mesomeric betaines can be classified in these 16 categories if they are isoconjugates of hydrocarbon anions or dianions (Section III) and this classification can be obviously extended to include the few known heterocyclic mesomeric betaines which are isoconjugates of hydrocarbon trianions (Section VII). All heterocyclic mesomeric betaines can therefore be classified as isoconjugates of hydrocarbon anions, dianions, trianions and possibly tetra-anions. This classification (Sections III and VII) reveals that some categories are heavily occupied by a large number of different structural types, whereas the membership of some of the other categories is either sparse or non-existent. In these cases the categories are illustrated (Section III) by hypothetical examples. It is hoped that some of these gaps in our knowledge will be filled by successful synthetic efforts.

III. THE CLASSIFICATION OF HETEROCYCLIC MESOMERIC BETAINES AS ISOCONJUGATES OF ALTERNANT AND NON-ALTERNANT HYDROCARBON ANIONS AND DIANIONS†

Isoconjugate relations are indicated between the structural formulae of betaines and the hydrocarbon anions listed in Schemes 3–6, by the equivalent pairing of formula numbers in the following 16 categories.

1. *Conjugated heterocyclic mesomeric betaines isoconjugate with odd alternant hydrocarbon anions* (Scheme 3)

Although many examples of this class of conjugated heterocyclic mesomeric betaines are scattered throughout the literature,† the topic was not comprehensively reviewed until 1980.[20] The key to a well-based understanding of the chemistry of this class of conjugated mesomeric betaines was the recognition[13] that all known members were isoconjugates of the odd alternant hydrocarbon anions listed in Scheme 3.

The benzyl anion **12** is a particularly instructive example of a monocyclic odd alternant hydrocarbon anion and a large number of conjugated mesomeric betaines is easily recognised as being isoconjugate with the benzyl anion **12**. This class includes pyridinium-3-olates **50**,[29–31] pyrylium-3-olates **51**,[32–34] thiopyrylium-3-olates **52**,[35] pyridinium-3-aminides **53**,[36] pyridazinium-3-olates **54**,[37,38] pyridazinium-5-olates **55**,[38–43] and 1,2,4-triazinium-5-olates **56**.[44] The starring system,[1] as applied to the benzyl anion **12**, is illustrated in formula **57** and comparison of this formula **57** with the dipolar structures **50–56** illustrates the important point that the positively charged heteroatom is always located at an unstarred position. The fundamental significance of this common structural feature has already been emphasised.[20]

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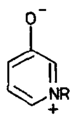
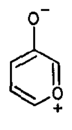
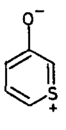
† Throughout this Report, we have often used parent structures to represent known compounds, whereas in some cases only substituted derivatives have been synthesised. In such cases the original literature should be consulted to verify the structures of known heterocycles.


50 ≡ 12


51 ≡ 12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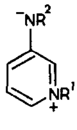
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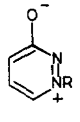
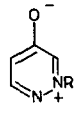
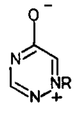
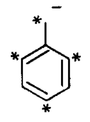
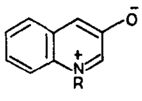

54 ≡ 12

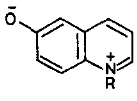

55 ≡ 12

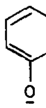

56 ≡ 12

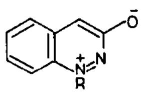

57 ≡ 12

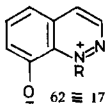
Known bicyclic mesomeric betaines involving systems of eleven conjugated atoms include quinolinium-3-olates **58**,[45] quinolinium-6-olates **59**,[8,46] quinolinium-8-olates **60**,[47] cinnolinium-3-olates **61**,[48] cinnolinium-8-olates **62**,[49] isoquinolinium-4-olates **63**,[50] isoquinolinium-4-aminides **64**,[51] phthalazinium-1-olates **65**,[37,52] cinnolinium-4-olates **66**,[53] cinnolinium-4-thiolates **67**,[54] 1,2,3-benzotriazinium-4-olates **68**,[55] 1,2,3-benzotriazinium-4-aminides **69**,[56] 1,2,3-benzotriazinium-4-thiolates **70**,[57] 1,7-naphthyridinium-4-olates **71**,[58] quinolizinium-1-olates **72**,[59] quinolizinium-3-olates **73**,[59] 1,9-naphthyridinium-4-olates **74**,[60] pyrido[2,1-*f*][1,2,4]-triazinium-1-olates **75**,[61] 2-benzopyrylium-4-olates **76**,[62] and 2-benzothiopyrylium-4-olates **77**.[63] It is important to recognise that these twenty classes of bicyclic conjugated mesomeric betaines are isoconjugate with just two odd non-alternant hydrocarbon anions, the α-naphthyl methyl anion **17** and the β-naphthyl methyl anion **18**. Starring of these two anions leads to the structures **78** and **79** respectively. This provides an even more dramatic demonstration that in the dipolar structures **58**–**77** the positively charged heteroatoms are always located at unstarred positions (see **78** and **79**).

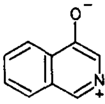

58 ≡ 18


59 ≡ 18


60 ≡ 17


61 ≡ 18


62 ≡ 17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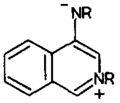
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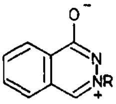
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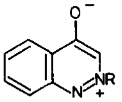
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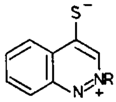
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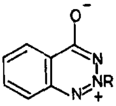
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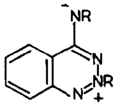
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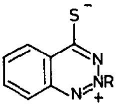
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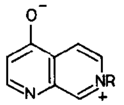
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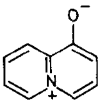
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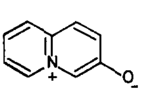
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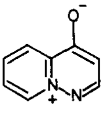
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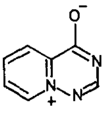
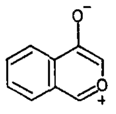
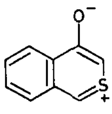
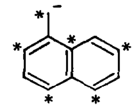

75 ≡ 17


76 ≡ 17


77 ≡ 17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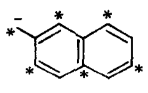
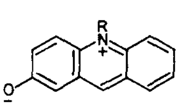
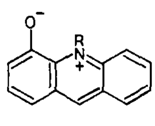

79

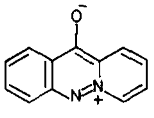
Known tricyclic mesomeric betaines include acridinium-2-olates **80**,[64] acridinium-4-olates **81**,[64] pyrido[1,2-*b*]cinnolinium-11-olates **82**,[65] pyrido[1,2-*b*]cinnolinium-11-aminides **83**,[65] pyrido[1,2-*b*]cinnolinium-11-thiolates **84**,[65] pyrido[1,2-*b*]cinnolinium-11-methylides **85**,[65] 5,8,10-triazabenzo[*a*]quinolizinium-11-olates **86**[44] and phenanthridinium-2-olates **87**.[66] These eight classes of tricyclic conjugated mesomeric betaines **80**–**87** are isoconjugate with five classes **19**–**23** of odd alternant hydrocarbon anions. Again, the positively charged heteroatoms in the dipolar structures **80**–



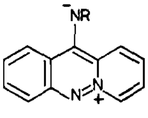
80 ≡ 20



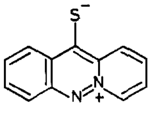
81 ≡ 19



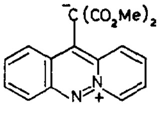
82 ≡ 21



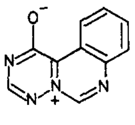
83 ≡ 21



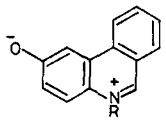
84 ≡ 22



85 ≡ 21



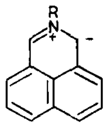
86 ≡ 22



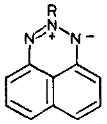
87 ≡ 23

87 are always located at unstarred positions of the corresponding odd alternant hydrocarbon anions.

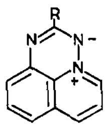
Tricyclic conjugated mesomeric betaines which are isoconjugate with the odd alternant phenalenyl anion **24** include the naphtho[1,8-*c*,*d*]pyridines **88**,[67] naphtho[1,8-*d*,*e*]triazines **89**[68] and quinolino[8,1-*e*,*f*][1,2,4]triazines **90**.[69] The synthesis of pyrido[1,2,3-*d*,*e*]quinoxalines **91** has been recently reported.[70,71] Our investigations[71] were certainly encouraged by our interest in synthesising novel heterocyclic mesomeric betaines isoconjugate with phenalenyl anion **24**.



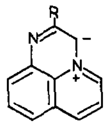
88 ≡ 24



89 ≡ 24



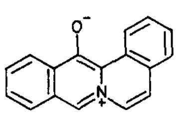
90 ≡ 24



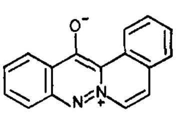
91 ≡ 24

Tetracyclic conjugated mesomeric betaines which are isoconjugate with the odd alternant hydrocarbon anion **26** are represented by the dibenzo[*a*,*g*]quinolizinium-13-olates **92**[72] and their 8-aza-derivatives **93**.[73]

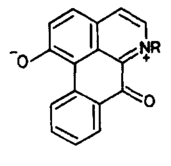
The recognition of a number of alkaloids[74] as derivatives of phenanthro[4,10-*b*,*c*]azinium-6,11-diolate **94** isoconjugate with the odd alternant hydrocarbon anion **27** is an interesting development.



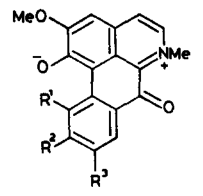
92 ≡ 26



93 ≡ 26



94 ≡ 27

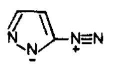


95 $R^1 = H$, $R^2 = R^3 = OMe$
96 $R^1 = H$, R^2, $R^3 = OCH_2O$
97 $R^1 = OMe$, $R^2 = R^3 = H$

These alkaloids[74] usually have striking colours and are exemplified by violet corunnine **95**, dark green nandazurine **96**, and the green alkaloid PO-3 **97**.

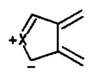
2. *Conjugated heterocyclic mesomeric betaines isoconjugate with odd non-alternant hydrocarbon anions* (Scheme 4)

Heterocyclic diazo-compounds (diazoazoles)[75] such as diazopyrazole **98** are well-known representatives of this class of mesomeric betaine. The role of diradicals **99** in certain base catalysed isomerisations has been emphasised[76] and this has led to the suggestion[20] that such diradicals could give rise to intermediate betaines **100**. Related betaines **101** have also been proposed[77] as carbonyl ylide intermediates in some photochemical rearrangements and these postulated intermediates have been trapped. The betaines **100** and **101** are isoconjugate with the odd non-alternant hydrocarbon anions **28** and **32** respectively.

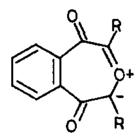


98

99



100 ≡ 28

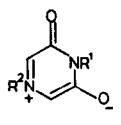


101 ≡ 32

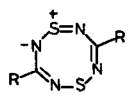
In 99 and 100 X = O, NR, or S

3. *Conjugated heterocyclic mesomeric betaines isoconjugate with even alternant hydrocarbon dianions* (Scheme 5)

Only two types of conjugated mesomeric betaines are known which belong to this class. These are (i) the 1,4-disubstituted-1,2-dihydro-2-oxopyrazinium-6-olates **102**[78] which are isoconjugate with the even alternant hydrocarbon dianion **34b** and (ii) the 1,5-dithia-2,4,6,8-tetrazocines **103**[79] which are isoconjugate with the cyclo-octatetraenyl dianion **36** (Section VI).



102 ≡ 34b



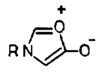
103 ≡ 36

4. *Conjugated heterocyclic mesomeric betaines isoconjugate with even non-alternant hydrocarbon dianions* (Scheme 6)

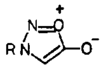
The membership of this class is extensive and includes meso-ionic heterocycles (types A and B),[4–6] the heteropentalenes (types A, B, C and D),[14] and a large variety of miscellaneous heterocycles for which conjugated mesomeric betaine structures have been proposed.

Type A meso-ionic heterocycles are exemplified by the 1,3-oxazolium-5-olates (munchnones; **104**), the 1,2,3-oxadiazolium-5-olates (sydnones; **105**) and the 1,2,3,4-tetrazolium-5-thiolates **106**. Type B meso-ionic heterocycles are exemplified by the 1,2-oxazolium-4-olates **107**, 1,2-diazolium-4-aminides **108** and the 1,2,3,4-tetrazolium-5-thiolates **109**.

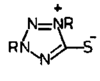
Since the general concept of meso-ionic heterocycles was proposed by Baker and Ollis in 1949,[22] many representatives of this large family of structurally related 5-membered dipolar heterocycles have been synthesised. In 1976, Ollis and Ramsden[4] emphasised the advantages to be gained by restricting the description "meso-ionic" only to 5-membered dipolar heterocycles represented by the two general formulae **110** and **111** which are applicable to type **A** and type **B** meso-ionic heterocycles respectively. Using reasonable combinations of carbon, nitrogen, oxygen and sulphur atoms, then 144 classes of type **A** meso-ionic heterocycles and 84 classes of type **B** meso-ionic heterocycles were regarded as reasonable targets for synthesis. The most recent count[6] of known classes of meso-ionic heterocycles in 1982 was type **A**, 60 classes represented, and type **B**, 13 classes represented.



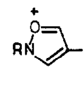
104 ≡ 41a



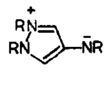
105 ≡ 41a



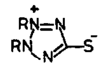
106 ≡ 41a



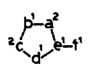
107 ≡ 41a



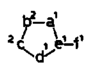
108 ≡ 41a



109 ≡ 41a

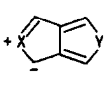


110
Type A

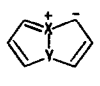


111
Type B

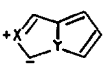
Our classification[4–6] of meso-ionic heterocycles into type **A** and type **B** was originally based upon the identification of the atoms or groups (a, b, c, d, e and f) which contribute p-electrons to the π-electron systems of the molecules. Using this method, type **A** meso-ionic heterocycles are represented by the formulation **110** and type **B** meso-ionic heterocycles by the formulation **111** in which the superscripts 1 and 2 indicate the number of contributed p-electrons.



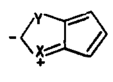
112 ≡ 44a
Type A



113 ≡ 44b
Type B

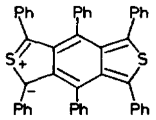


114 ≡ 44c
Type C

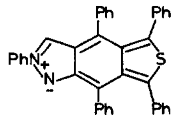


115 ≡ 44d
Type D

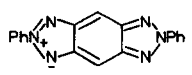
The classification of heteropentalenes into type **A 112**, type **B 113**, type **C 114** and type **D 115**, where X and Y are appropriate heteroatoms, has already been described in detail.[14] Our present comments are therefore restricted to the recognition that these four types of heteropentalenes are isoconjugate with canonical forms of the same even non-alternant hydrocarbon dianion: **112** ≡ **44a**; **113** ≡ **44b**; **114** ≡ **44c** and **115** ≡ **44d**.



116 ≡ 45



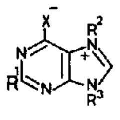
117 ≡ 45



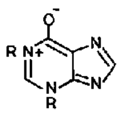
118 ≡ 45

The compounds **116**,[80] **117**,[80] and **118**[81] have been synthesised and their representation as conjugated mesomeric betaines emphasises their structural relation to type **A** heteropentalenes **112**. The heterocycles **116**, **117**, and **118** are isoconjugate with the even non-alternant hydrocarbon dianion **45** and they are 14π-electron homologues of the 10π-electron system of the heteropentalenes.

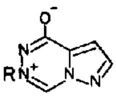
Derivatives of the compounds **119** (X = O),[82a,b] **119** (X = S),[83] **120**,[84] and **121**[85] have been described. They are isoconjugate with the canonical forms of the same even non-alternant hydrocarbon dianion: **119** ≡ **43a**; **120** ≡ **43b**; and **121** ≡ **43c**. The natural product, herbipolin, isolated from the



119 ≡ 43a



120 ≡ 43b

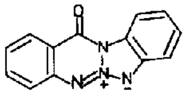


121 ≡ 43c

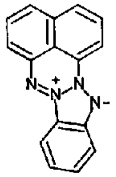
giant sponge, *Geodia gigas*, has been identified as the 7,9-dimethyl guanine **119** ($X = O$; $R^1 = NH_2$, $R^2 = R^3 = Me$) which is a conjugated heterocyclic mesomeric betaine.[82a]

Recently great interest has developed in the discovery that many unusual bases (7–15 modified nucleotide residues) are present in transfer-RNA molecules (73–93 nucleotide residues per molecule). Many of these unusual bases are *N*-methyl or *N*,*N*′-dimethyl derivatives of the usual ribonucleosides, adenosine, guanosine, uridine, and cytidine.[82b] A typical example is 7-methylguanosine **119** ($X = O$; $R^1 = NH_2$, $R^2 = Me$, $R^3 =$ D-ribosyl) isolated from the transfer-RNA from many sources.[82c] The biological role of these unusual bases in nucleic acids is uncertain, but it is clear that the presence in transfer-RNA of modified nucleotides containing residues which are conjugated heterocyclic mesomeric betaines **119** ($X = O$; $R^1 = OH$ or NH_2, $R^2 = Me$, $R^3 =$ D-ribosyl) could have significant biochemical consequences. For example, *N*-methylation could have a profound influence upon the base-pairing process, thus making some bases available for other interactions. Furthermore, the presence of dipolar residues would alter the hydrophilic character of certain regions of the transfer-RNA molecules and this could influence their interaction with aminoacyl synthetases and ribosomal proteins.

Since 1975, dramatic developments in our understanding of the structure and function of messenger-RNAs have occurred.[82d] Most cellular messenger-RNAs are terminated by the 7-methylguanosine residue **119** ($R^1 = NH_2$, $R^2 = Me$, $R^3 =$ D-ribosyl) linked by a 5′-5′ triphosphate group to the terminal nucleotide which is also *O*-methylated in the 2′-position. This terminal oligonucleotide is called a *cap structure* and *capping* is a vital step in messenger-RNA biosynthesis.[82d] It is interesting to speculate upon the reasons for Nature's selection of the conjugated heterocyclic mesomeric betaine **119** ($R^1 = NH_2$, $R^2 = R^3 = Me$) as the termini of most messenger-RNAs. Whatever the reasons are, the *cap structure* has been well chosen because it not only stabilises the messenger-RNA but it also facilitates the binding of the ribosomes prior to the initiation of the translation of eukaryotic messenger-RNAs.



122 ≡ 46



123 ≡ 49

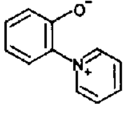
The conjugated mesomeric betaines **122**[86] and **123**[87] have been reported. They are isoconjugate with the even non-alternant hydrocarbon dianions **46** and **49** respectively.

The true nature of Besthorn's Red **10** is now clear. It is a conjugated mesomeric betaine isoconjugate with the even non-alternant hydrocarbon dianion **40**.

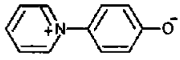
5. *Conjugated heterocyclic* N-*ylides and related compounds isoconjugate with odd alternant hydrocarbon anions* (Scheme 3)

Compounds of this general type have been known for many years and include pyridine *N*-oxides **124** ($Y = O$),[9,10] pyridine *N*-ylides **124** ($Y = CR_2$),[11,12] and pyridine-*N*-aminides **124** ($Y = NR$).[9] The derivatives **125**[88,89] and **126**[88,89] are best classified as pyridinium-*N*-ylides, but their formulation as

124 ≡ 12



125 ≡ 14

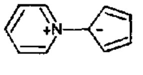


126 ≡ 16

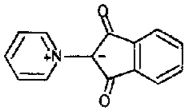
pyridinium phenolates is, of course, entirely acceptable. The pyridinium-2-phenolates **125** and the pyridinium-4-phenolates **126** are conjugated mesomeric betaines whereas the pyridinium-3-phenolates **139** (Section III, 9) are cross-conjugated mesomeric betaines.

6. *Conjugated heterocyclic* N-*ylides and related compounds isoconjugate with odd non-alternant hydrocarbon anions* (Scheme 4)

The *N*-ylides **127**[90] and **128**[91,92] are known examples of this class of mesomeric betaine.



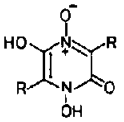
127 ≡ 29



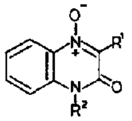
128 ≡ 33

7. *Conjugated heterocyclic* N-*ylides and related compounds isoconjugate with even alternant hydrocarbon dianions* (Scheme 5)

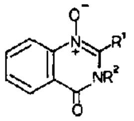
The *N*-oxides **129–133** are known representatives of *N*-ylides isoconjugate with even alternant hydrocarbon dianions (Scheme 5). Several mould metabolites including pulcherriminic acid **129** (R = $Me_2CH—CH_2$) are known[93] which are cyclic hydroxamic acids containing an *N*-oxide group. The synthesis of the *N*-oxides **130** and **131** has been described.[94]



129 ≡ 34c



130 ≡ 35



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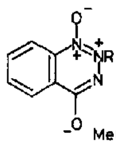

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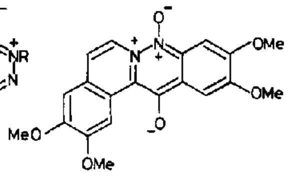

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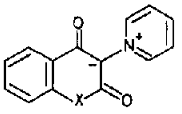


134

The structure of the benzo-1,2,3-triazine *N*-oxides **132** was the subject of controversy and investigation extending over 50 years. Their constitution was finally settled by McKillop and Kobylecki.[95] The reductive transformation (**132** → **68**) occurs with stannous chloride.[55]

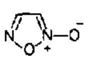
A remarkable transformation occurs when 6′-nitropapaverine is oxidised by iodine yielding the dark red azaberbinone *N*-oxide **133**.[96]

The decision to represent the *N*-oxides by the tetrapolar structures **132** and **133** requires comment. These compounds can also be represented by dipolar structures, but the tetrapolar structures **132** and **133** are preferred because this emphasises more obviously their *N*-oxide character.

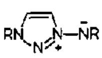
The compound **134** (X = NR) has recently been synthesised by heating isatoic anhydride with the pyridinium methylide **124** [Y = $C(CO_2Et)_2$].[97] The compound **134** (X = O) is also known.[97] The *N*-ylide **134** is isoconjugate with an even alternant hydrocarbon dianion and as such is a novel addition to the class of conjugated mesomeric betaines of which the *N*-ylides are a subdivision.

8. *Conjugated heterocyclic* N-*ylides and related compounds isoconjugate with even non-alternant hydrocarbon dianions* (Scheme 6)

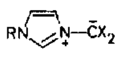
N-Ylides and related compounds isoconjugate with the fulvene dianion **41a** and **41b** are very well known. Examples include the furazan-*N*-oxides **135**,[9,10] the azole-*N*-aminide **136**,[4] and the imidazolium methylides **137**.[98]



135 ≡ 41b



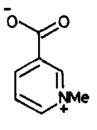
136 ≡ 41a



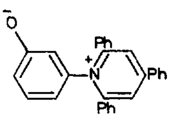
137 ≡ 41a

9. *Cross-conjugated heterocyclic mesomeric betaines isoconjugate with odd alternant hydrocarbon anions* (Scheme 3)

This category is represented by only two known examples, the alkaloid, trigonelline **138**,[99] and the pyridinium-3-phenolate **139** synthesised by the condensation of 2,4,6-triphenylpyrylium perchlorate and *m*-aminophenol.[89,100]



138 ≡ 13

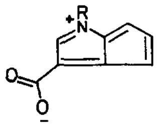


139 ≡ 15

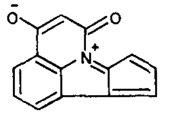
Compound **5** has not yet been synthesised, but it is an instructive example of a cross-conjugated mesomeric betaine isoconjugate with the odd alternant hydrocarbon anion **25**. The distinction between the cross-conjugated heterocycle **5** and its pseudo-cross-conjugated isomer **6** is discussed later (Section IV).

10. *Cross-conjugated heterocyclic mesomeric betaines isoconjugate with odd non-alternant hydrocarbon anions* (Scheme 4)

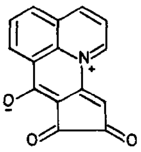
To our knowledge, no member of this category of mesomeric betaines has been synthesised, so the structures **140**, **141** and **142** are included as hypothetical examples.



140



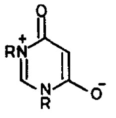
141



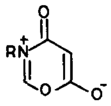
142

11. *Cross-conjugated heterocyclic mesomeric betaines isoconjugate with even alternant hydrocarbon dianions* (Scheme 5)

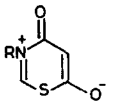
Recently considerable interest has developed in the synthesis and the chemistry of this class of cross-conjugated heterocyclic mesomeric betaines. This important feature of their structure has not been generally appreciated and compounds have not been named in accord with standard principles of nomenclature. The correct names of known compounds are given in order to be helpful, but it is appreciated that trivial or abbreviated names will often be used. However, it is incorrect, for example, to refer to the compounds **143** as "pyrimidinium-4,6-diolates".



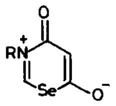
143 ≡ 34d



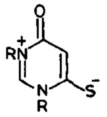
144 ≡ 34d



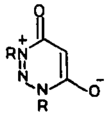
145 ≡ 34d



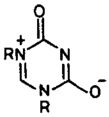
146 ≡ 34d



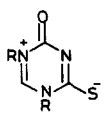
147 ≡ 34d



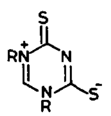
148 ≡ 34d



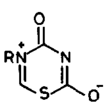
149 ≡ 34d



150 ≡ 34d

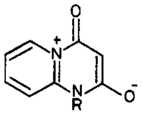


151 ≡ 34d

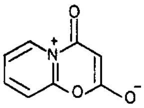


152 ≡ 34d

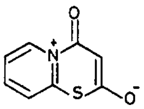
Known examples of cross-conjugated mesomeric betaines which are isoconjugate with the canonical form **34d** of the *m*-quinodimethane dianion (**34a** ↔ **34b** ↔ **34c** ↔ **34d**) include the following compounds: 1,3-disubstituted-3,6-dihydro-6-oxopyrimidinium-4-olates **143**,[101–117] 3-substituted-4-oxo-4*H*-1,3-oxazinium-6-olates **144**,[118–120] 3-substituted-4-oxo-4*H*-1,3-thiazinium-6-olates **145**,[110,121,122] 3-substituted-4-oxo-4*H*-1,3-selenazinium-6-olates **146**,[123] 1,3-disubstituted-3,6-dihydro-6-oxopyrimidinium-4-thiolates **147**,[123] 1,3-disubstituted-3,6-dihydro-6-oxo-1,2,3-triazinium-4-olates **148**,[124] 1,3-disubstituted-3,6-dihydro-6-oxo-1,3,5-triazinium-4-olates **149**,[125] 3,6-disubstituted-3,6-dihydro-6-oxo-1,3,5-triazinium-4-thiolates **150**,[125] 3,6-disubstituted-3,6-dihydro-6-thioxo-1,3,5-triazinium-4-thiolates **151**,[125] and 3-substituted-4-oxo-4*H*-1,3,5-thiadiazinium-4-olates **152**.[126]



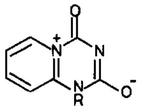
153 ≡ 35



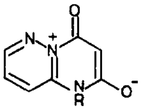
154 ≡ 35



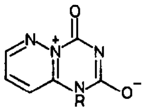
155 ≡ 35



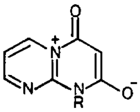
156 ≡ 35



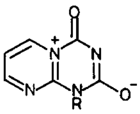
157 ≡ 35



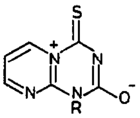
158 ≡ 35



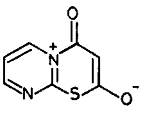
159 ≡ 35



160 ≡ 35



161 ≡ 35

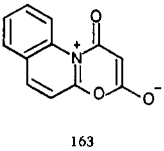


162 ≡ 35

Bicyclic cross-conjugated mesomeric betaines isoconjugate with the even alternant hydrocarbon dianion **35** include the compounds: 1-substituted-1,4-dihydro-4-oxo-5λ^5-pyrido[1,2-*a*]-pyrimidin-5-ylium-2-olates **153**,[110,111,115,116,120,127–134] 4-oxo-4*H*-5λ^5-pyrido[2,1-*b*][1,3]-oxazin-5-ylium-2-olates **154**,[118,120] 4-oxo-4*H*-5λ^5-pyrido[2,1-*b*][1,3]thiazin-5-ylium-2-olates **155**,[110,121] 1-substituted-1,4-dihydro-4-oxo-5λ^5-pyrido-[1,2-*a*][1,3,5]triazin-5-ylium-2-olates **156**,[116,135] 1-substituted-1,4-dihydro-4-oxo-5λ^5-pyrimido[1,2-*b*]pyridazin-5-ylium-2-olates **157**,[136] 1-substituted-1,4-dihydro-4-oxo-5λ^5-pyridazino[1,6-*a*][1,3,5]triazin-5-ylium-2-olates **158**,[136] 1-substituted-1,4-dihydro-4-oxo-5λ^5-pyrimido[1,2-*a*]pyrimidin-5-ylium-2-olates **159**,[110,137] 1-substituted-1,4-dihydro-4-oxo-5λ^5-pyrimido[1,2-*a*][1,3,5]triazin-5-ylium-2-olates **160**,[138] 1-substituted-1,4-dihydro-4-thioxo-5λ^5-pyrimido[1,2-*a*][1,3,5]triazin-5-ylium-2-olates **161**,[138] and 4-oxo-4*H*-5λ^5-pyrimido[1,2-*a*][1,3]thiazin-5-ylium-2-olates **162**.[110,121]

Tricyclic derivatives **163** of 4-oxo-4*H*-1,3-oxazinium-6-olates **144** have been reported.[120,139]

The cross-conjugated mesomeric betaine structure **164** was recently proposed[140a] for the products of the reaction of salicaldehyde anils and carbon suboxide. This proposal was, however, short-lived



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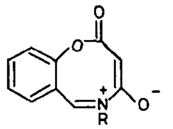
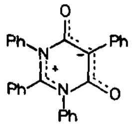


164 ≡ 39

because Boulton[140b] recognised that these products are, in fact, the known anilides of coumarin-3-carboxylic acid.

The appreciation of the structure and the interpretation of the chemistry of this diverse family of cross-conjugated dipolar heterocycles **143–152** have been the source of considerable confusion and misunderstanding. Some of the confusion has been generated by the adoption of the term meso-ionic to describe the 6-membered dipolar heterocycles **143–152**. This practice is not in accord with our definition[4] of the term meso-ionic (Section I), and to advocate the extension of our definition, which is restricted to 5-membered heterocyclic mesomeric betaines, to include the 6-membered heterocyclic mesomeric betaines **143–152** is strongly deprecated. We believe that it is much more informative to emphasise the fundamental distinction between the conjugated 6-membered mesomeric betaines **50–56** and **102** and the cross-conjugated 6-membered mesomeric betaines **143–152**.

This distinction between conjugated and cross-conjugated cyclic mesomeric betaines is crucial:[13] it is a fundamental feature of the systematic classification now proposed. We believe that as soon as this important difference between the bonding within conjugated and cross-conjugated heterocyclic mesomeric betaines is appreciated, then the origin of the striking differences between the chemical reactions and the physical properties of conjugated mesomeric betaines and cross-conjugated mesomeric betaines becomes clear.



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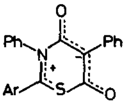

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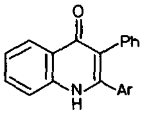
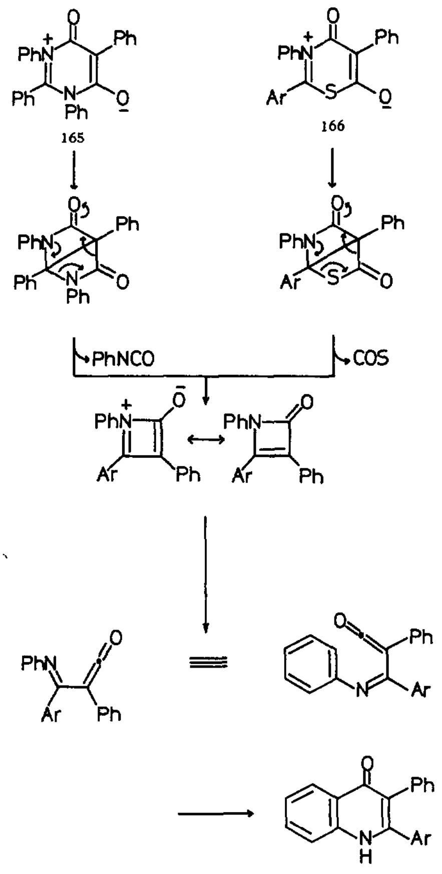


167

Important experimental evidence has been produced by Kratky and Kappe[117] which provides dramatic support for the concept that the 6-membered mesomeric betaines **143** are cross-conjugated. The crystal structure of the tetraphenylpyrimidinium mesomeric betaine **165**[117] demonstrates that the 6-membered heterocyclic ring is planar with C_s symmetry. The interatomic distances (C_4—C_5 = C_5—C_6 = 1.41 Å; N_1—C_2 = C_2—N_3 = 1.33 Å) show delocalisation and double bond character. In contrast, the interatomic distances (N_1—C_6 = N_3—C_4 = 1.48 Å) show that these bonds are essentially single and that they are not obviously involved in delocalisation. Thus, the crystal structure of the compound **165** provides excellent support for its cross-conjugated structure and the restriction of the delocalised positive and delocalised negative charges to separate parts of the π-electron system of the molecule. This result[117] for the cross-conjugated molecule **165** is in dramatic contrast with the results of the X-ray crystallographic investigation of conjugated mesomeric betaines such as type A meso-ionic heterocycles[4–6] (Section III, 4). The interatomic distances in these 5-membered conjugated mesomeric betaines all show bond shortening which is to be expected for delocalisation involving all the atoms and all the bonds comprising the 5-membered heterocyclic ring.

A striking contrast has been observed between the cycloaddition reactions of conjugated mesomeric betaines and cross-conjugated mesomeric betaines. This is discussed in detail in Section V, but at this point it is emphasised that this dramatic difference in chemical reactivity is precisely in accord with mechanistic expectation. Cross-conjugated mesomeric betaines would be predicted to react as 1,4-dipoles (Section V).

The formation of 2,3-diarylquinolones **167** by the thermolysis of the tetraphenylpyrimidinium mesomeric betaines **165**[108] and the 4*H*-1,3-thiazinium mesomeric betaines **166**[122] are further examples of reactions of cross-conjugated mesomeric betaines which are encouraged by intramolecular charge neutralisation (Scheme 7). Thus, each precursor (**165** or **166**) could be transformed into bicyclic covalent isomers which, by extrusion of phenyl isocyanate or carbon oxysulphide, could yield a common



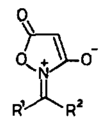
Scheme 7. Thermal transformations of the cross-conjugated heterocyclic mesomeric betaines **165** and **166**.[108,122]

monocyclic intermediate which is transformable *via* a ketene intermediate into the corresponding 2,3-diarylquinolone **167** (Scheme 7).

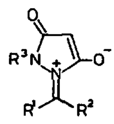
12. *Cross-conjugated heterocyclic mesomeric betaines isoconjugate with even non-alternant hydrocarbon dianions* (Scheme 6)

Recently there has been great interest in the synthesis and properties of this class of heterocyclic mesomeric betaines which includes derivatives of 2-methylene-2,5-dihydro-5-oxo-isoxazolium-3-olate **168**;[141,142] 1-methylene-2-substituted-2,3-dihydro-3-oxopyrazolium-5-olate **169**;[142] 1-oxo-1*H*-4λ^5-pyrazolo[1,2-*a*]pyrazol-4-ylium-3-olate **170**[141–143] and 11-oxo-11*H*-8λ^5-naphtho[1,8-*d*,*e*]pyrazolo[1,2-*a*][1,3,5]triazin-8-ylium-9-olate **171**.[142]

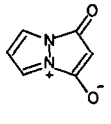
However, we now believe that the true nature of their structure has not been previously recognised. One of the purposes of this Report is to present the case for classifying these heterocyclic systems **168**, **169**, **170** and **171** as cross-conjugated heterocyclic mesomeric betaines.



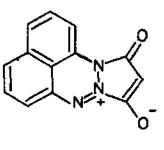
168 ≡ 47



169 ≡ 47



170 ≡ 42



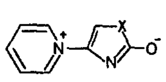
171 ≡ 48

The fundamental distinction between conjugated mesomeric betaines and cross-conjugated mesomeric betaines was first recognised by Ramsden in 1977[13] and was exemplified by the known conjugated 1,4-disubstituted-1,2-dihydro-2-oxopyrazinium-6-olates **102** (Section III, 3) and the isomeric cross-conjugated 1,3-disubstituted-3,6-dihydro-6-oxopyrimidinium-4-olates **143** (Section III, 11). The classification of the 5-membered heterocycles **168**, **169**, **170** and **171** as cross-conjugated mesomeric betaines is now proposed. This is an acceptable proposal because the standard term, cross-conjugated, is used to emphasise the fundamental electronic character of these molecules.

Alternative general descriptions of the structures **168**, **169**, **170** and **171** have been proposed, but we do not recommend their adoption. The terms which have been suggested are "para-ionic compounds"[142] and "meso-ionic $4n\pi$-heterocycles".[143]

Potts *et al.*[142] clearly recognised that the heterocycles **168**, **169**, **170** and **171** are not meso-ionic and they proposed the term "para-ionic" to emphasise the absence of conjugation between the anionic and cationic delocalised systems present in their structures. "Para-ionic" compounds are described by them as "a new class of unique, heterocyclic zwitterions containing stable 1,4-dipoles".[142] The term "para-ionic" was coined by Potts *et al.*[142] for the heterocycles **168**, **169**, **170** and **171** to demonstrate a similarity to and a distinction from meso-ionic heterocycles. The adjective "para-ionic" originates from the translation of the Greek word *para* (*παρα*), meaning alongside. Although we agree that compounds **168**, **169**, **170** and **171** are not meso-ionic, we nevertheless feel that the introduction of the new term "para-ionic" is unnecessary and could lead to confusion. For example, the term "para-ionic" might be incorrectly applied as a descriptor for dipolar 1,4-disubstituted derivatives of benzene such as the pyridinium phenolate **126**. We therefore advocate that the heterocycles **168**, **169**, **170** and **171** should just be called cross-conjugated mesomeric betaines. This use of standard nomenclature is obviously advantageous because these terms can be precisely defined (Section I) and are generally accepted by organic chemists.

The compounds **170** are not meso-ionic so their description as "meso-ionic $4n\pi$-heterocycles"[143] is not acceptable.



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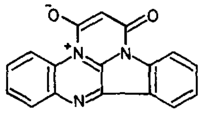
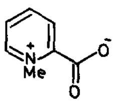


173

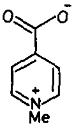
The synthesis of the heterocycles **172** (X = O, S and NR) has been recently reported.[144] They are obviously cross-conjugated mesomeric betaines.

Kappe and Lube[129] have described the novel mesomeric betaine **173**. This is now recognised to be a cross-conjugated mesomeric betaine isoconjugate with an even non-alternant hydrocarbon dianion.

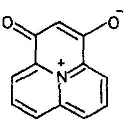
13. *Pseudo-cross-conjugated heterocyclic mesomeric betaines isoconjugate with odd alternant hydrocarbon anions* (Scheme 3)



174 ≡ 13



175 ≡ 13



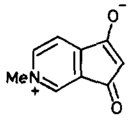
6 ≡ 25

N-Methylpyridinium-2-carboxylate **174**[99] and *N*-methylpyridinium-4-carboxylate **175**[99] are known examples of pseudo-cross-conjugated mesomeric betaines isoconjugate with the odd alternant hydrocarbon anion **13**. These pseudo-cross-conjugated isomers **174** and **175** provide an interesting contrast with trigonelline **138** which is cross-conjugated (Section III, 9).

The tricyclic compound **6** is as yet unknown, but this is another example of a pseudo-cross-conjugated heterocyclic mesomeric betaine.

14. *Pseudo-cross-conjugated heterocyclic mesomeric betaines isoconjugate with odd non-alternant hydrocarbon anions* (Scheme 4)

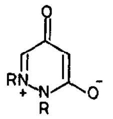
This category is at present represented by only one known mesomeric betaine which has the structure **176**.[145]



176 ≡ 31

15. *Pseudo-cross-conjugated heterocyclic mesomeric betaines isoconjugate with even alternant hydrocarbon dianions* (Scheme 5)

Hypothetical representatives of this class include the pyridazine derivative **3** and the tricyclic derivative **177**.



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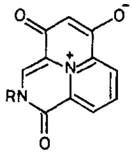
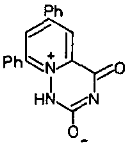


177 ≡ 37



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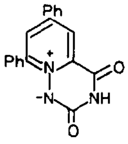
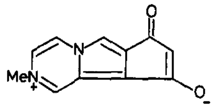


179

One possible known representative of this class of pseudo-cross-conjugated mesomeric betaines is the compound **178**.[146] However, on the evidence available, it is not possible to discriminate between the tautomeric structures **178** and **179**. The structure **179** is that of an *N*-ylide isoconjugate with an even alternant hydrocarbon dianion (Section III, 7).

16. *Pseudo-cross-conjugated heterocyclic mesomeric betaines isoconjugate with even non-alternant hydrocarbon dianions* (Scheme 6)

To our knowledge, no member of this category has yet been synthesised, so the structure **180** is included as a hypothetical example.



180

IV. THE IDENTIFICATION OF CONJUGATED, CROSS-CONJUGATED, AND PSEUDO-CROSS-CONJUGATED HETEROCYCLIC MESOMERIC BETAINES

The proposal (Section I) that heterocyclic mesomeric betaines should be classified into three categories is most easily appreciated on the basis of examples. However, once this need is realised, then it is obviously necessary to be able to identify the type of mesomeric betaine to which a particular heterocycle belongs. We have found that the following three methods are useful.

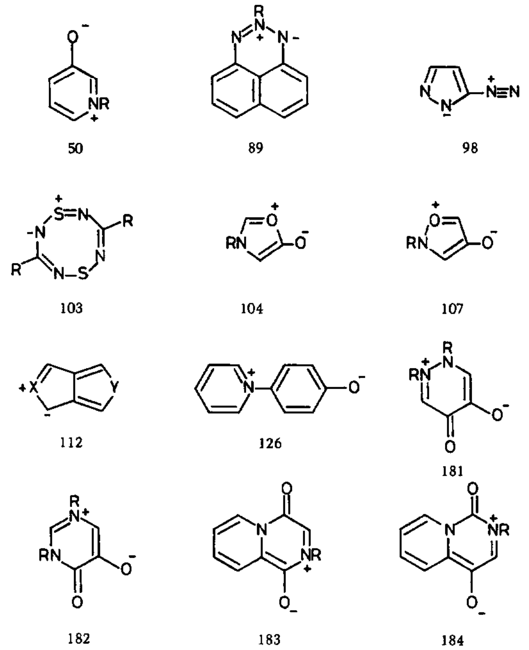
(i) *The valence bond approach.* This method is based upon an inspection of dipolar canonical forms and the identification of atoms which can be associated with positive and negative charges.

(ii) *The identification of dipole type.* This method is based upon the association of heterocyclic mesomeric betaines with particular types of 1,2-, 1,3- and 1,4-dipoles and their vinylogues.

(iii) *The perturbation molecular orbital approach.* This method is based upon (a) the orbital properties of alternant and non-alternant hydrocarbons, (b) the relation between heterocyclic mesomeric betaines and their isoconjugate hydrocarbon equivalents, and (c) the type recognition of the anionoid fragment of the heterocycle.

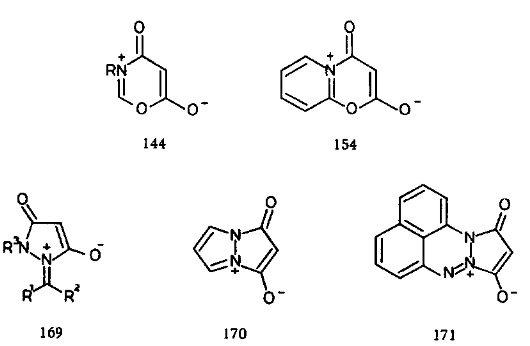
However, before discussing the application of these three methods, the identification of the three types of heterocyclic mesomeric betaines is illustrated by some examples.

The concepts of conjugation and cross-conjugation have been widely used in discussions of polyolefinic systems.[1] However, it was not until 1977[13] that the corresponding distinction was recognised explicitly between heterocycles which are conjugated mesomeric betaines and heterocycles which are cross-conjugated mesomeric betaines. Examples of conjugated mesomeric betaines are given in Scheme 8 and examples of cross-conjugated mesomeric betaines are given in Scheme 9.

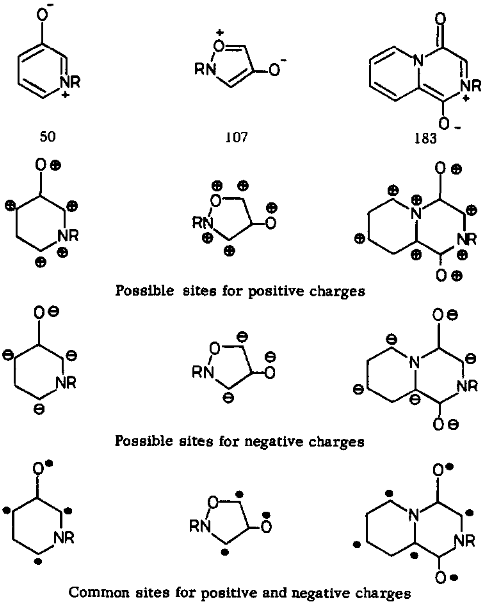


Scheme 8 Examples of conjugated heterocyclic mesomeric betaines.

The valence bond approach. The differences between the conjugated mesomeric betaines (Scheme 8) and the cross-conjugated mesomeric betaines (Scheme 9) are important and the distinctive features of these two types of mesomeric betaines are most easily appreciated using the valence bond approach. This method is illustrated in Scheme 10 using the conjugated mesomeric betaines **50**, **107** and **183** as examples. Possible sites for the location of formal positive charges and formal negative charges are determined by inspection of dipolar canonical forms. Then the common sites are determined which can provide a location either for positive or for negative charges. The existence of these common sites



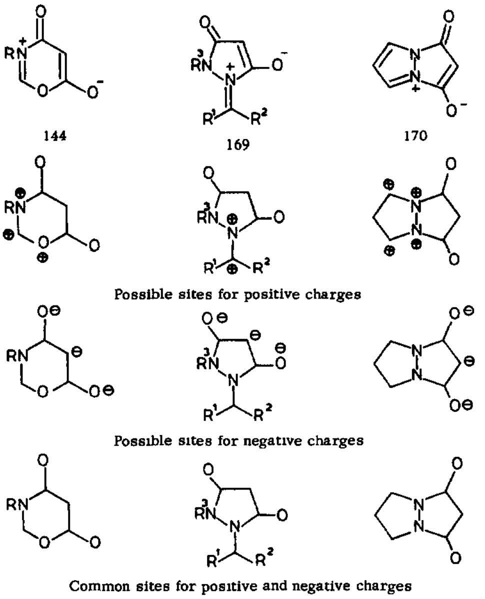
Scheme 9. Examples of cross-conjugated heterocyclic mesomeric betaines.



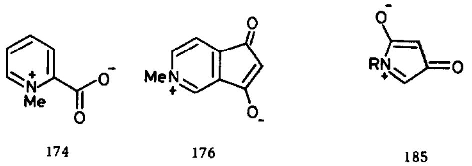
Scheme 10. Valence bond method for the identification of the heterocycles **50**, **107** and **183** as conjugated heterocyclic mesomeric betaines.

demonstrates that the positive and negative charges are not restricted to separate parts of the π-electron system of the molecule. The positive and negative charges are in mutual conjugation. Thus, the existence of common sites for the formal location in canonical forms of both positive and negative charges is characteristic of conjugated mesomeric betaines. The application of this method (Scheme 10) to the examples listed in Scheme 8 identifies all these molecules as conjugated mesomeric betaines.

In contrast, when the same method (Scheme 11) is applied to cross-conjugated mesomeric betaines, then it is found by canonical form inspection that no common sites exist for the accommodation of formal positive and negative charges. Thus, the positive and negative charges can be shown to be exclusively restricted to separate parts of the π-electron system of the molecule. This is characteristic of cross-conjugated mesomeric betaines. The application of this method (Scheme 11) to the examples listed in Scheme 9 identifies all these molecules as cross-conjugated mesomeric betaines.



Scheme 11. Valence bond method for the identification of the heterocycles **144**, **169** and **170** as cross-conjugated heterocyclic mesomeric betaines.

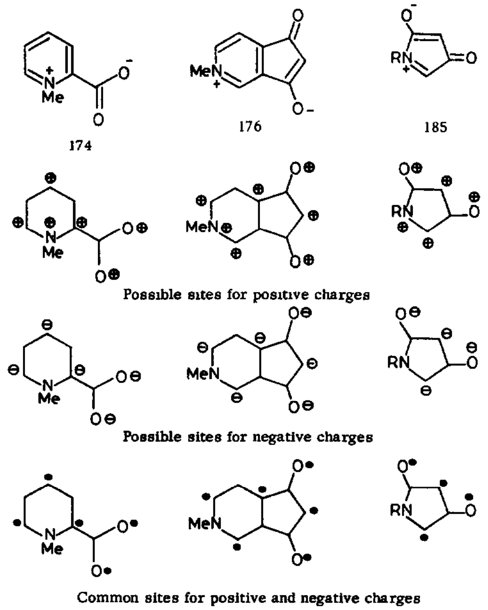


Scheme 12. Examples of pseudo-cross-conjugated heterocyclic mesomeric betaines.

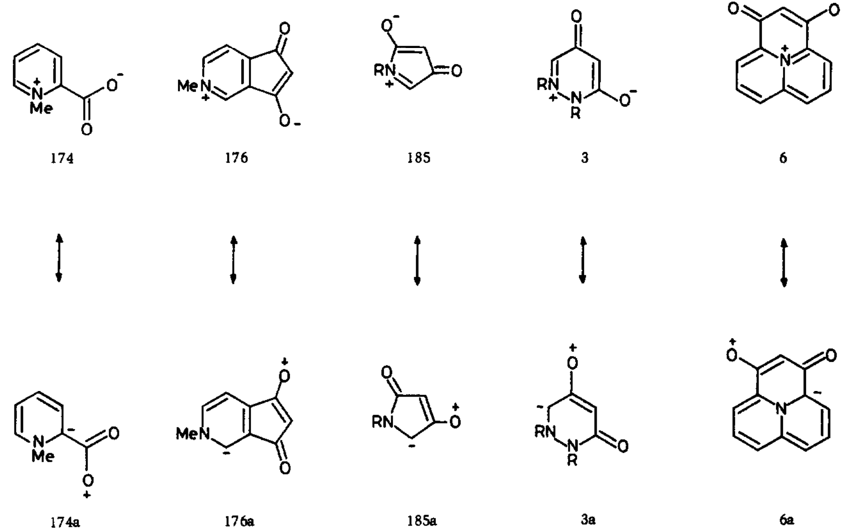
At first sight, the betaines listed in Scheme 12 also appear to be cross-conjugated mesomeric betaines. However, closer inspection (Scheme 13) of their canonical forms reveals that the formal positive and negative charges are effectively but not exclusively restricted to separate parts of the π-electron systems of these molecules **174**, **176** and **185**. These molecules are therefore classified as pseudo-cross-conjugated mesomeric betaines to emphasise that they belong to a distinct class of mesomeric betaines with relationships to both conjugated and cross-conjugated mesomeric betaines.

Inspection of the canonical forms of pseudo-cross-conjugated mesomeric betaines shows that these canonical forms do have common sites for the location of their formal positive and negative charges (Scheme 13). In this respect, pseudo-cross-conjugated mesomeric betaines (Scheme 13) resemble conjugated mesomeric betaines (Scheme 10). However, there is an obvious distinction between these two types of mesomeric betaine. The dipolar canonical forms associated with conjugated mesomeric betaines are either electron octet formulae or electron sextet formulae associated with internal electron octet stabilisation. In contrast, the dipolar canonical forms associated with pseudo-cross-conjugated mesomeric betaines include not only electron octet formulae and electron sextet formulae associated with internal electron octet stabilisation, but also electron sextet formulae without internal electron octet stabilisation. The canonical forms **174a**, **176a**, **185a**, **3a** and **6a** are examples of electron sextet formulae without internal electron octet stabilisation which are associated with the pseudo-cross-conjugated systems **174**, **176**, **185**, **3** and **6** (Scheme 14). The canonical forms **174a**, **176a**, **185a**, **3a** and **6a** with electron sextets no doubt make only a small mesomeric contribution to the ground state of these molecules, but they could be associated with the direction of a preferred course for a chemical reaction.

This description of dipolar canonical forms of heterocyclic mesomeric betaines in terms of either (i) electron octet structures, (ii) electron sextet structures with internal electron octet stabilisation, or (iii) electron sextet structures without internal electron octet stabilisation is a direct extension of the same descriptions adopted by Huisgen in his generally accepted classification of 1,3-dipoles.[2] This recognition that all mesomeric betaines can be assigned to one of two classes, either acyclic mesomeric betaines (for example, 1,3- and 1,5-dipoles) or heterocyclic mesomeric betaines (this Report), has an



Scheme 13. Valence bond method for the identification of the heterocycles **174**, **176** and **185** as pseudo-cross-conjugated heterocyclic mesomeric betaines.



Scheme 14. Selected canonical forms of pseudo-cross-conjugated heterocyclic mesomeric betaines. Formulae **174**, **176**, **185**, **3** and **6** are electron octet structures. Formulae **174a**, **176a**, **185a**, **3a** and **6a** are electron sextet structures without internal electron octet stabilisation.

important consequence. We believe that the extension of Huisgen's original classification[2] of acyclic mesomeric betaines to include all mesomeric betaines is all-embracing and fundamentally sound.

The identification of the type of heterocyclic mesomeric betaine based upon the valence bond approach involves the following three rules.

RULE 1. Conjugated mesomeric betaines are associated with dipolar canonical forms which include (i) electron octet structures and (ii) electron sextet structures with internal octet stabilisation *but exclude* (iii) electron sextet structures without internal octet stabilisation. The dipolar canonical forms *do provide* common sites for formal positive and negative charges.

RULE 2. Cross-conjugated mesomeric betaines are associated with dipolar canonical forms which include (i) electron octet structures and (ii) electron sextet structures with internal octet stabilisation *but exclude* (iii) electron sextet structures without internal octet stabilisation. The dipolar canonical forms *do not provide* any common sites for formal positive and negative charges.

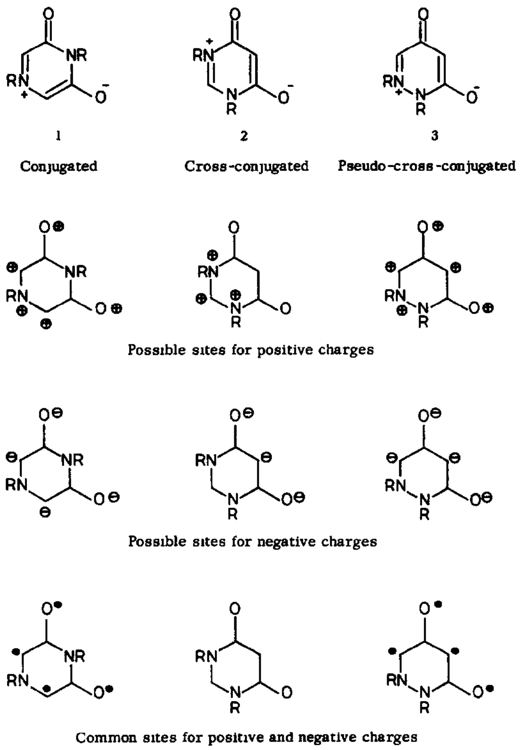
RULE 3. Pseudo-cross-conjugated mesomeric betaines are associated with dipolar canonical forms which include (i) electron octet structures, (ii) electron sextet structures with internal octet stabilisation *and* (iii) electron sextet structures without internal octet stabilisation. The dipolar canonical forms *do provide* common sites for formal positive and negative charges.

These three rules provide an excellent foundation for the classification of heterocyclic mesomeric betaines. The theoretical basis for the rules is considered later. Meanwhile the application of these three rules for the identification of the heterocyclic mesomeric betaines **1**, **2** and **3** (Scheme 15) and **4**, **5** and **6** (Scheme 16) is now presented.

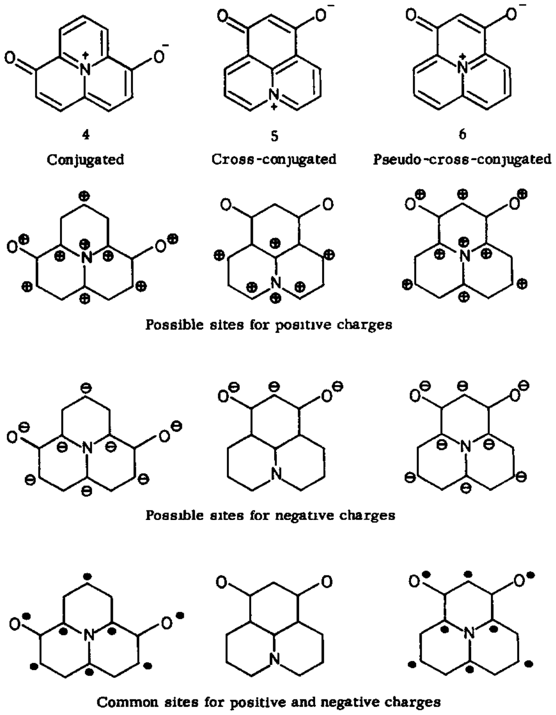
By inspection of dipolar canonical forms (Scheme 15), it can be recognised that (i) the betaines **1** and **3** both have common sites at which formal positive and negative charges can both be located, (ii) the betaine **2** has no such common sites, and (iii) only the betaine **3** is associated with electron sextet formulae (Scheme 14, **3a**) without internal electron octet stabilisation. These facts identify these three isomers (Scheme 15). Betaine **1** is a conjugated mesomeric betaine, betaine **2** is a cross-conjugated mesomeric betaine, and betaine **3** is a pseudo-cross-conjugated mesomeric betaine.

By a similar analysis (Scheme 16) the three isomers are also identified. Betaine **4** is a conjugated mesomeric betaine. Betaine **5** is a cross-conjugated mesomeric betaine. Betaine **6** is a pseudo-cross-conjugated mesomeric betaine associated with, for example, formula **6a** (Scheme 14) which is an electron sextet structure without internal electron octet stabilisation.

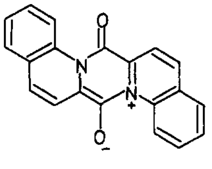
Finally, it is important to direct attention to a hazard in the use of the valence bond method for the classification of mesomeric betaines. The danger will be illustrated by an example of some historical interest.



Scheme 15. Valence bond method for the identification of the heterocycles **1**, **2** and **3** as conjugated, cross-conjugated, and pseudo-cross-conjugated heterocyclic mesomeric betaines, respectively.



Scheme 16. Valence bond method for the identification of the heterocycles **4**, **5** and **6** as conjugated, cross-conjugated and pseudo-cross-conjugated heterocyclic mesomeric betaines, respectively.



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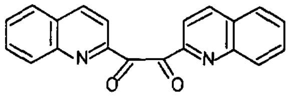


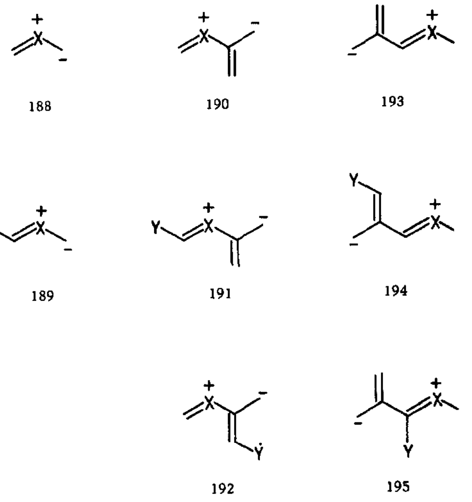
187

Brown and Hammick[7d] reported that quinoline-2-aldehyde and aqueous potassium cyanide yielded a product, $C_{20}H_{12}O_2N_2$, which was originally formulated as the mesomeric betaine **186**. Subsequently Buehler and Harris[147a] demonstrated that the structure **186** was incorrect and that the product was just the α-diketone **187** produced by atmospheric oxidation of the expected intermediate benzoin condensation product. This was confirmed by an X-ray crystal structure determination.[147b]

Although the constitution **186** does not represent a known compound, it is nevertheless instructive to use this structure **186** as a test of our methods for the classification of mesomeric betaines. Casual inspection of the dipolar formulation **186** suggests that this structure represents a cross-conjugated mesomeric betaine because the positive and negative charges appear to be exclusively restricted to separate parts of the molecule. This conclusion is not correct. In fact, the dipolar formulation **186** is that of a conjugated mesomeric betaine and this immediately becomes clear when it is appreciated that the mesomeric betaine **186** is a symmetrical structure which must be associated with pairs of equivalent canonical forms. The unusual circumstance is that these pairs of equivalent canonical forms are not interconverted (on paper!) by simple two-electron shifts. However, inspection of all the canonical forms associated with the dipolar structure **186** immediately provides twelve common sites for positive and negative charges. It therefore follows that the formulation **186** must represent a conjugated mesomeric betaine.

This situation corresponds exactly to the problem of classifying the mesomeric betaine **181**. Again, the incorrect conclusion might be drawn that the betaine **181** is cross-conjugated. However, as soon as it is appreciated that the betaine **181** is symmetrical and that it must also be associated with pairs of equivalent canonical forms, then its classification as a conjugated mesomeric betaine follows (Scheme 8).

The classification of heterocyclic mesomeric betaines by dipole-type recognition. There are specific associations of various types of dipoles with conjugated, cross-conjugated, and pseudo-cross-



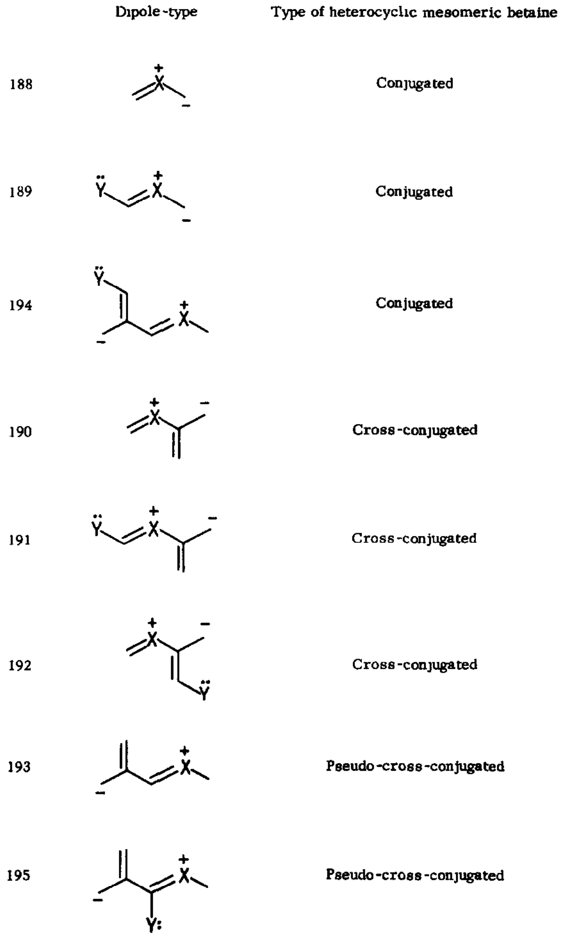
Scheme 17. The generation of the dipole types 188–195 by the union[1] of the heterocation $H_2C{=}\overset{+}{X}{-}H$ with (i) the methyl carbanion, (ii) the allyl carbanion, and (iii) the hetero-system $\ddot{Y}{-}H$.

conjugated mesomeric betaines. This is appreciated most easily by the systematic generation of eight dipole-types (Scheme 17) and then identifying these dipole-types within the dipolar structural formulae of the sixteen classes (Section III) of heterocyclic mesomeric betaines.

The systematic derivation of eight dipole-types **188–195** is presented in Scheme 17. These dipoles are generated by *union* of the heterocation ($H_2C{=}\overset{+}{X}{-}H$) with carbanions and the hetero-system ($\ddot{Y}{-}H$). The term *union* is used[4] in the sense defined by Dewar:[1] union is a process in which two conjugated molecules combine in such a way that their two π-electron systems unite into a larger one.

The dipoles **188**, **190** and **193** are generated by the *union* of the heterocation ($H_2C{=}\overset{+}{X}{-}H$) with carbanions. *Union* of the heterocation with the methyl carbanion gives the dipole **188**. *Union* of the heterocation at its two different sites with the allyl anion gives rise to two new dipole types **190** and **193**. *Union* of these three dipoles **188**, **190** and **193** with the hetero-system $\ddot{Y}{-}H$ at positions where the heteroatom ($\ddot{Y}$) can conjugate, leads to five additional dipole types **189**, **191**, **192**, **194** and **195**. Thus, *union* of **188** and $\ddot{Y}{-}H$ gives **189**, *union of* **190** and $\ddot{Y}{-}H$ gives **191** and **192**, and *union* of **193** and $\ddot{Y}{-}H$ gives **194** and **195**. The dipoles **188**, **190** and **193** are associated with one heteroatom (X) and the dipoles **189**, **191**, **192**, **194** and **195** are associated with two heteroatoms. Each of these eight dipoles can be associated with either conjugated, cross-conjugated, or pseudo-cross-conjugated mesomeric betaines (Scheme 18). This association can be regarded as an intellectual reverse of the process advocated by Ollis and Ramsden[4] for the generation of the 144 type-A meso-ionic heterocycles by the *union* of nine 1,3-dipoles with ten heterocumulenes.

The association of the eight dipole-types (Scheme 17) with the three classes of heterocyclic mesomeric betaines (Scheme 18) has obvious implications in providing a rational foundation for correlating the chemical reactions of these compounds (Section V). The dipole-type can usually be easily identified by inspection of a canonical form of a heterocyclic mesomeric betaine, so that using the associations given in Scheme 18, this identifies the heterocyclic mesomeric betaines as either



Scheme 18. The association of the dipole-types **188–195** with the type of heterocyclic mesomeric betaine.

conjugated, cross-conjugated, or pseudo-cross-conjugated. Sometimes the dipole-types **188**–**195** are not present as such in the dipolar canonical form which is being inspected. In these cases, the dipole actually present may just be a vinylogue of one of the dipoles **188**–**195**, so when this occurs, the dipole-type of the parent is used for classification of the mesomeric betaine.

The presence of one of the dipole-types **188**, **189** or **194** in the structure of a heterocyclic mesomeric betaine necessarily identifies the molecule as a conjugated mesomeric betaine. However, care must be exercised in identifications which are based upon the dipole-types **190**, **191**, **192**, **193** and **195**. The associations depicted in Scheme 18 are correct provided that the positive and negative sites are not connected by an additional π-electron system which permits mutual conjugation between the positive and negative charges. In these circumstances, the additional route for mutual conjugation would necessarily place the molecule in the category of a conjugated mesomeric betaine. This is the reason why occasionally more than one dipole-type can be dissected from the structure of a heterocyclic mesomeric betaine. For example, the two dipole-types **188** and **193** can be dissected from the structure of pyridinium-3-olate **50**. However, this does not prejudice the identification of pyridinium-3-olate **50** as a conjugated mesomeric betaine. The dipole-type **188** is present and this is characteristic of a conjugated mesomeric betaine. The dipole-type **193**, which is also present, is transformed into a conjugated π-electron system by its connection with an additional 2π-electron system (CH=CH).

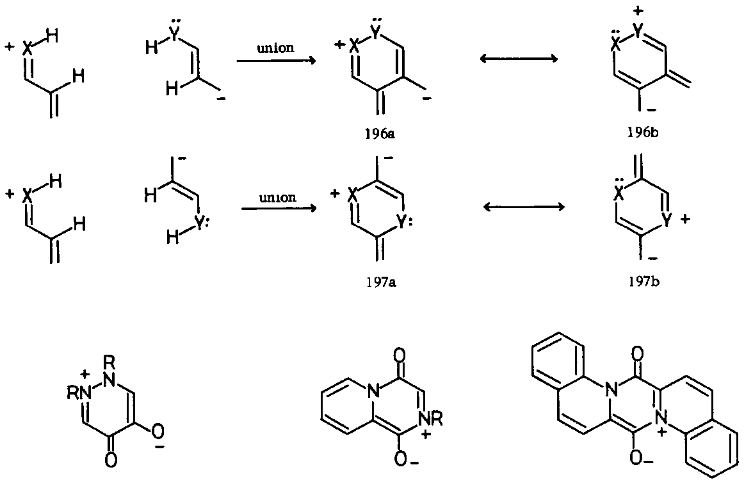
Dipole recognition for the three heterocyclic mesomeric betaines **181**, **183** and **186** presents another interesting problem. None of the eight dipole-types **188**–**195** listed in Scheme 18 can be associated with these structures **181**, **183** and **186** and their recognition (Scheme 19) as conjugated mesomeric betaines requires the consideration of two additional dipole-types **196** and **197**. Examination of the pairs of the canonical forms **196a** and **196b** and **197a** and **197b** of these two dipole-types clearly demonstrates their conjugated nature and their association with the structures of conjugated mesomeric betaines follows.

The two dipoles **196** and **197** are generated by two alternative modes of *union* of the heterocation $CH_2{=}CH{-}CH{=}\overset{+}{X}{-}H$ and the substituted allyl carbanion $H{-}\ddot{Y}{-}CH{=}CH{-}\bar{C}H_2$ (Scheme 19). The term *union* is used in the sense defined by Dewar[1] and the generation of the two conjugated systems **196** and **197** by the two modes of *union* depicted in Scheme 19 are dramatic examples of Dewar's definition[1] that *union* is a process in which two conjugated systems combine in such a way that their two π-electron systems unite into a larger one.

The associations of dipole-types (Scheme 18) with the structures of heterocyclic mesomeric betaines which are listed in this Report are now summarised.

188—Conjugated Heterocyclic Mesomeric Betaines
(**1**, **4**, **11**, **50**–**56**, **58**–**77**, **80**–**98**, **100**, **101**, **103** and **122**–**128**);
189—Conjugated Heterocyclic Mesomeric Betaines
(**10**, **104**–**106**, **112**–**121**, **131**, **136**, **137** and **182**);
194—Conjugated Heterocyclic Mesomeric Betaines
(**9**, **107**–**109** and **184**);
196—Conjugated Heterocyclic Mesomeric Betaines
(**181**);
197—Conjugated Heterocyclic Mesomeric Betaines
(**183** and **186**);
190—Cross-conjugated Heterocyclic Mesomeric Betaines
(**5** and **138**–**142**);
191—Cross-conjugated Heterocyclic Mesomeric Betaines
(**2**, **143**–**166**, **170**, **171** and **173**);
192—Cross-conjugated Heterocyclic Mesomeric Betaines
No known examples;
193—Pseudo-cross-conjugated Heterocyclic Mesomeric Betaines
(**6**, **174**–**176** and **185**);
195—Pseudo-cross-conjugated Heterocyclic Mesomeric Betaines
No known examples, but the structure **180** belongs to this group.

Fourteen heterocyclic mesomeric betaines **3**, **102**, **129**, **130**, **132**–**135**, **168**, **169**, **172**, **177**, **178** and **179** which are also listed in the Report are not relatable to the ten dipole-types listed in Schemes 18 and 19. However, this is no cause for concern because Schemes 18 and 19 can obviously be extended by using



Scheme 19 The generation of the dipole types **196** and **197** by the union[1] of the heterocation $H_2C{=}CH{-}CH{=}\overset{+}{X}{-}H$ with the substituted allyl carbanion $H{-}\ddot{Y}{-}CH{=}CH{-}\bar{C}H_2$. The association of the dipole type **196** with the conjugated heterocyclic mesomeric betaine **181** and the association of the dipole type **197** with the conjugated heterocyclic mesomeric betaines **183** and **186**.

additional modes of *union*. This gives additional dipole-types which can then be used to accommodate the fourteen heterocyclic mesomeric betaines listed above.

The perturbation molecular orbital approach. The analysis in terms of their molecular orbitals, of the structures of heterocyclic mesomeric betaines, was advocated by Ramsden in 1977.[13] Subsequently, this treatment was developed[20] in a number of important respects, particularly in relation to the following classes:

Conjugated heterocyclic mesomeric betaines isoconjugate with odd alternant hydrocarbon anions (Section III, 1).

Conjugated heterocyclic mesomeric betaines isoconjugate with even alternant hydrocarbon dianions (Section III, 3).

Cross-conjugated heterocyclic mesomeric betaines isoconjugate with odd alternant hydrocarbon anions (Section III, 9).

Cross-conjugated heterocyclic mesomeric betaines isoconjugate with even alternant hydrocarbon dianions (Section III, 11).

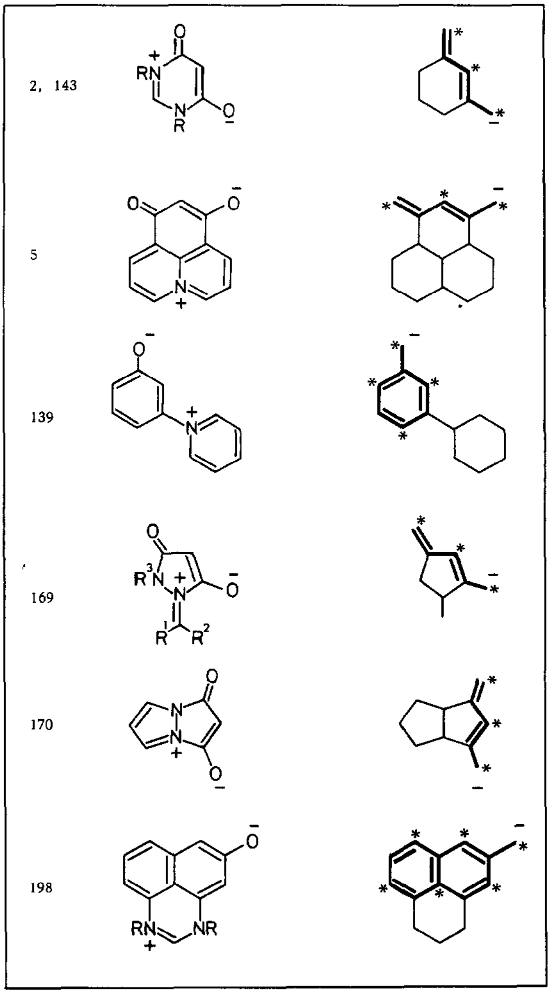
Consideration will now be given to the use of the molecular orbital method to identify heterocyclic mesomeric betaines in terms of the new classification (Sections III and VII).

The identification of mesomeric betaines which are conjugated is straightforward and it is unnecessary to repeat the details of the molecular orbital treatment of conjugated mesomeric betaines which have already been published.[13,20] There is, however, one general feature of the structures of some conjugated mesomeric betaines which should be emphasised. Conjugated mesomeric betaines isoconjugate with odd alternant hydrocarbon anions constitute a very large class of dipolar heterocycles (Section III, 1). The dipolar structures of this class all conform to a simple general rule.

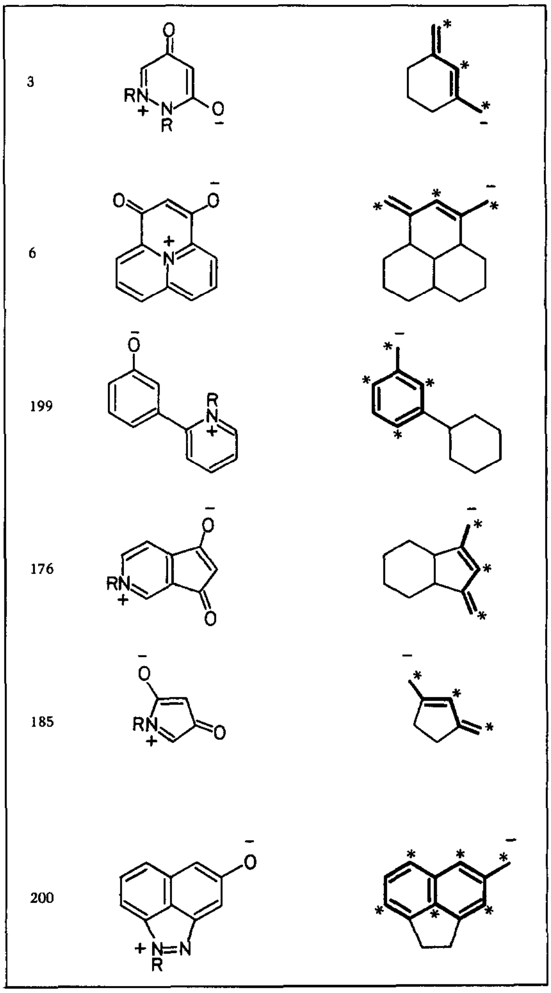
RULE 4. For conjugated heterocyclic mesomeric betaines which are isoconjugate with odd alternant hydrocarbon anions, the heteroatom which contributes two electrons to the total π-electron system must be located at one of the unstarred positions of the isoconjugate odd alternant hydrocarbon anion.

This rule is well illustrated by comparison of the following groups of structures: **50–56** with **57** and **58–77** with **78** and **79**.

The molecular orbital description of structure provides a very direct method for the identification of cross-conjugated and pseudo-cross-conjugated heterocyclic mesomeric betaines. In cross-conjugated and pseudo-cross-conjugated heterocyclic mesomeric betaines, the delocalised negative charge is almost invariably associated with a fragment which is isoconjugate with an odd alternant hydrocarbon



Scheme 20. The association of the delocalised negative charge of cross-conjugated heterocyclic mesomeric betaines with odd alternant hydrocarbon anion fragments (thick lines).



Scheme 21. The association of the delocalised negative charge of pseudo-cross-conjugated heterocyclic mesomeric betaines with odd alternant hydrocarbon anion fragments (thick lines).

anion (Schemes 20 and 21). This is true for all known cross-conjugated (Section III, 9–12) and pseudo-cross-conjugated (Section III, 13–16) heterocyclic mesomeric betaines. Exceptions to this generalisation may be envisaged (*vide infra*), but hypothetical dipolar molecules such as **142** do not constitute a serious challenge to the usefulness of the following generalisations (Rule 5).

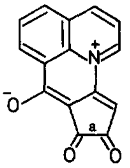
RULE 5. If (i) the delocalised negative charge of the heterocyclic mesomeric betaine is associated with a fragment which is isoconjugate with an odd alternant hydrocarbon anion, (ii) this fragment is connected through its unstarred positions to the remainder of the π-electron system of the molecule, and (iii) this fragment does not contain the heteroatom accommodating the positive charge, then the heterocyclic mesomeric betaine is either cross-conjugated or pseudo-cross-conjugated.

The application of Rule 5 to cross-conjugated and pseudo-cross-conjugated heterocyclic mesomeric betaines is illustrated in Schemes 20 and 21. The diagrams which correspond with each structural formula depict the total π-electron system of the heterocyclic mesomeric betaine (thin line) and the fragment of the π-electron system associated with the delocalised negative charge (thick line). One instructive general feature which emerges from Schemes 20 and 21 is that, although the heterocyclic mesomeric betaines are isoconjugate either with alternant (**2, 3, 5, 6, 139, 198** and **199**) or with non-alternant (**169, 170, 176, 185** and **200**) systems, the delocalised negative charges are all associated with odd alternant hydrocarbon anion fragments.

The identification of cross-conjugated heterocyclic mesomeric betaines and pseudo-cross-conjugated heterocyclic mesomeric betaines by the application of Rule 5 is straightforward.

Molecular orbital theory obviously provides a firm foundation for the division of heterocyclic mesomeric betaines into two main classes: (i) conjugated mesomeric betaines, and (ii) cross-conjugated and pseudo-cross-conjugated mesomeric betaines. However, unlike the valence bond method, the molecular orbital method does not provide a distinction between cross-conjugated and pseudo-cross-conjugated systems. On the basis of molecular orbital theory, cross-conjugated and pseudo-cross-conjugated systems have very similar electronic structures, so the question could well be asked whether the distinction between cross-conjugated and pseudo-cross-conjugated systems is necessary and useful. The true nature of pseudo-cross-conjugated mesomeric betaines will eventually become clearer when more examples have been synthesised and their chemistry has been explored.

Reference has already been made to the possible existence of cross-conjugated mesomeric betaines in which the delocalised negative charge is not associated with an odd alternant fragment. No betaines of this type are known, but the hypothetical betaine **142** is an example. In this case, Rule 5 is not applicable because condition (i) is not satisfied. The delocalised charge of the hypothetical mesomeric betaine **142** is associated with a non-alternant fragment simply because this fragment contains a 5-membered ring and any conjugated system containing an odd-membered ring must be non-alternant.



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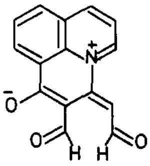

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The nature of the delocalisation present in the hypothetical mesomeric betaine **142** does not invalidate the general principles put forward in this section. Comparison of the tetracyclic mesomeric betaine **142** with the tricyclic mesomeric betaine **201** is instructive. The tricyclic mesomeric betaine **201** in which delocalisation of the negative charge involves an alternant fragment is transformed by intramolecular union[1] at unstarred positions into the tetracyclic mesomeric betaine **142** in which the negative charge is delocalised over a non-alternant fragment. The *union* creates bond *a* (see **142**) but there is no real distinction between the π-electron systems of the mesomeric betaines **142** and **201** because intramolecular *union* has occurred at unstarred positions. The fact that Rule 5 cannot be applied to the mesomeric betaine **142** can be justifiably regarded as a special case.

V. CYCLOADDITION REACTIONS OF HETEROCYCLIC MESOMERIC BETAINES

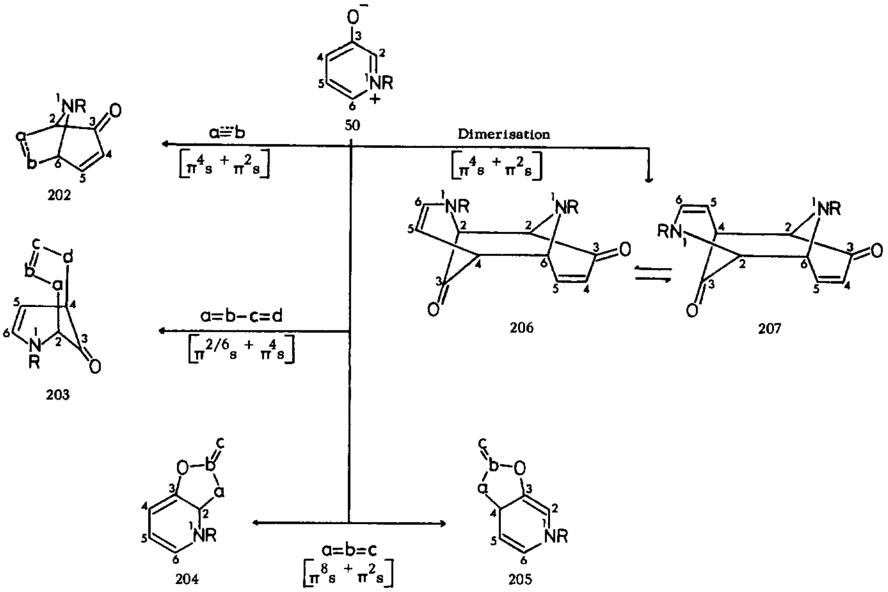
Many cycloaddition reactions of heterocyclic mesomeric betaines have been reported. A summary of these results is now presented, following the same classification as that used in Section III.

The majority of the cycloaddition reactions of heterocyclic mesomeric betaines can be correctly described as cycloadditions using the criteria advocated by Huisgen.[148a] However, there are a few reactions leading to cycloadducts in which small molecules or ions are eliminated from dipolar intermediates. Such reactions do not match the criteria advocated by Huisgen for cycloadditions, so we have adopted the very useful proposal made by Ege and Gilbert[148b] that such reactions should be called cycloreactions.

1. *Conjugated heterocyclic mesomeric betaines isoconjugate with odd alternant hydrocarbon anions*

Cycloaddition reactions are shown by a number of the members of class (1). These include the monocyclic mesomeric betaines **50**, **51** and **52**, the bicyclic mesomeric betaines **58**, **63**, **64**, **65**, **66**, **76** and **77** and the tricyclic mesomeric betaine **82**. The tricyclic mesomeric betaines **88**, **89**, **90** and **91**, which are isoconjugate with the odd alternant phenalenyl anion **24**, also participate in an interesting group of cycloaddition reactions.

A remarkable array of novel cycloaddition reactions has been discovered by Katritzky in his extensive and systematic investigation of pyridinium-3-olates **50**.[30,31,149] These results are summarised in Scheme 22. Pyridinium-3-olates **50** participate as 2π, 4π, 6π and 8π components in a variety of thermal and photochemical processes. The stereochemistry and regiochemistry of these



Scheme 22. Cycloaddition reactions of pyridinium-3-olates **50**.[30,31,149]

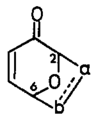
processes (Scheme 22) have been firmly established and a satisfying rationalisation of these results has been proposed on the basis of frontier molecular orbital theory.[31,149]

Pyridinium-3-olates **50** participate in a large number of cycloaddition reactions with π-electron excessive and π-electron deficient alkenes (a=b) which function as 1,3-dipolarophiles yielding the cycloadducts **202** by a concerted $[_\pi 4_s + _\pi 2_s]$ pathway.[31,149,150] Corresponding cycloadditions are also observed with acetylenic 1,3-dipolarophiles (a≡b).

Pyridinium-3-olates **50** can function as $_\pi 2/6_s$ components towards 1,3-dienes (a=b—c=d) and yield cycloadducts **203** by a concerted $[_\pi 2/6_s + _\pi 4_s]$ pathway.[31,149,150] Pyridinium-3-olates **50** function as $[_\pi 8_s]$ components towards heterocumulenes (a=b=c) such as ketenes and yield cycloadducts **204** and **205** apparently by a concerted $[_\pi 8_s + _\pi 2_s]$ pathway.[151]

The stereochemistry of the dimerisation of pyridinium-3-olates (**50** → **206** and **207**) is considered[31,149,150,152] to be in accord with their formation by concerted $[_\pi 6_s + _\pi 4_s]$ processes. The kinetically favoured dimer **206** is formed initially, but this can then equilibrate with the thermodynamically favoured dimer **207**. This equilibration would involve the cycloreversion–cycloaddition sequence (**206** → **50** → **207**).[31,149,150,152]

Some derivatives of pyrylium-3-olate **51** are stable, but the majority are reactive compounds which have been trapped by dipolarophiles. Alkenes (a=b) and acetylenes (a≡b) yield 2,6-cycloadducts **208**,[32–34,153] and 1,3-dienes (a=b—c=d) yield 2,4-cycloadducts **209**.[153]



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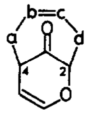

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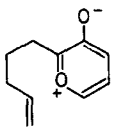
The intramolecular cycloaddition (**210** → **211**) shows *exo*-stereospecificity. This type of reaction has been cleverly applied for the total synthesis of several natural perhydroazulenes and *cis*-fused 1-decalones such as (±)-bulnesene **212** and (±)-fauronyl acetate **213**.[153]

The *syn*-structure **214** proposed[34] for the dimer of pyrylium-3-olate **51** does not correspond with the isomeric *anti*-structures **206** and **207** proposed for the dimers of pyridinium-3-olates.[150,152] However, thiopyrylium-3-olate **52** forms one dimer with the *syn*-configuration **215** (R = H), whereas 5-methyl-thiopyrylium-3-olate yields the *syn*-dimer **215** (R = Me) and the *anti*-dimer **216** (R = Me) in the ratio 12 : 1.[35] These dimerisations of thiopyrylium-3-olates **52** occur when 3-hydroxy-thiopyrylium perchlorates in tetrahydrofuran solution are treated with triethylamine at 0°C. The regiochemistry



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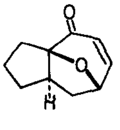

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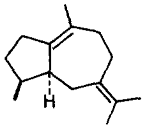

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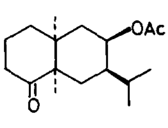

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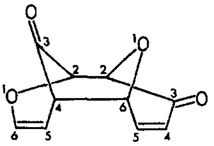

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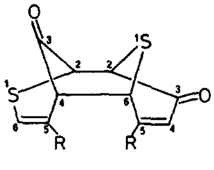
associated with the formation of the dimers **215** and **216** corresponds with that of the dimer **206**, but does not correspond with that of the dimer **207**.

Cycloaddition reactions between the monocyclic conjugated mesomeric betaines **52–56** and 1,3-dipolarophiles have not been reported. The formation of thiopyrylium-3-olates **52** in the presence of 1,3-dipolarophiles yielded only the dimers **215** and **216**: products from competition by 1,3-dipolar cycloaddition were not observed.[35]



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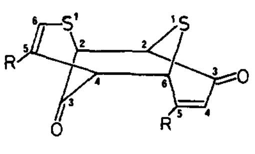

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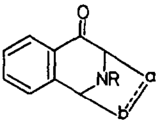
The bicyclic conjugated mesomeric betaines **63**,[50,154] **64**,[51,155] **65**,[37,52,156] **66**[53,157] and **76**[62,158] all react similarly towards olefinic 1,3-dipolarophiles (a=b). The reactions of **63** are typical yielding the cycloadduct **217**. Corresponding cycloadditions are observed with acetylenic dipolarophiles (a≡b). Quinolinium-3-olates **58** and 1,3-dienes yield the cycloadducts **218**.[45]



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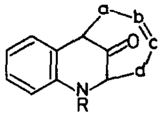

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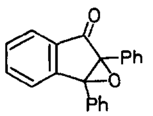
An unusual dimerisation was observed when 2,3-diphenylindenone oxide **219** was transformed into its valence isomer **220** either thermally[158] or photochemically.[62] The products are the isomeric epoxides **221** and **222** and they can be regarded as cycloadducts formed by the addition of the carbonyl group of the epoxide **219** to the conjugated mesomeric betaine **220**. When the epoxide **219** is heated in the presence of various 1,3-dipolarophiles, then the betaine **220** is trapped as its cycloadduct[62,158] (*cf* **208**).

In contrast with the remarkable sequence (**219** → **220** → **221** + **222**) which occurs when 2,3-diphenylindenone oxide **219** is heated (150°C; 7 hr) in benzene under pressure, when the parent betaine, 2-benzopyrylium-4-olate **76**, is generated in trifluoroacetic acid at room temperature (1 hr), then the *syn*-dimer **223** and the *anti*-dimer **224** are produced.[159] Similarly, when 2-benzothiopyrylium-4-olate **77** is generated in tetrahydrofuran–acetonitrile at room temperature (1 hr) then the *syn*-dimer **225** and



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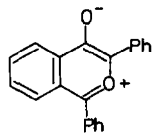

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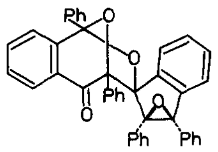

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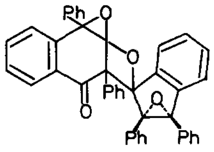

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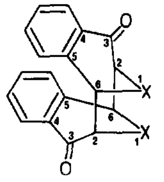
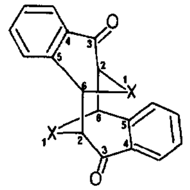
the *anti*-dimer **226** are produced.[160] The regiochemistry for the formation of the *syn*-dimers **223** and **225** and the *anti*-dimers **224** and **226** is different from the regiochemistry for the formation of the dimers **206**, **207**, **214** and **215**. The success of frontier molecular orbital theory in rationalising the constitutions of the dimers **206** and **207**[31,149,150,152] is not so compelling when the constitutions of the other dimers **214**, **215**, **223**, **224**, **225** and **226** are considered. The production of the *syn*-dimer **225** and *anti*-dimer **226** by a non-concerted process has been proposed[160] and it is clear that these dimerisations need not involve a concerted $[_\pi 4_s + _\pi 6_s]$ process.



223 X = O

225 X = S

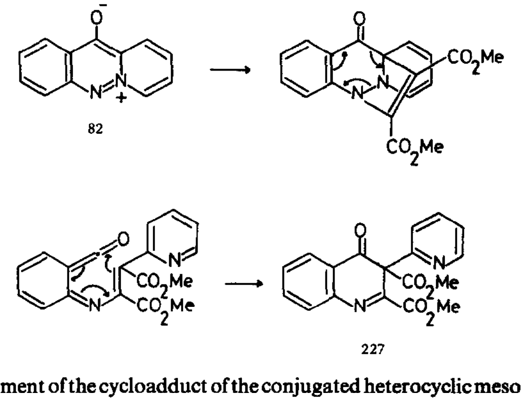


224 X = O

226 X = S

Only one of the tricyclic conjugated mesomeric betaines **80–87** has been shown to undergo cycloaddition reactions. The pyrido[1,2-*b*]cinnolinium-11-olate **82** and dimethyl acetylenedicarboxylate (100°C; 30 hr) yielded the 3,4-dihydroquinolin-4-one **227** by a sequence of reactions (Scheme 23) initiated by a 1,3-dipolar cycloaddition.[65] Incidentally, we suggest that the compound **82** should not be described as "meso-ionic"[65] for the reasons already given (Section I). The compound **82** should just be described as a conjugated heterocyclic mesomeric betaine.

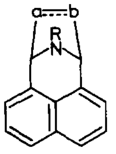
There is a remarkable contrast in the behaviour of the tricyclic mesomeric betaines **88–91** towards dipolarophiles. The conjugated mesomeric betaines **88**, **90** and **91** function as 1,3-dipoles towards olefinic (a=b) and acetylenic (a≡b) dipolarophiles giving the cycloadducts **228**,[67,161] **230**[69,161,162]



Scheme 23. Thermal rearrangement of the cycloadduct of the conjugated heterocyclic mesomeric betaine **82**.[65]

and **231**.[70,71] In contrast, the betaine **89**[68] functions as a 1,11-dipole towards dimethyl acetylenedicarboxylate yielding the cycloadduct **229** which then undergoes dehydrogenation.

The periselectivity between the 1,3-dipolar cycloadditions (**88** → **228**), (**90** → **230**) and (**91** → **231**) and the 1,11-dipolar cycloaddition (**89** → **229**) could be a consequence of the relative thermodynamic stability of the cycloadducts. The 1,3-cycloaddition $[{}_{\pi}4_{s} + {}_{\pi}2_{s}]$ and the 1,11-cycloaddition $[{}_{\pi}12_{s} + {}_{\pi}2_{s}]$ are both associated with acceptable HOMO (dipole)–LUMO (dipolarophile) interactions (**232**, **233** and **234**). Thus, the cycloadducts which are isolated could be kinetically determined but it must be emphasised that the sequence (cycloaddition $\rightleftarrows$ cycloreversion $\rightleftarrows$ cycloaddition) could give the cycloadduct which is thermodynamically more stable. Thus, the application of FMO theory to interpret the observed periselectivity in such cases could be irrelevant if the products are determined by relative thermodynamic stabilities.



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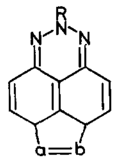

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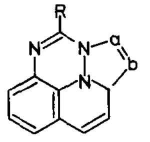

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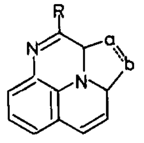

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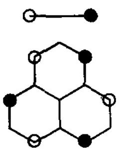

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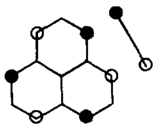

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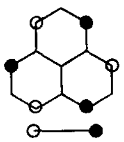

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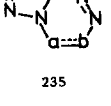
2. *Conjugated heterocyclic mesomeric betaines isoconjugate with odd non-alternant hydrocarbon anions*

3-Diazo-indazole was first prepared in 1899, but many years elapsed before this and other diazo-azoles such as 3-diazopyrazole **98** were recognised as conjugated mesomeric betaines.[75] The investigation of the cycloaddition reactions of diazo-azoles has taken place only during the past decade. This has included an examination of their reactions towards ynamines,[163] diazoalkanes,[148b] isocyanates[164] and phosphonium, sulphonium, and pyridinium ylides.[148b,165] Although no mechanistic studies have been reported, these reactions are likely to be two-step processes involving dipolar intermediates.

An interesting study has been recently reported[166] of the higher order dipolar cycloaddition reactions of diazo-azoles **98** towards electron-rich dienophiles including enamines, ynamines, and vinyl ethers. These reactions with alkenes (a=b) and with acetylenes (a≡b) yield 1,7-cycloadducts **235** and it has been proposed by Padwa *et al.*[166] that the 1,7-cycloadducts **235** are not formed directly, but that the 1,7-cycloadducts **235** are in fact produced by a stepwise reaction involving the 1,3-dipolar cycloadduct **236** as an intermediate. This intermediate **236** then undergoes a [1,5]sigmatropic shift (**236** → **235**) giving the final product **235**. This opinion was based upon the recognition of intermediates by NMR spectrometry. The experimental evidence and its interpretation is now carefully considered.



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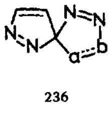

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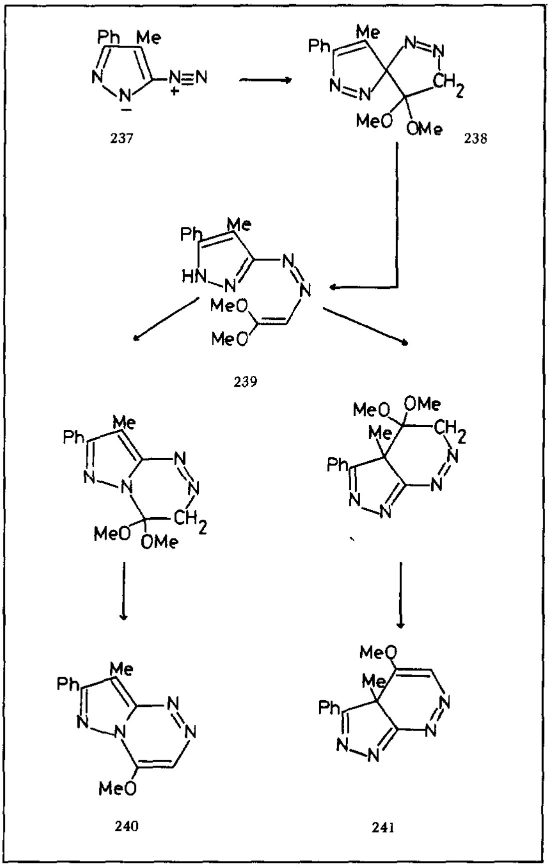
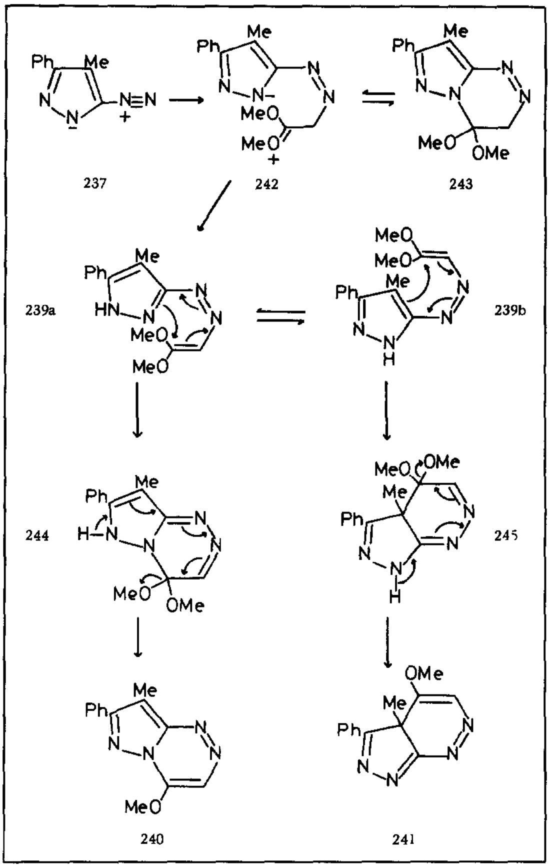
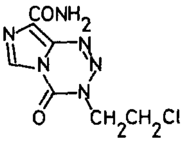


Scheme 24. Mechanism proposed for the cycloaddition reaction between 3-diazo-4-methyl-5-phenylpyrazole **237** and dimethoxyethene.[166]



Scheme 25. Alternative mechanism for the cycloaddition reaction between 3-diazo-4-methyl-5-phenylpyrazole **237** and dimethoxyethene.

The intermediates **238** and **239** have been proposed[166] for the reaction between 3-diazo-4-methyl-5-phenylpyrazole **237** and dimethoxyethene which yields **240** and **241** as the final products (Scheme 24). This reaction took place in deuteriochloroform during 72 hr at 25°C. However, if the reaction was monitored by NMR spectrometry then after 20 min the starting material **237** had reacted but the final products **240** and **241** had not yet been formed. After a reaction time of 20 min, a substance (m.p. 139–142°C decomp) was isolated which rapidly rearranged to the final products **240** and **241**. On the basis of its spectroscopic properties, this substance (m.p. 139–142°C decomp) was shown to be the intermediate **239** which could then cyclise in two ways giving the products **240** and **241**. It was then discovered[166] that a further intermediate was also formed after 90 sec. This thermally unstable intermediate was assigned the spiro-structure **238** and was regarded as the product of a direct 1,3-dipolar cycloaddition. The sequence (**237** → **238** → **239** → **240** + **241**) was therefore proposed (Scheme 24).[166] However, we now believe that the alternative mechanism (Scheme 25) is more acceptable even though replacement of Scheme 24 by Scheme 25 does require a different set of structures for the intermediates in the transformation (**237** + dimethoxyethene → **240** + **241**).



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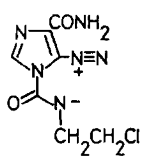

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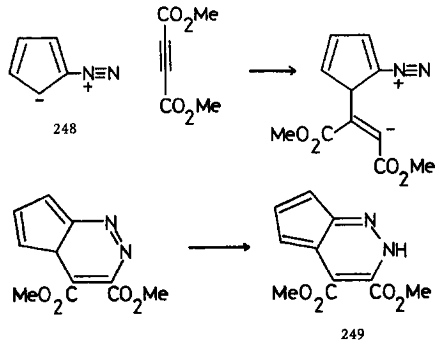
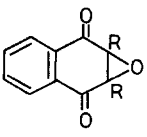
The basis for the replacement of Scheme 24 by Scheme 25 is provided by the discovery that the antitumour agent **246** is formed from 5-diazoimidazole-4-carboxamide and 2-chloroethylisocyanate.[167] This reaction probably involves the dipolar intermediate **247**. Similarly, the reaction of 3-diazo-4-methyl-5-phenylpyrazole and dimethoxyethene could involve the dipolar intermediate **242** which could then play a central role in the formation of the intermediates detected by NMR spectroscopy. We consider that the replacement of the proposed chiral spiro-structure **238** by the achiral structure **243** is certainly encouraged by the spectroscopic properties (s, 3H, δ 2.61; s, 6H, δ 3.36; s, 2H, δ 4.51) reported[166] for the intermediate formed after 90 sec. This structure **243** was considered by Padwa *et al.* (ref. 166, footnote 26), but was discarded. We prefer the structure **243** and the alternative mechanism (Scheme 25) because the dipolar intermediate **242** can participate either in the equilibration (**242** $\rightleftharpoons$ **243**) or in the prototropic rearrangement (**242** → **239**) which can then yield the products **240** and **241** by the electrocyclisations (**239a** → **244**) and (**239b** → **245**). The rejection of the structure **238** for the intermediate removes the need to propose[166] that diazo-azoles yield 1,7-cycloadducts **235** *via* the intermediates **236**.

Thus, all the reactions of diazo-azoles **98** towards ynamines,[163] diazo-alkanes,[148] isocyanates,[164,167] ylides,[148] and electron-rich dienophiles appear to us to be non-concerted cycloadditions or cycloreactions[148a] involving dipolar intermediates. A model for these reactions is the formation of the 2*H*-cyclopenta[*c*]pyridazine **249** by the reaction between diazocyclopentadiene **248** and dimethyl acetylenedicarboxylate in boiling tetrahydrofuran (Scheme 26).[168]



Scheme 26. Cycloreaction of diazocyclopentadiene **248** with dimethyl acetylenedicarboxylate.[168]

Photo-irradiation of 2,3-epoxynaphthaquinones **250** in the presence of dipolarophiles (a=b) yield cycloadducts **251**.[77] The dipolarophiles which have been used successfully include norbornene, *N*-phenylmaleimide, maleic anhydride, dimethyl maleate, and dimethyl fumarate. The formation of the cycloadducts has been formulated as involving the allowed disrotatory photo-isomerisation (**250** → **101**) of the oxirane to the carbonyl ylide and the intermediate heterocyclic mesomeric betaine **101** is then trapped by the dipolarophile (a=b) yielding the cycloadduct **251**.



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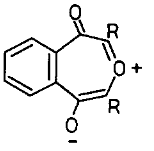

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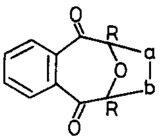
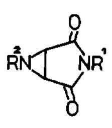


251

3. *Conjugated heterocyclic mesomeric betaines isoconjugate with even alternant hydrocarbon dianions*

Two methods have been used for the synthesis of the 1,4-disubstituted-1,2-dihydro-2-oxopyrazinium-6-olates **102**.[78] These are (i) photoisomerisation of the aziridines **252** and (ii) dehydrogenation of 1,4-disubstituted-2,6-dioxo-1,2,3,4,5,6-hexahydropyrazines **253**. The 1,4-disubstituted-1,2-dihydro-2-oxopyrazinium-6-olates **102** have not been isolated, but they have been trapped as cycloadducts **254** by their generation in the presence of dipolarophiles (a=b).

The aziridines **252** are obtained by thermolysis of the triazines prepared by cycloaddition of alkyl or aryl azides with *N*-alkyl- or *N*-arylmaleimides.[78] The aziridines **252** are reasonably stable to heat, but photolysis of the aziridines **252** occurs easily by the disrotatory mode giving the azomethine ylides **102** which have been trapped.[78]



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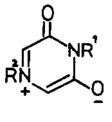

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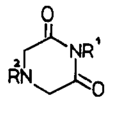

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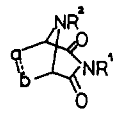

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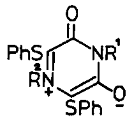

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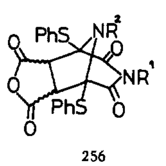

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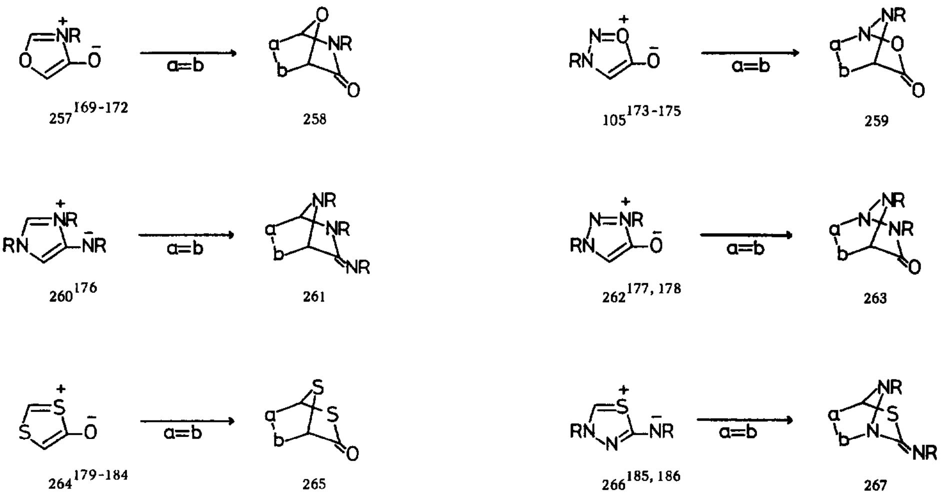
Oxidative transformation of 1,4-disubstituted-2,6-dioxo-1,2,3,4,5,6-hexahydropyrazines **253** to the conjugated mesomeric betaines **102** occurs on heating with nitrobenzene–acetic anhydride at 170–175°C (5 hr), but the products **102** have not been isolated directly. In the absence of 1,3-dipolarophiles, dimerisation occurs and in the presence of 1,3-dipolarophiles, the cycloadducts **254** are formed.[78]

A remarkable reaction has been described by Honzl *et al.*[78] Heating 1,4-disubstituted-2,6-dioxo-1,2,3,4,5,6-hexahydropyrazines **253** with benzenesulphonyl chloride in pyridine yields the conjugated mesomeric betaines **255** containing two phenylmercapto groups. The details of the mechanism of this reaction (**253** → **255**) are unknown, but clearly oxidation–reduction processes are involved as well as electrophilic substitution. The conjugated mesomeric betaines **255** give the cycloadducts **256** with maleic anhydride in boiling benzene.[78]

4. *Conjugated heterocyclic mesomeric betaines isoconjugate with even non-alternant hydrocarbon dianions*

An important part of Huisgen's classical investigations[2] of 1,3-dipolar cycloaddition reactions was his discovery that a large number of different classes of meso-ionic heterocycles reacted with 1,3-dipolarophiles. All of these meso-ionic heterocycles were of type **A** (Section III, 4) and it was very satisfying when it was recognised by Huisgen[2] that the common feature of type **A** meso-ionic heterocycles which dominated their role in cycloadditions was the presence of the 1,3-dipole **189** (Scheme 18) in their molecular structure.

The dipolarophiles which have been used include electron-deficient and strained alkenes (a=b), electron-deficient alkynes (a≡b) and various heterocumulenes (a=b=c). The electron-deficient alkenes include ethyl acrylate, acrylonitrile, dimethyl maleate, dimethyl fumarate, maleic anhydride, *N*-phenylmaleimide, and the azo-analogues, diethyl azodicarboxylate and *N*-phenyltriazolinedione. The electron-deficient alkynes include methyl propiolate, benzoylacetylene, dibenzoylacetylene and dimethyl acetylenedicarboxylate. Heterocumulenes which have been studied include carbon disulphide, carbonyl sulphide, alkyl and aryl isocyanates, and alkyl and aryl isothiocyanates.



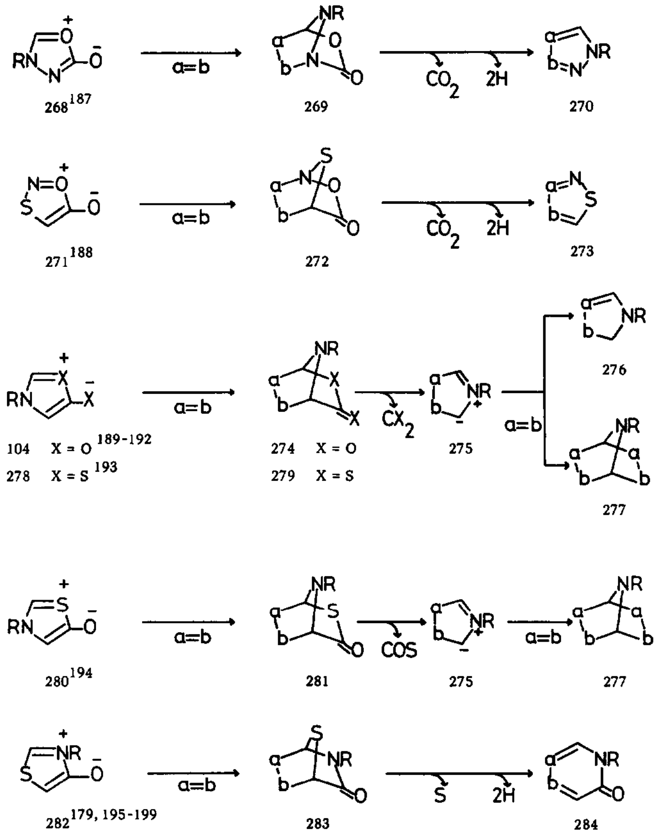
Scheme 27. Cycloaddition reactions of type **A** meso-ionic heterocycles with olefinic dipolarophiles.

The reaction of type **A** meso-ionic heterocycles with olefinic dipolarophiles conforms to the single theme of 1,3-dipolar cycloaddition. However, some remarkable variations upon this general theme have been observed.

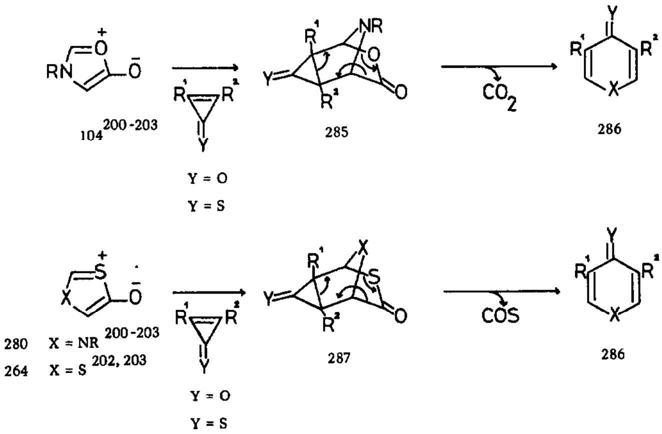
The meso-ionic heterocycles **257**,[169–172] **105**,[173–175] **260**,[176] **262**,[177,178] **264**[179–184] and **266**[185,186] react with olefinic dipolarophiles yielding cycloadducts which can be isolated and characterised (Scheme 27).

The meso-ionic heterocycles **268**,[187] **271**,[188] **104**,[189–192] **278**,[193] **280**[194] and **282**[179,195–199] also participate in 1,3-dipolar cycloaddition reactions with olefinic dipolarophiles (Scheme 28). However, the intermediate cycloadducts are frequently unstable and they then undergo one of four general types of reaction: (i) elimination of small molecules (CO_2, COS or CX_2) and fragmentation yielding 1,3-dipoles which are then dehydrogenated yielding the 5-membered conjugated heterocycles (**269** → **270**) and (**272** → **273**), (ii) fragmentation yielding 1,3-dipoles which then isomerise (**274** → **275** → **276**), (iii) fragmentation yielding 1,3-dipoles which are then trapped by further reaction with the dipolarophile (a=b) (**279** → **275** → **277**) and (**281** → **275** → **277**), and (iv) extrusion of sulphur and dehydrogenation yielding 6-membered α-pyridones (**283** → **284**). The factors controlling the selectivity between the possible reaction pathways (i) to (iv) are subtle. For example, a 2-phenyl-1,3-thiazolium-5-olate **280** (R = Ph) yields a stable cycloadduct **281** with maleic anhydride in ether (30 min, room temp), whereas, under similar conditions in acetone, fragmentation of the intermediate cycloadduct (**281** → **275**) occurred followed by a second cycloaddition yielding the product **277**.

Small-ring strained cyclic olefins are well known for their reactivity as dienophiles and many interesting examples of their complementary reactivity as 1,3-dipolarophiles towards type **A** meso-ionic heterocycles have been recently discovered. Three-membered cyclopropenones, cyclopropenethiones and cyclopropenimines react with 1,3-oxazolium-5-olates **104**, 1,3-thiazolium-5-olates **280**, and 1,3-dithiolium-4-olates **264**[200–203] yielding 6-membered heterocycles **286** (Scheme 29). These reactions take place under mild conditions (benzene, room temp) (acetic anhydride, 85°C), and the products **286** are formed by fragmentation of the intermediate cycloadducts **285** and **287** (arrows) by elimination (CO_2 or COS).

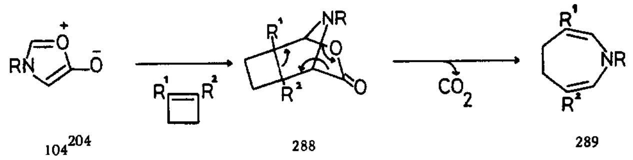


Scheme 28. Cycloaddition reactions of type A meso-ionic heterocycles with olefinic dipolarophiles.



Scheme 29. Cycloaddition reactions of type A meso-ionic heterocycles with cyclopropenones and cyclopropenethiones.

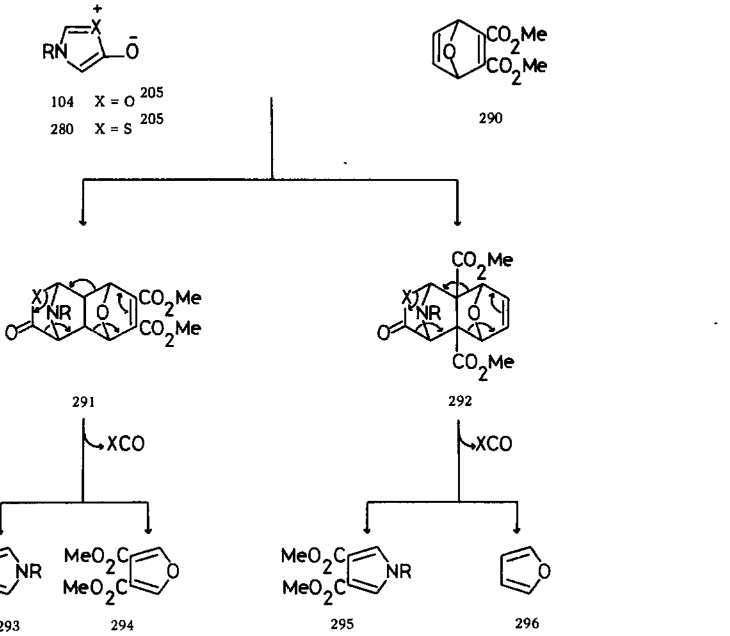
Four-membered cyclobutenes react with 1,3-oxazolium-5-olates **104**[204] by an analogous sequence of reactions (Scheme 30). Fragmentation of the intermediate cycloadduct **288** (arrows) with elimination (CO_2) yields the 7-membered dihydro-azepines **289**.



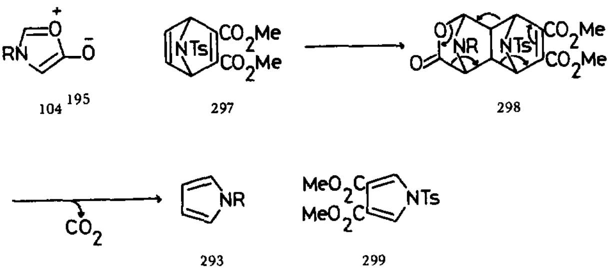
Scheme 30. Cycloaddition reactions of type A meso-ionic heterocycles with cyclobutenes.[204]

The cycloaddition reactions of type A meso-ionic heterocycles with 5-membered strained alkenes which are derivatives of 7-oxabicyclo[2.2.1]hepta-2,5-diene **290** and 7-azabicyclo[2.2.1]hepta-2,5-diene (**297** and **300**) also follow the general reaction pathway of cycloaddition followed by fragmentation.

1,3-Oxazolium-5-olates **104** and dimethyl 7-oxabicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate **290** undergo a rapid reaction (benzene, room temp, 15 min) yielding the four products **293**, **294**, **295** and



Scheme 31. Cycloaddition reactions of type A meso-ionic heterocycles with dimethyl 7-oxobicyclo-[2.2.1]hepta-2,5-diene-2,3-dicarboxylate **290**.[205]

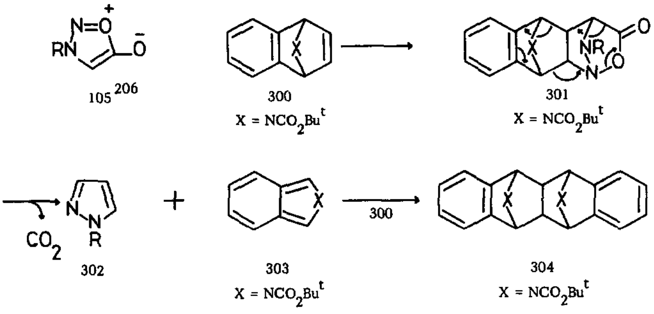


Scheme 32. Cycloaddition reactions of type A meso-ionic heterocycles with dimethyl 7-*p*-toluenesulphonyl-7-azabicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate **297**.[195]

296 which clearly involve the two cycloadducts **291** and **292** as intermediates (Scheme 31).[205] The four products **293**, **294**, **295** and **296** were similarly formed in higher yields when 1,3-thiazolium-5-olates **280** were heated with the diene **290** in boiling benzene. Corresponding cycloadditions were also observed with 1,3-dithiolium-4-olates **264**[205] and 1,3-thiazolium-4-olates **282**.[205] 1,3-Dithiolium-4-olates **264** yielded a stable cycloadduct (*cf* **291**) in which periselectivity in favour of cycloaddition to the less-hindered double bond of the diene **290** was observed. 1,3-Thiazolium-4-olates **282** yielded two cycloadducts (*cf* **291**; 48% yield and **292**; 33% yield).

1,3-Oxazolium-5-olates **104** reacted with the 7-aza[2.2.1]heptadiene **297** under mild conditions (benzene, 40°C) yielding the products **293** and **299** by the fragmentation reaction **298** (arrows)[195] (Scheme 32).

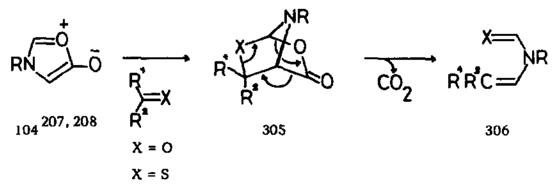
1,2,3-Oxadiazolium-5-olates (sydnones) and the 1,4-imino-1,4-dihydronaphthalene **300** in boiling toluene (23 hr) gave two diastereoisomeric forms of the product **304**.[206] This reaction involves the formation of the cycloadduct **301** which then fragments yielding CO_2, the pyrazole **302**, and the iso-indole **303**. The iso-indole **303** is then trapped by the original dienophile **300** yielding the final product **304** (Scheme 33).



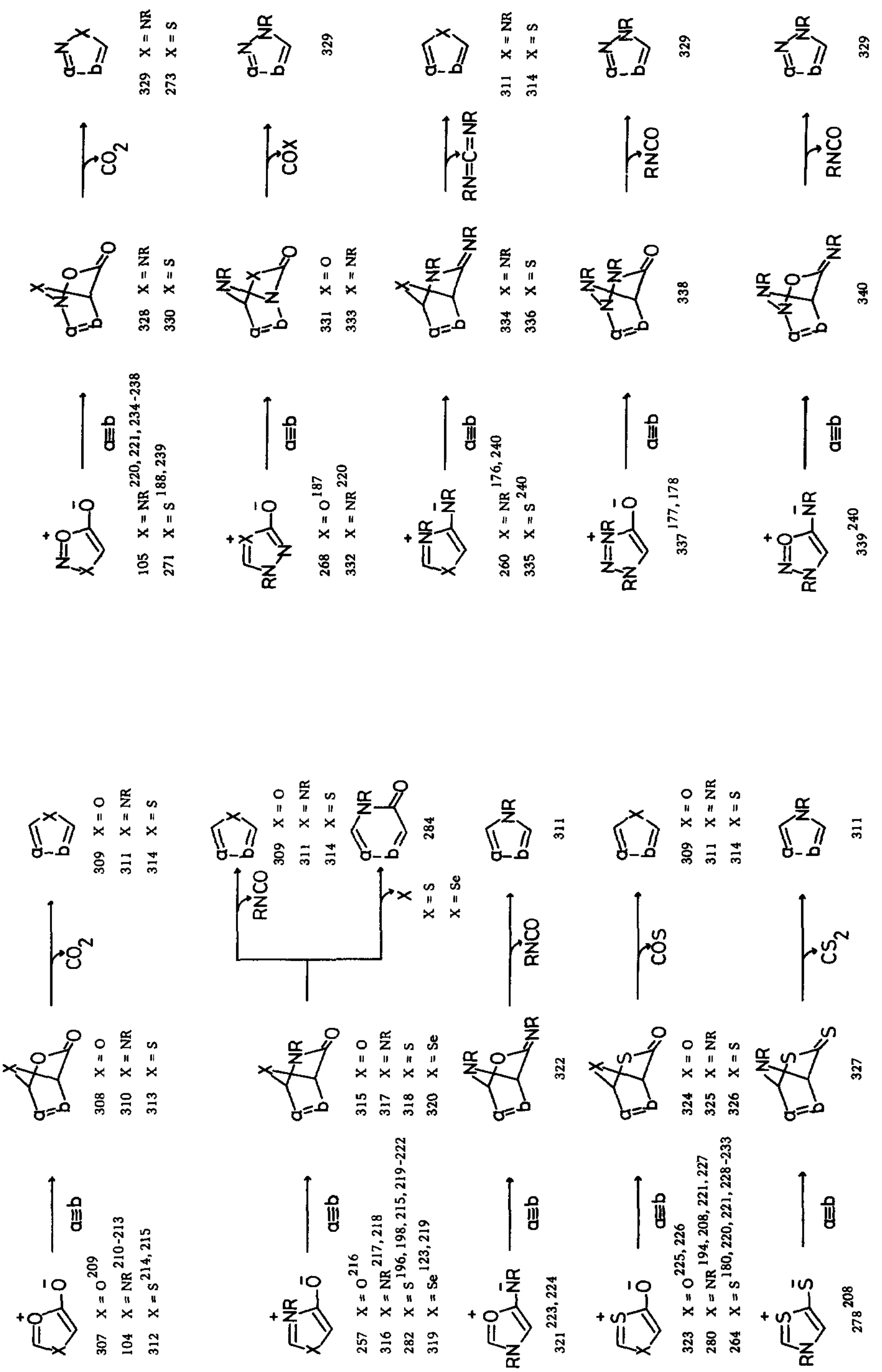
Scheme 33. Cycloaddition reactions of type A meso-ionic heterocycles with 1,4-[(7-*tert*-butoxycarbonyl)imino]-1,4-dihydronaphthalene **300**.[206]

1,3-Oxazolium-5-olates (**104**) form cycloadducts **305** with ketones and with thioketones.[207,208] These cycloadducts then undergo fragmentation **305** (arrows) and elimination (CO_2) yielding the products **306** (Scheme 34).

Type A meso-ionic heterocycles show a remarkable array of 1,3-dipolar cycloaddition reactions towards acetylenic dipolarophiles (Schemes 35). However, all of these reactions belong to one general type which involves a sequence of cycloaddition followed by fragmentation–elimination. In two reactions, the intermediate cycloadducts **315**[216] and **318**[220,221] have been isolated and characterised. Cycloadducts of the type **315** formed by cycloadditions with benzyne show interesting differences in

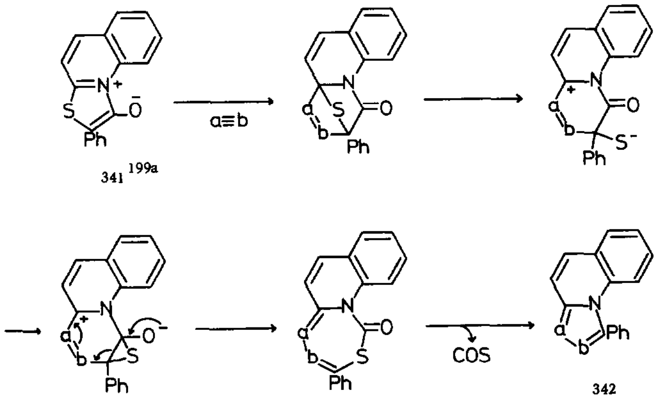


Scheme 34. Cycloaddition reactions of type A meso-ionic heterocycles with ketones and thioketones.[207,208]



Scheme 35. Cycloaddition reactions of type A meso-ionic heterocycles with acetylenic dipolarophiles.

their thermal and photochemical behaviour.[220] Heating in boiling xylene results in an elimination (RNCO) and the formation of the corresponding benzo[c]thiophen (**318** → **314**), whereas photoirradiation results in sulphur extrusion and the formation of the corresponding quinolone (**318** → **284**). Extrusion of selenium with the formation of α-pyridones **284** is always observed in the cycloaddition reactions of 1,3-selenazolium-5-olates **319**.[123,219]



341[199a]

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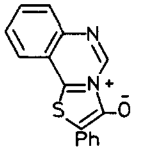
Scheme 36. Cycloaddition reaction of 2-phenylthiazo[3,2-*a*]quinolinium-1-olate (**341**) with acetylenic dipolarophiles.[199a]

The cycloaddition reactions of 1,3-thiazolium-4-olates **282** have been extensively investigated.[196,198,215,219–222] The cycloadducts **318** exhibit two types of fragmentation–elimination reaction: (i) elimination (RNCO) yielding thiophenes (**318** → **314**) and (ii) extrusion of sulphur yielding α-pyridones (**318** → **284**). It is therefore particularly noteworthy that the reaction (Scheme 36) of the derivative **341** of 1,3-thiazolium-4-olate **282** with electron-deficient acetylenic dipolarophiles, dimethyl acetylenedicarboxylate and ethyl propiolate, take a completely different course. The transformation (**341** → **342**) involves elimination of carbonyl sulphide which was firmly identified, but the proposed mechanism[199a] (Scheme 36) has no precedent.



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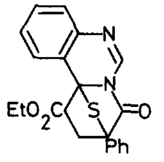

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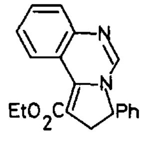

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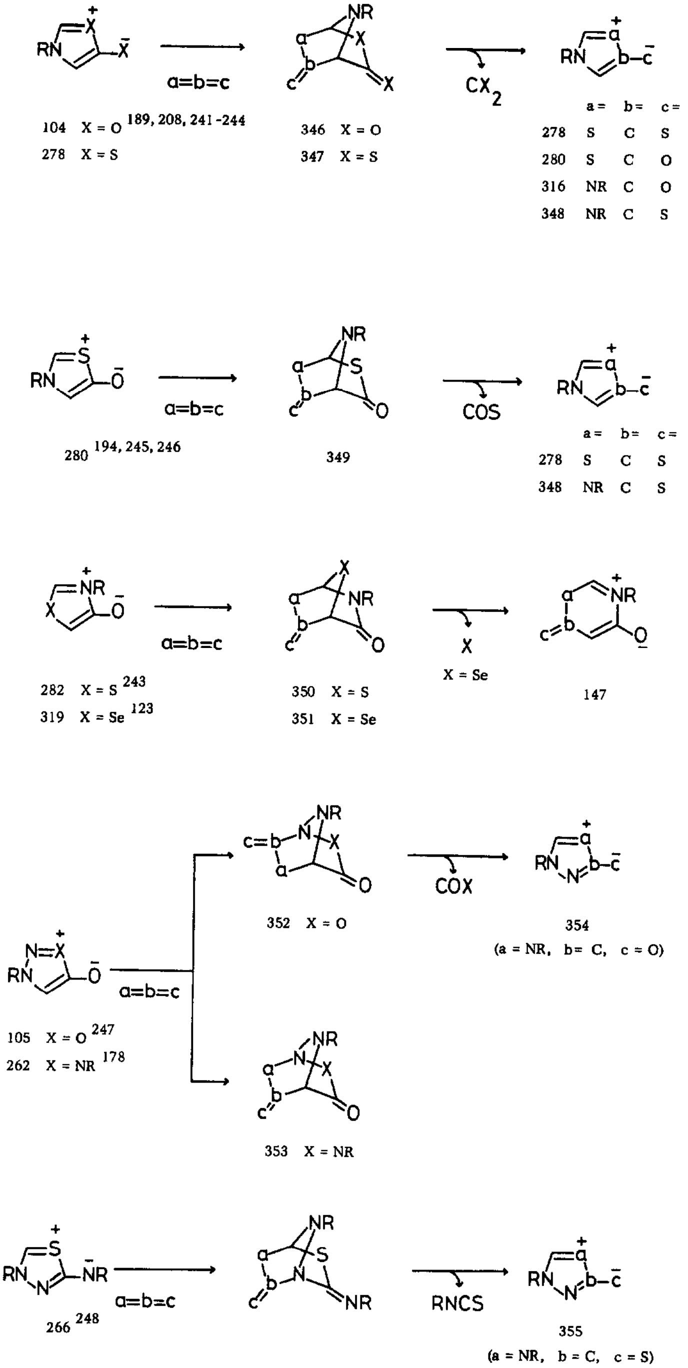
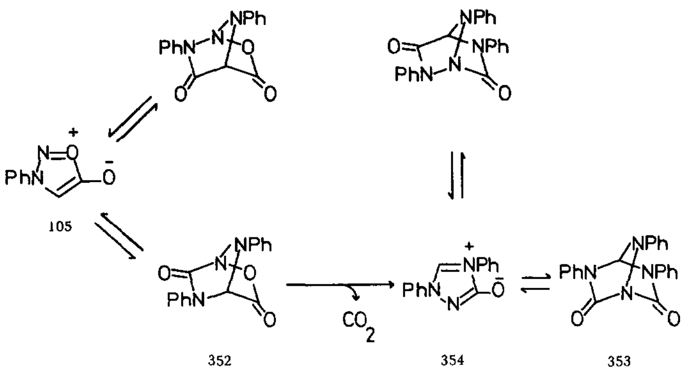
A closely related reaction involving cycloaddition and elimination of carbonyl sulphide is observed in the reaction between the 1,3-thiazolium-4-olate **343** and ethyl acrylate.[199b] In this case a remarkable difference is observed when the reaction is carried out either in excess ethyl acrylate (99°C; 5 hr) or in boiling xylene (*ca* 140°C; 12 hr) with ethyl acrylate (1.1 equiv). Reaction in neat ethyl acrylate gave the 1:1 cycloadduct **344**, whereas the reaction in boiling xylene gave the product **345** formed by extrusion of carbonyl sulphide. However, in connection with the mechanism proposed for the closely related reaction (Scheme 36),[199a] it must be emphasised that the cycloadduct **344** is not transformed into the product **345** by prolonged heating in xylene.[199b] We look forward to further work on these interesting reactions involving carbonyl sulphide elimination.

Type A meso-ionic heterocycles participate in 1,3-dipolar cycloadditions (Scheme 37) with a variety of heterocumulenes including carbon disulphide, carbonyl sulphide, aryl isocyanates, aryl isothiocyanates and acyl isocyanates (benzoyl isocyanate, chlorosulphonyl isocyanate and *p*-toluenesulphonyl isocyanate). The majority of these reactions take place under mild conditions (20–70°C; few hours), but in some cases the reactants are heated in boiling benzene or xylene. For example, the transformation **104** → **278** is achieved merely by dissolving 1,3-oxazolium-4-olates **104** in carbon disulphide (20°C). The yield of the product **278** is quantitative and the reaction is complete when the evolution of carbon dioxide ceases (10 hr).



Scheme 37. Cycloaddition reactions of type A meso-ionic heterocycles with heterocumulenes.

The intermediate cycloadducts are usually not isolable so the reaction of type A meso-ionic heterocycles with heterocumulenes is a good method for the direct transformation of one class of meso-ionic heterocycle into another. In a few cases stable cycloadducts have been isolated. *N*-Benzoylsarcosine reacts with activated isocyanates (benzoyl isocyanate and *p*-toluenesulphonyl isocyanate) in acetic anhydride (60°C; 5 min) yielding the intermediate, 1,3-oxazolium-5-olate **104** (R = Me, X = O) which is then trapped *in situ* yielding the cycloadduct **346** (a = ArCON or $ArSO_2N$, b = C, c = O).[243] The reaction of 3-methyl-1,3-diphenyloxazolium-5-olate **104** (X = O) with phenyl isocyanate in xylene (70°C; 4 hr) similarly yields an adduct which is transformed into the corresponding 1,3-diazolium-4-olate **316** by boiling xylene (30 min): no decision was made between the two regioisomeric structures which are possible for the cycloadduct in the transformation (**104** →



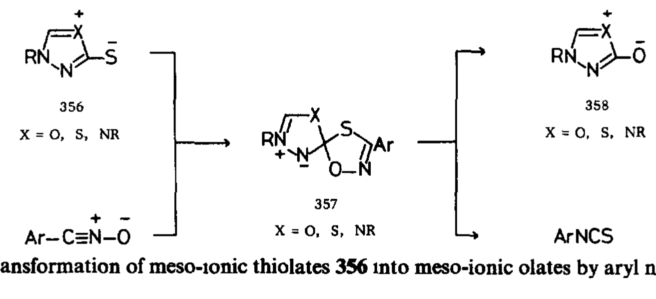
Scheme 38. Proposed mechanism for the cycloaddition reaction of *N*-phenylsydnone **105** with phenyl isocyanate.

316).[244] 1,3-Thiazolium-4-olates **282** react with cyanates and isothiocyanates giving isolable cycloadducts **350**.[243] The transformation (**282** → **350**) occurs with activated acyl isocyanates in benzene at room temperature whereas the reaction with aryl isocyanates and aryl isothiocyanates required boiling benzene (15 min). 1,3-Dimethyltriazolium-4-olate **262** (R = Me) and phenyl isocyanate in boiling xylene (10 hr) yield the isolable cycloadduct **353** (R = Me, a = Ph, b = C, c = O).[178]

With one exception (**105** → **354**), all the cycloaddition reactions of type A meso-ionic heterocycles show corresponding regiospecificity in their cycloadditions (Scheme 37). At first sight, one might be tempted to interpret the observed regiospecificity in terms of HOMO–LUMO interaction. However, we believe that it is more likely that the regiospecificity which is observed (Scheme 37) may just be associated with the fact that the initial cycloaddition reactions could be reversible. Thus, unsymmetrical reactants could form two possible cycloadducts and either one could participate in subsequent reactions. This approach provides an excellent basis for understanding the rather curious reactions of *N*-phenylsydnone **105** (R = Ph) with phenyl isocyanate.[247] Four reactions have been reported[247] (Scheme 38): (i) *N*-phenylsydnone and phenyl isocyanate (120–130°C; 3 hr) yield 1,4-diphenyl-1,2,4-triazolium-3-olate **354** (R = Ph), (ii) *N*-phenylsydnone and phenyl isocyanate (162°C; 3 hr) yield the cycloadduct **353**, (iii) 1,4-diphenyl-1,2,4-triazolium-4-olate **354** (R = Ph) and phenyl isocyanate (162°C; 3 hr) yield the cycloadduct **353**, (iv) the cycloadduct **353** reverts to 1,4-diphenyl-1,2,4-triazolium-4-olate **354** (R = Ph) on heating in diphenyl ether (190–200°C; 20 min). These reactions [(i)–(iv)] are rationalised in Scheme 38 and it is immediately obvious that questions relating to the apparently anomalous regiospecificity of the reaction **105** → **354** may have nothing to do with HOMO–LUMO interactions.

The formation of α-pyridones **284** by the extrusion of selenium is always observed in the cycloaddition reactions of 1,3-selenazolium-5-olates **319**[123,219] (Scheme 35). The corresponding reaction (**319** → **147**) is observed in the corresponding reaction of 1,3-selenazolium-5-olates **319** with heterocumulenes. Thus, 1,3-selenazolium-5-olates **319** and phenyl isothiocyanate in boiling xylene (72 hr) yielded 1,3-disubstituted-3,6-dihydro-6-oxopyrimidinium-4-thiolates **147**. This is the first example of the direct transformation of a conjugated mesomeric betaine **319** into a cross-conjugated mesomeric betaine **147**.

Grashey *et al.*[249] have applied a known reaction[250,251] for the transformation of thioketones to ketones. Meso-ionic thiolates are transformed into olates by reaction with mesitonitriloxide in acetonitrile or methylene chloride (Scheme 39). On the basis of earlier mechanistic studies by

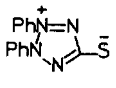


Scheme 39. Transformation of meso-ionic thiolates **356** into meso-ionic olates by aryl nitrile oxides.[249]

Dondoni[250] and Huisgen,[251] it is proposed that the meso-ionic thiolates **356** undergo a cycloaddition reaction (Scheme 39) which is quite different mechanistically from all those previously discussed (Schemes 27–38). Dipolar cycloaddition at the exocyclic C=S bond leads to the intermediate 1,4,2-oxothiazole **357** which then fragments with aryl migration giving the olate **358** and the aryl isothiocyanate by a Beckmann-type rearrangement.

Extensive investigations of the cycloaddition reactions of type **A** meso-ionic heterocycles which involve thermal equilibration with their covalent valence tautomers have been reviewed.[2,4] This topic has not therefore been discussed in this Section, but certain aspects of the cycloaddition reactions of type **A** meso-ionic heterocycles involving ketenoid valence tautomers are considered later (Scheme 79). Meanwhile, the recent recognition[253–255] of the importance of valence tautomerism which has led to a satisfying rationalisation of the cycloaddition reactions of type **B** meso-ionic heterocycles is now highlighted.

Dehydrodithizone **9** is a type **B** meso-ionic heterocycle and it displays a fascinating variety of chemical reactivity in several different types of cycloaddition reaction. Difficulties in the mechanistic interpretation of a number of reactions of dehydrodithizone **9** which were noted by Ollis and Ramsden[4] have now been removed by the demonstration that some of the structures initially proposed[252] for a number of cycloadducts are incorrect. The careful investigations by Boyd[253–255] have demonstrated that dehydrodithizone **9** can participate in two distinct types of cycloaddition. The two types of cycloaddition (**9** → **360**) and (**359** → **361**) can be acceptably interpreted in terms of an equilibrium involving the valence tautomers **9** and **359**.



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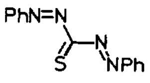

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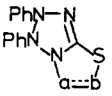

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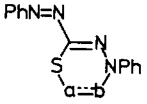

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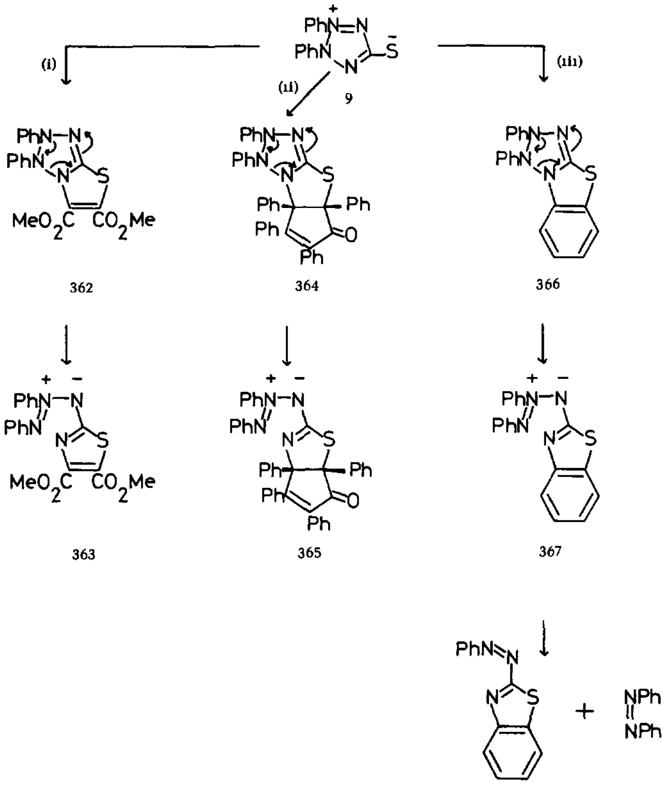
The cycloaddition reactions of dehydrodithizone towards electron-deficient dipolarophiles are summarized in Scheme 40. The reaction of dehydrodithizone **9** with dimethyl acetylenedicarboxylate was first interpreted[252] as yielding the cycloadduct **362**. However, an X-ray crystallographical investigation[255] has shown that this cycloadduct is, in fact, the 1,3-dipolar azo-imide **363**, presumably formed by a retro-1,5-electrocyclisation **362** (arrows). The transformation (**362** → **363**) may well be encouraged by the thermodynamic instability associated with lone pair–lone pair interaction in the triazane system present in the structure **362**. Similarly, dehydrodithizone **9** and tetraphenylcyclopentadienone yield the azo-imide **365** by a similar retro-1,5-electrocyclisation **364** (arrows).[254] A related reaction is the formation of 2-phenylazobenzothiazole **368** and azobenzene by reaction of dehydrodithizone with benzyne produced from anthranilic acid.[255] This mechanistic conundrum may be interpreted (Scheme 40) by a sequence involving (i) cycloaddition (**9** → **366**), (ii) retro-1,5-electrocyclisation **366** (arrows), and (iii) fragmentation of the intermediate azo-imide **367** yielding 2-phenylazobenzothiazole **368** and phenylnitrene which then dimerises giving azobenzene.[255]

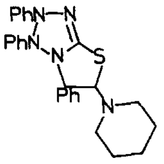
The cycloaddition reactions of dehydrodithizone **9** with electron-rich enamines were also interpreted as analogous 1,3-dipolar cycloadditions.[252] This led to the proposal[252] of the constitutions **369**, **370** and **371** for the cycloadducts derived from β-piperidinostyrene, 1,2,5,6-tetrahydro-1-methyl-4-morpholinopyridine and pyrrolidinocyclohexene, respectively. These structures are incorrect and on the basis of an X-ray crystallographical investigation[253] these three incorrect structures **369**, **370** and **371** should be replaced by the three correct structures **372**, **373** and **374**. The three correct structures are obviously related to the valence tautomer **359**, and could be derived by a $[{}_\pi 4_s + {}_\pi 2_s]$ cycloaddition (**359** → **361**) characteristic of other azadienes.[256,257]

A similar cycloaddition has been observed for dehydrodithizone **9** and enamines **375** derived from indan-2-one.[253] The reaction products are the spiro-compounds **378** and they could be produced by a sequence involving cycloaddition (**375** → **376**) and rearrangements (**376** → **377** → **378**) (Scheme 41).



Reagents
(i) dimethyl acetylenedicarboxylate
(ii) tetraphenylcyclopentadieneone
(iii) isopentyl nitrite–anthranilic acid

Scheme 40. 1,3-Dipolar cycloaddition reactions of the type **B** meso-ionic heterocycle, dehydrodithizone **9**.[254,255]



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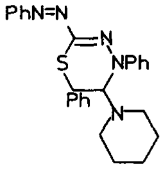

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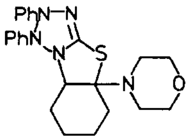

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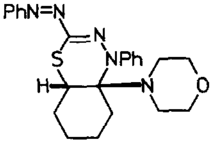

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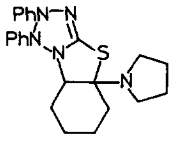

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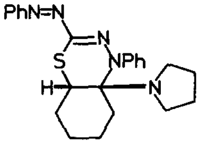

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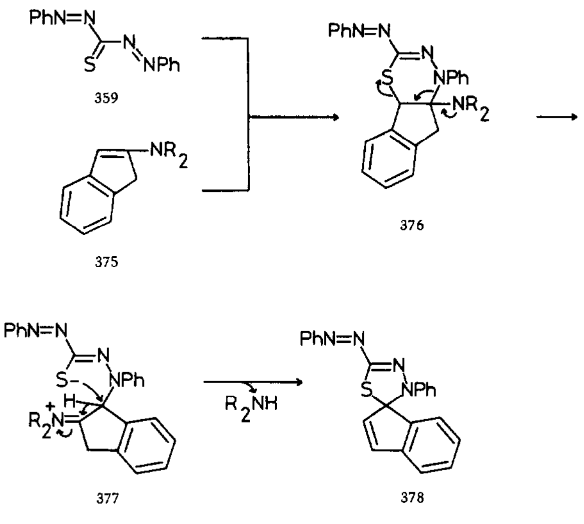
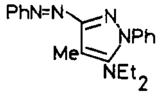


In formulae 375 - 377 (a) R_2N = pyrrolidino;
(b) R_2N = piperidino,
(c) R_2N = morpholino

Scheme 41. Cycloaddition reaction of dehydrodithizone **9** with 2-dialkylamino-indenes.^{253}

The reaction of dehydrothizone (**9**$\rightleftharpoons$**359**) and electron-rich ynamines has also been studied.^{253} Thus, diethylaminopropyne yields the major product **379** and the minor product **380** : the constitution **379** of the major product was established by X-ray crystallography.^{253} The mechanism proposed (Scheme 42) for the formation of the pyrazole **379** involves cycloaddition and extrusion of sulphur. The same mechanism may be proposed for the formation of the regioisomer **380** obtained as a minor product.



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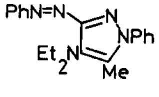

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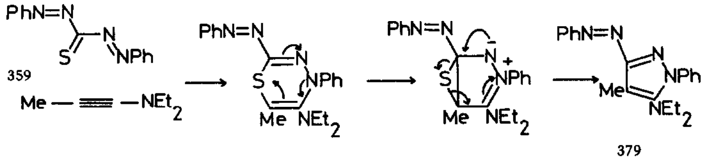
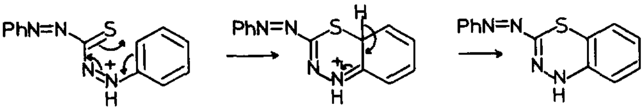
Although the loss of sulphur is formally represented as extrusion of S_1, equivalent intermolecular processes permitting the more acceptable extrusion of singlet $^1S_2$ can be envisaged.^{258} The elimination of sulphur in the formation of pyrazoles from 6H-1,3,4-thiadiazines is also believed to involve an episulphide intermediate^{259} or its bimolecular equivalent.^{258} It is interesting to note that enamines and dehydrodithizone (**9**$\rightleftharpoons$**359**) yield cycloadducts **372**, **373** and **374** in which sulphur is retained, whereas ynamines and dehydrodithizone (**9**$\rightleftharpoons$**359**) yield intermediate cycloadducts which lose sulphur (Scheme 42).

Boyd^{253} has put forward an appealing rationalisation of the two distinct pathways which are followed by dehydrodithizone (**9**$\rightleftharpoons$**359**) in its reactions with electron-deficient and electron-rich alkenes and acetylenes. Using FMO theory, it is concluded that cycloaddition of dehydrodithizone with electron-deficient dipolarophiles (Scheme 40) is controlled by interaction of the HOMO of dehydrodithizone with the LUMO of the electron-deficient dipolarophile. The observed reactions (Scheme 40) may therefore proceed in a concerted fashion. In contrast, a concerted 1,3-dipolar cycloaddition of dehydrodithizone (**9**$\rightleftharpoons$**359**) with electron-rich alkenes or acetylenes would be controlled by interaction of the LUMO of dehydrodithizone with the HOMO of the electron-rich



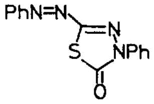
Scheme 42. Cycloaddition reaction of dehydrodithizone **9** with diethylaminopropyne.^{253}



Scheme 43. Acid catalysed isomerisation of dehydrodithizone **9**.[260]

dipolarophile. The LUMO of dehydrodithizone has a zero coefficient at sulphur so the cycloaddition (**9** → **360**) does not occur and the alternative (**359** → **361**) supervenes with electron-rich dipolarophiles.

The acid-catalysed isomerisation[260] (Scheme 43) of dehydrodithizone is the electrocyclic equivalent of the intermolecular cycloaddition (**359** → **361**). Dehydrodithizone reacts with pentacarbonyl iron yielding the thiadiazolinone **381**.[261] This is a novel type of carbonyl insertion reaction which proceeds in good yield (80%).



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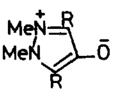
There is little information on the cycloaddition reactions of the other classes of type **B** meso-ionic heterocycles. The reactions of 1,2-diazolium-4-olates **382** (R = H, Me or Ph) with various dipolarophiles have been examined in some detail, but no reactions with dienes, activated alkenes, or alkynes have been reported.[262]



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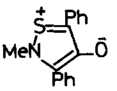

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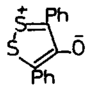

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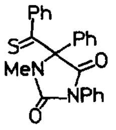

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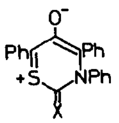


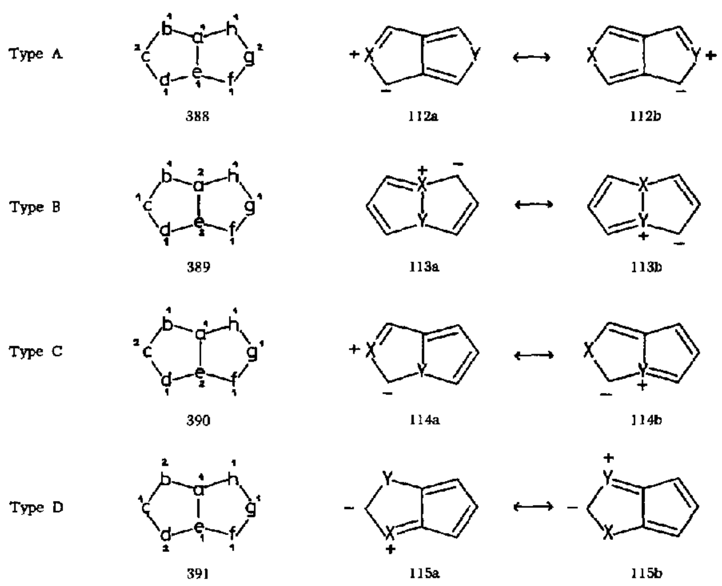
386 X = O

387 X = S

The 1,2-thiazolium-4-olate **383** reacts with phenylisocyanate yielding the product **385**.[263] 3,5-Diphenyl-1,2-dithiolium-4-olate **384** reacts with phenylisocyanate yielding the product **386**.[263] Similarly, phenyl isothiocyanate yields the product **387**.[263]

Ten general types of heterocyclic systems have been recognised which are isoconjugate with the 10π-electron system of the pentalenyl dianion.[14–19] Six of these types can be represented by covalent formulations, whereas four types are conjugated mesomeric betaines (Scheme 44). These four types are associated with the location of the atoms which contribute two electrons to the 10π-electron system. This feature is represented by the diagrams **388**, **389**, **390** and **391** in which the letters a, b, c, d, e, f, g and h represent acceptable combinations of carbon and hydrogen atoms in association with oxygen, nitrogen and sulphur as heteroatoms: the superscripts 1 or 2 indicate the origin of the 10π-electrons.[14]

Each of the four types **A**, **B**, **C** and **D** of heteropentalenes (Scheme 44) is associated with one pair of non-equivalent mesomeric forms (**112a** ↔ **112b**, **113a** ↔ **113b**, **114a** ↔ **114b** and **115a** ↔ **115b**), and this may be associated with the regiochemistry of their cycloaddition reactions with 1,3-dipolarophiles. Type **A** heteropentalenes (**112a** ↔ **112b**) show two types of cycloaddition reactions with olefinic dipolarophiles (Scheme 45) and with acetylenic dipolarophiles (Scheme 46). Type **B** heteropentalenes (**113a** ↔ **113b**) show two types of cycloaddition reactions towards acetylenic dipolarophiles (Scheme 47). Type **C** heteropentalenes show two types of cycloaddition reactions (Scheme 48). No cycloadditions of type **D** heteropentalenes have yet been reported, but two types of cycloadditions associated with the mesomeric structures (**115a** ↔ **115b**) can be envisaged. The periselectivity of the cycloaddition reactions of type **A**, type **B**, and type **C** heteropentalenes is now considered.



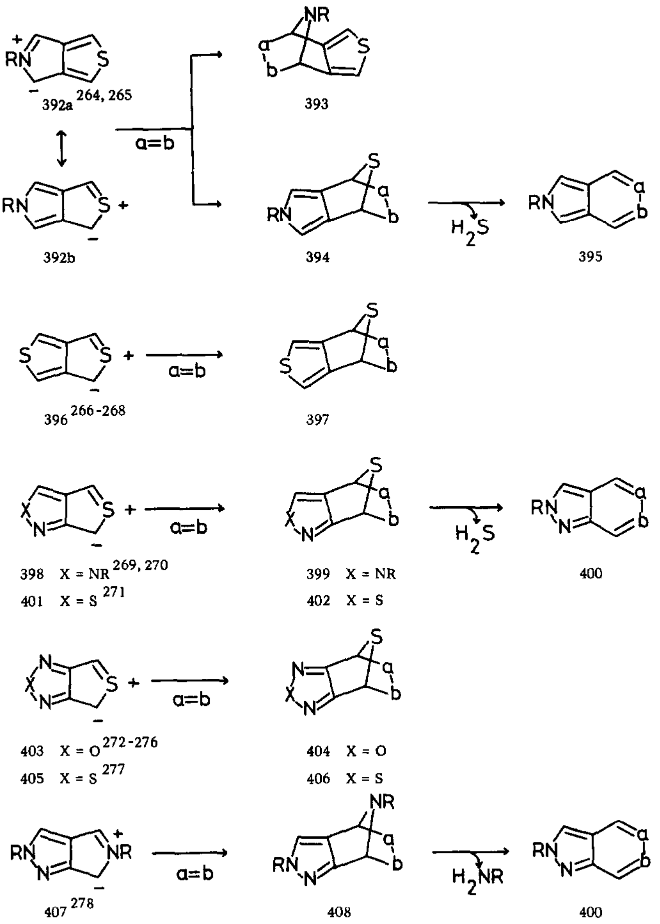
Scheme 44. The four general types of heteropentalenes which are conjugated heterocyclic mesomeric betaines.

Type A heteropentalenes (Scheme 45) participate in a variety of reactions with 1,3-dipolarophiles including diethyl maleate, diethyl fumarate, fumaronitrile, acrylonitrile, ethyl acrylate and *N*-phenylmaleimide. These reactions are usually carried out in boiling benzene, toluene, xylene or *o*-dichlorobenzene. Only one type of 1,3-dipole, the thiocarbonyl ylide, can be associated with the thieno[3,4-*c*]thiophenes **396** and this type of reactivity is shown in their cycloadditions.$^{266-268}$ In contrast, all the other type A heteropentalenes **392**, **398**, **401**, **403**, **405** and **407** are potentially associated with two different 1,3-dipoles, so each of these systems could, in principle, participate in two different 1,3-dipolar cycloaddition reactions. Periselectivity which might be associated with the indicated 1,3-dipoles has been examined with derivatives of the following type A heteropentalenes: thieno-[3,4-*c*]pyrroles **392** (thiocarbonyl ylide and azomethine ylide),^{264,265} thieno[3,4-*c*]pyrazoles **398** (thiocarbonyl ylide and azomethine imine),^{269,270} thieno[3,4-*c*]isothiazole **401** (thiocarbonyl ylide and thiocarbonyl imine),^{271} thieno[3,4-*c*]1,2,5-oxadiazole **403** (thiocarbonyl ylide and nitroso-imine),$^{272-276}$ thieno[3,4-*c*]1,2,5-thiadiazole **405** (thiocarbonyl ylide and thionitroso-imine)^{277} and pyrrolo[3,4-*c*]pyrazole **407** (azomethine ylide and azomethine imine).^{278}

Thieno[3,4-*c*]pyrroles **392** participate in two different dipolar cycloadditions with olefinic dipolarophiles.^{264,265} In boiling benzene, cycloadducts **393** are formed which are derived from the masked azomethine ylide 1,3-dipole. However, by heating for longer periods in higher boiling point solvents (toluene, xylene or *o*-dichlorobenzene), the cycloadducts **394** are formed which are derived from the masked thiocarbonyl ylide 1,3-dipole. Clearly, the cycloaddition is reversible (**392** $\rightleftharpoons$ **393**) so that the cycloadduct **393** is formed under kinetic control in boiling benzene, but at higher temperatures equilibration occurs yielding the cycloadduct **394**. The cycloadduct **394** is accompanied by the iso-indole **395**. The thermal transformation (**394** $\rightarrow$ **395**) presumably involves cheletropic extrusion of sulphur followed by dehydrogenation by the extruded sulphur. The cycloadduct **394**, obtained from fumaronitrile, is transformed into the corresponding iso-indole **395** by the base catalysed elimination of hydrogen sulphide promoted by sodium methoxide in methanol at room temperature.

Derivatives of thieno[3,4-*c*]thiophene **396** undergo cycloadditions with *N*-phenylmaleimide yielding *endo*- and *exo*-cycloadducts **397**.$^{266-268}$ The first synthesis of a non-classical thiophene (*cf* **396**) was achieved by Cava and Pollack.^{266} However, the 1,3-dimethylthieno[3,4-*c*]thiophene and 1,3-dicarbomethoxythieno[3,4-*c*]thiophene (*cf* **396**) were too unstable to be isolated so their formation was demonstrated by their trapping *in situ* using *N*-phenylmaleimide.^{266,267} 1,3,4,6-Tetraphenylthieno[3,4-*c*]thiophene (*cf* **396**) was subsequently obtained as a stable crystalline solid (reddish-purple needles, m.p. 257–258°C) and it also gave *endo*- and *exo*-cycloadducts with *N*-phenylmaleimide in boiling xylene.^{268}

Derivatives of thieno[3,4-*c*]pyrazole **398** have been prepared by an interesting synthesis involving cycloaddition of type A meso-ionic heterocycles.^{269} *N*-Phenylsydnone (*cf* **105**) and dibenzoylacetylene



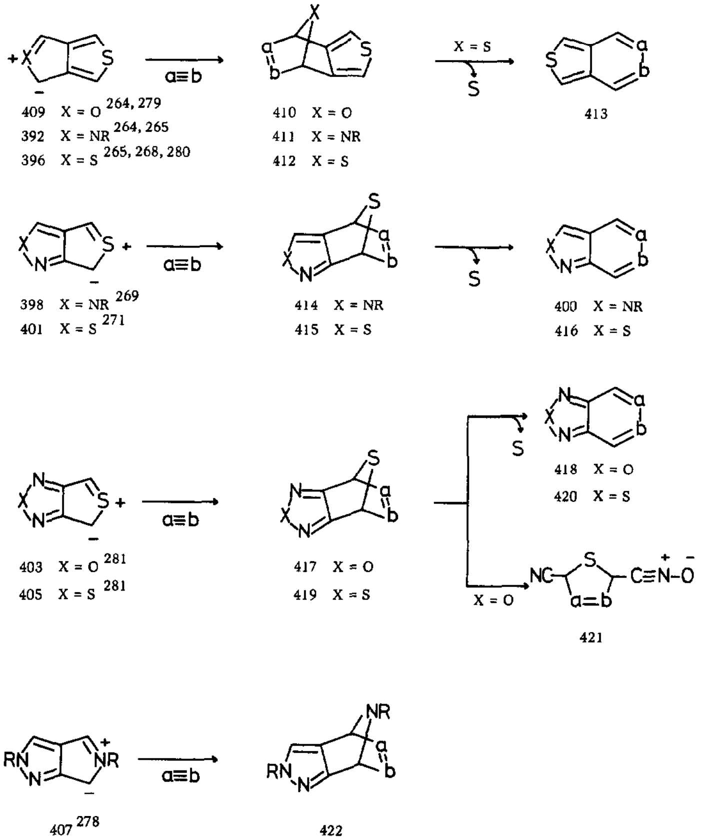
Scheme 45. Cycloaddition reactions of type A heteropentalene mesomeric betaines with olefinic dipolarophiles.

in boiling benzene yield 3,4-dibenzoyl-1-phenylpyrazole which is transformed into 2,4,6-triphenylthieno[3,4-*c*]pyrazole (*cf* **398**) by heating with phosphorus pentasulphide in pyridine. Thieno[3,4-*c*]pyrazoles **398** contain two masked 1,3-dipoles (thiocarbonyl ylide and azomethine imine), but only one type of cycloaddition with the thiocarbonyl ylide dipole is observed and with *N*-phenylmaleimide this yields mixtures of the *endo*- and *exo*-stereoisomers of the cycloadduct **399**.[269] With fumaronitrile as the 1,3-dipolarophile, cycloaddition (**398** → **399**) occurs, but the cycloadduct **399** then yields the indazole **400** directly.[269] Tricyclic and tetracyclic derivatives of thieno[3,4-*c*]pyrazoles **398** also yield cycloadducts **399** with *N*-phenylmaleimide and fumaronitrile, but thermal elimination of hydrogen sulphide from the cycloadduct **399** occurs under the conditions of the reaction, yielding the indazoles **400**[270] directly.

The triphenylthieno[3,4-*c*]isothiazole (*cf* **401**) was synthesised by a route involving the cycloaddition of the type A meso-ionic heterocycle, 4-phenyl-1,3,2-oxathiazolium-5-olate, with dibenzoylacetylene. Treatment of the intermediate, 3,4-dibenzoyl-5-phenylisothiazole, with phosphorus pentasulphide in boiling pyridine then yielded the triphenylthieno[3,4-*c*]isothiazole (*cf* **401**). These heteropentalenes react stereospecifically with dimethyl fumarate and dimethyl maleate yielding mixtures of *endo*- and *exo*-cycloadducts **402** which do not undergo cheletropic elimination of sulphur.[271]

Derivatives of thieno[3,4-*c*]1,2,5-oxadiazole **403** undergo cycloaddition reactions with olefinic dipolarophiles including dimethyl fumarate, dimethyl maleate, *N*-methylmaleimide, *N*-phenylmaleimide and norbornene.[272–276] The products are mixtures of *endo*- and *exo*-cycloadducts formed by reaction with the thiocarbonyl ylide dipole. Analogous results are obtained in the cycloaddition reactions of 2,5-diphenylthieno[3,4-*e*]2,1,3-benzothiadiazole (*cf* **405**).[277]

A tricyclic derivative of pyrrolo[3,4-*c*]pyrazole **407** undergoes cycloaddition with *N*-phenylmaleimide, but the reaction conditions (boiling xylene, 7 days) cause elimination of methylamine and



Scheme 46. Cycloaddition reactions of type A heteropentalene mesomeric betaines with acetylenic dipolarophiles.

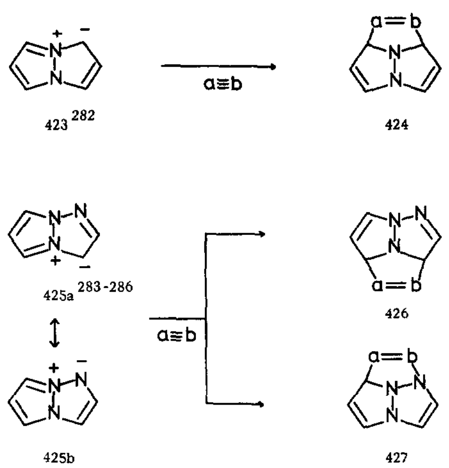
the formation of the corresponding indazole derivative **400**.[278] The tricyclic derivative used in this study is a pyrrolo[3′,4′:2,3]pyrazolo[1,5-*a*]pyridine with a 14π-electron system. It is a matter of opinion whether this compound should be regarded as a 10π-electron heteropentalene.[278]

1,3,4,6-Tetraphenylthieno[3,4-*c*]furan (*cf* **409**) has only a transient existence, but its formation can be convincingly demonstrated by its efficient trapping *in situ* (68% yield) with dimethyl acetylenedicarboxylate (Scheme 46).[264,279] Two different 1,3-dipoles are associated with the heteropentalene **409** and the formation of the cycloadduct **410** is associated with a preference for cycloaddition with the carbonyl ylide 1,3-dipole rather than the thiocarbonyl ylide 1,3-dipole.

There is an interesting distinction between the cycloaddition reactions of thieno[3,4-*c*]pyrroles **392** with olefinic dipolarophiles (Scheme 45) and with acetylenic dipolarophiles[264,265] (Scheme 46). Olefinic dipolarophiles participate in two cycloaddition reactions (**392** → **393**) and (**392** → **394**) involving the azomethine ylide **392a** and the thiocarbonyl ylide **392b**. On the other hand, acetylenic dipolarophiles apparently participate in only one type of cycloaddition (**392** → **411**) involving one preferred reaction with the azomethine ylide giving a stable 1 : 1 cycloadduct **411**.

The reaction of 1,3,4,6-tetraphenylthieno[3,4-*c*]thiophene (*cf* **396**) with acetylenic dipolarophiles is relatively slower than the corresponding reactions with olefinic dipolarophiles.[268,280] Furthermore, the intermediate cycloadducts **412** from acetylenic dipolarophiles are not isolable because they undergo cheletropic extrusion of sulphur yielding the corresponding isothianaphthene **413**.[268,280] Analogous cycloadditions are shown by derivatives of thieno[3,4-*c*]pyrazole **398**[269] and thieno-[3,4-*c*]isothiazole **401**.[271] The cycloadducts **414** and **415** formed by dimethyl acetylenedicarboxylate, dibenzoyl acetylene, and methyl propiolate were unstable and cheletropic extrusion of sulphur yielded the 2*H*-indazole **400**[269] or the benzo[*c*]isothiazole **416**.[271]

There is a remarkable difference between the cycloaddition reactions of the [1,2,5]oxadiazoles **403** and the [1,2,5]thiadiazoles **405** with acetylenic dipolarophiles including dimethyl acetylenedicarboxylate, dibenzoylacetylene, methyl propiolate, phenylacetylene and methyl phenylpropiolate. [1,2,5]Thiadiazoles **405** form 1 : 1 products **420** by a sequence of cycloaddition followed by



Scheme 47. Cycloaddition reactions of type **B** heteropentalene mesomeric betaines.

sulphur extrusion (**405** → **419** → **420**). [1,2,5]Oxadiazoles **403** also form a 1 : 1 product by an analogous sequence (**403** → **417** → **418**), but in addition a 2 : 1 cycloadduct is isolated. The route to the 2 : 1 cycloadduct involves the isomerisation of the primary 1 : 1 cycloadduct **417** to the cyanonitriloxide **421** which is also a 1,3-dipole, so it undergoes a second cycloaddition giving a 2 : 1 adduct. We encourage the reader to deduce the constitutions of the four isomeric 2 : 1 cycloadducts formed from 4,6-diphenylthieno[3,4-*c*] [1,2,5]oxadiazole (*cf* **403**) and methyl propiolate.[281]

A tricyclic derivative of pyrrolo[3,4-*c*]pyrazole (*cf* **407**) undergoes cycloaddition with dimethyl acetylenedicarboxylate yielding the corresponding cycloadduct **422**.[278]

There is meagre information (Scheme 47) on the cycloaddition reactions of type **B** heteropentalene mesomeric betaines (Scheme 44). Symmetrical type **B** heteropentalenes **113** (X = Y) could yield one cycloadduct whereas unsymmetrical type **B** heteropentalenes are associated with two different 1,3-dipoles (Scheme 44; **113a** and **113b**), so periselectivity between two types of cycloaddition is possible.

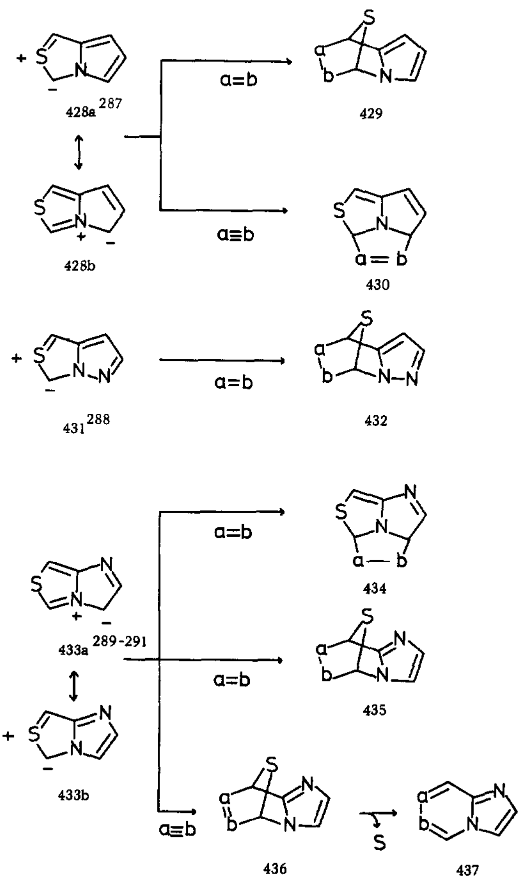
Symmetrical pyrazolo[1,2-*a*]pyrazoles **423** yield one cycloadduct **424** with dimethyl acetylenedicarboxylate.[282] Two types of cycloaddition have been observed with pyrazolo[1,2-*a*]1,2,3-triazoles **425**.[283–286] The dibenzo-derivatives (*cf* **425**) react as 1,3-dipolar azomethine imines **425b** towards acetylenic dipolarophiles yielding the cycloadducts **427**.[283,284] In contrast, the bicyclic pyrazolo[1,2-*a*]1,2,3-triazoles **425** function as 1,3-dipolar azomethine ylides **425a** towards acetylenic dipolarophiles yielding the cycloadducts **426**; reaction with dimethyl acetylenedicarboxylate occurs during 30 minutes at room temperature.[285] The cycloaddition reaction of a pentacyclic phenazine derivative of pyrazolo[1,2-*a*]1,2,3-triazole **425** with dimethyl acetylenedicarboxylate yields one cycloadduct of the type **426** derived from the 1,3-dipolar azomethine ylide **425a**.[286]

Examples of the cycloaddition reactions of type **C** heteropentalenes (Scheme 44) are rather sparse (Scheme 48), but periselectivity involving the various types of 1,3-dipoles which can be associated with their structures has been detected.

Derivatives of pyrrolo[1,2-*c*]thiazole **428** react with the olefinic dipolarophile, *N*-phenylmaleimide, yielding mixtures of the *endo*- and *exo*-cycloadducts **429**. In contrast, the acetylenic dipolarophile, dimethyl acetylenedicarboxylate, yields the cycloadduct **430**. The cycloaddition (**428** → **429**) involves the thiocarbonyl ylide **428a** whereas the cycloaddition (**428** → **430**) involves the azomethine ylide **428b**.[287]

Derivatives of thiazolo[3,4-*b*]indazole (*cf* **431**) have been synthesised[288] and they may be regarded as derivatives of pyrazolo[1,2-*c*]thiazole **431**. These compounds undergo the cycloaddition reaction (**431** → **432**) with *N*-phenylmaleimide yielding the 1 : 1 cycloadduct **432** (yield 65%) plus a second product (yield 29%) which is formed by aromatisation of the cycloadduct by loss of hydrogen sulphide.[288] The cycloaddition (**431** → **432**) involves the thiocarbonyl ylide **431**.

The association of dipolar reactivity with particular dipolarophiles in the cycloadditions (**428** → **429**),[287] (**428** → **430**)[287] and (**431** → **432**)[288] has been incorrectly summarised.[290] However, the need to provide a well-based rationalisation of the regiochemistry and stereochemistry (*endo*- versus *exo*-$[_{\pi}4_{s} + {}_{\pi}2_{s}]$ cycloaddition) of the cycloaddition reactions of type **C** heteropentalenes (Scheme 44) has been recognised.[289–291]



Scheme 48. Cycloaddition reactions of type C heteropentalene mesomeric betaines.

Derivatives of imidazo[1,2-*c*]thiazole **433** which have been examined include 1,3-diphenylthiazolo[3,4-*a*]benzimidazole[289] and 1,3,6-triphenylimidazo[1,2-*c*]thiazole.[290,291] 1,3-Diphenylthiazolo[3,4-*a*]benzimidazole (*cf* **433**) reacts with olefinic and acetylenic dipolarophiles yielding cycloadducts (*cf* **435** and **436**) associated with the thiocarbonyl ylide **433b**. The cycloadducts **435** are stable whereas the cycloadducts **436** undergo cheletropic elimination yielding aromatic systems (*cf* **437**).

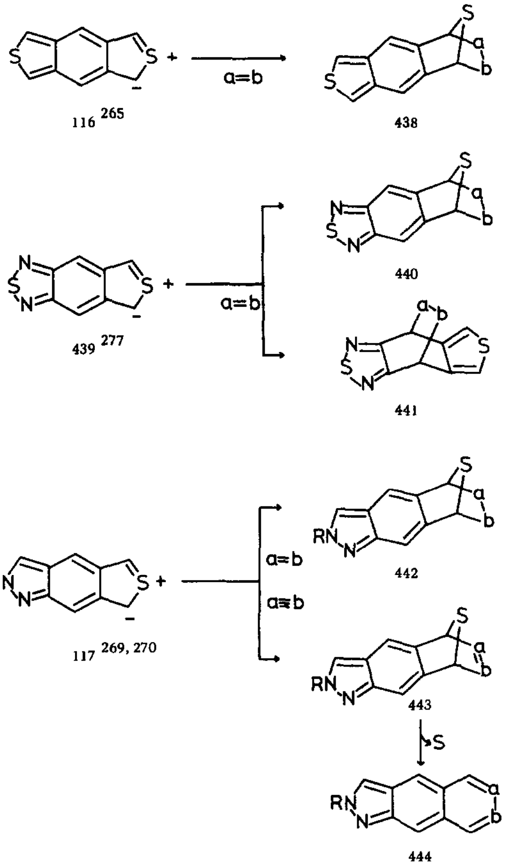
Experimental information on the factors which control the periselectivity between the cycloaddition reactions (**433** → **434**) and (**433** → **435**) has been provided by careful studies[290,291] on the reactions between imidazo[1,2-*c*]thiazoles **433** and olefinic dipolarophiles. In benzene or pyridine (room temp or 80°C), cycloadducts **434** are obtained as mixtures of *endo*- and *exo*-diastereoisomers: the formation of these two cycloadducts **434** involves the azomethine ylide **433a**. In dramatic contrast, at higher temperatures (benzene, 80°C; pyridine, 115°C; or xylene, 140°C), then only the cycloadducts **435** are obtained as mixtures of *endo*- and *exo*-diastereoisomers: the formation of these two cycloadducts **435** involves the thiocarbonyl ylide **433b**. This striking influence of reaction temperature upon product ratio is most easily accommodated by proposing that the cycloadducts **434** are formed under conditions of kinetic control, whereas the cycloadducts **435** are formed under the conditions which permit equilibration at the higher temperatures. The demonstration that the cycloaddition reactions (**433** $\rightleftharpoons$ **434**) and (**433** $\rightleftharpoons$ **435**) are reversible has emphasised the need to be cautious in using frontier molecular orbital theory to try to rationalise the stereochemistry and regiochemistry of the cycloaddition reaction of heteropentalenes. Frontier molecular orbital theory must not be used to try to interpret product ratios when the competing reactions which are involved are reversible and are occurring under equilibration conditions.

Some very interesting results have also been obtained[291] from an examination of the regiochemistry and stereochemistry of the cycloaddition reactions between imidazo[1,2-*c*]thiazoles **433** and unsymmetrical olefinic dipolarophiles including methyl acrylate, acrylonitrile, methacrylonitrile, methyl methacrylate, methyl crotonate and citraconic anhydride.[291] In principle, eight products could have been produced from each pair of unsymmetrical reactants, but in fact only one product was formed in good yield in each case. All the reactions were carried out under the same conditions (benzene, 80°C) so it is not known whether the cycloadditions are or are not taking place under equilibration conditions. However, the constitutions of all the products do conform to regiospecific cycloaddition associated with the thiocarbonyl ylide **433b**. We do not accept the view[291] that the observed regiospecificity can be associated with charge distribution in the thiocarbonyl ylide. The regiospecificities which have been observed in the cycloaddition reactions of the type C heteropentalenes **433** with unsymmetrical electron-deficient olefinic dipolarophiles must surely be controlled by the interaction between the mesomeric betaine HOMO and the dipolarophile LUMO. If the reactions are not reversible then secondary orbital interactions presumably determine the stereoselection between *endo*- or *exo*-diastereoisomers. However, although all the cycloadducts **435** obtained from methyl acrylate, acrylonitrile, methacrylonitrile, methyl methacrylate, methyl crotonate and citraconic anhydride are formed stereospecifically, some have the *endo*-configuration, whereas the rest have the *exo*-configuration. This dichotomy may mean that the stereospecific formation of one cycloadduct in each case is due to the involvement of reversible reactions which under equilibration conditions yield one thermodynamically favoured regio-isomer.

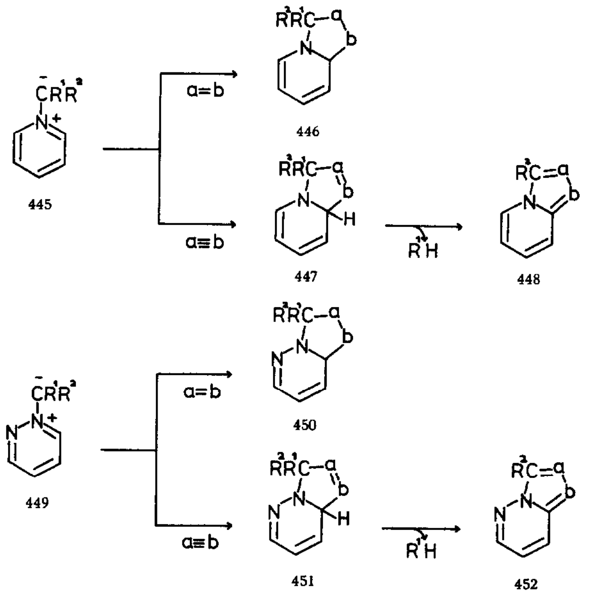
No cycloaddition reactions have yet been reported for type **D** heteropentalenes (Scheme 44).

Tricyclic 14π-electron analogues **116**, **117** and **439** (Scheme 49) of the bicyclic 10π-electron type **A** heteropentalenes (Scheme 44) have been synthesised by interesting sequences involving cycloaddition of dibenzoylacetylene. Thus, tetraphenyl[3,4-*c*]thiophene (*cf* **396**) (Scheme 46) and dibenzoylacetylene gave 5,6-dibenzoyl-1,3,4,7-tetraphenylisothianaphthene (*cf* **413**) which with phosphorus pentasulphide yielded hexaphenylthieno[3,4-*f*]isothianaphthene (*cf* **116**).[265] Treatment of this compound (*cf* **116**) with fumaronitrile in boiling xylene yielded one primary cycloadduct (*cf* **438**)[265] and a similar cycloaddition involving the thiocarbonyl ylide occurs with *N*-phenylmaleimide[265] (Scheme 49).

2,5-Diphenylthieno[3,4-*e*]2,1,3-benzothiazole (*cf* **439**) is not sufficiently stable to be isolated, but its



Scheme 49. Cycloaddition reactions of the tricyclic 14π-electron analogues of the 10π-electron heteropentalenes.



Scheme 50. Cycloaddition reactions of pyridinium- and pyridazinium-*N*-ylides.[294–313]

transient existence was demonstrated by its trapping *in situ* with *N*-phenylmaleimide.[277] This reaction gave four cycloadducts corresponding to *endo*- and *exo*-cycloaddition to the thiocarbonyl ylide (**439** → **440**) and to the diene system (**439** → **441**).

2,4,5,7,8-Pentaphenylthieno[3,4-*f*]2*H*-indazole (*cf* **117**) was prepared from 2,4,6-triphenylthieno[3,4-*c*]pyrazole (*cf* **398**) by the sequence (**398** → **400** → **117**) achieved by cycloaddition with dibenzoylacetylene followed by reaction with phosphorus pentasulphide. 2,4,5,7,8-Pentaphenylthieno[3,4-*f*]2*H*-indazole (*cf* **117**) behaves as a thiocarbonyl ylide towards *N*-phenylmaleimide yielding the *endo*-cycloadduct (*cf* **442**).[269]

A pentacyclic derivative of thieno[3,4-*f*]2*H*-indazole **117** undergoes cycloaddition with dimethyl acetylenedicarboxylate yielding an intermediate cycloadduct (*cf* **443**) which is aromatised by cheletropic extrusion of sulphur (*cf* **443** → **444**).[270]

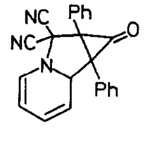
5. *Conjugated heterocyclic* N-*ylides and related compounds isoconjugate with odd alternant hydrocarbon anions*

The 1,3-dipolar cycloaddition reactions of pyridinium-*N*-ylides **445** with olefinic and acetylenic dipolarophiles have been extensively investigated[12,292,293] (Scheme 50). Electron-deficient alkenes including ethyl acrylate, acrylonitrile, *N*-phenylmaleimide and phenyl vinyl sulphoxide are particularly reactive towards pyridinium-*N*-ylides **445**. The primary 1 : 1 cycloadducts **446** are usually isolable,[294–298] but in some cases aromatisation[299–301] or dehydrogenation[302] occurs.

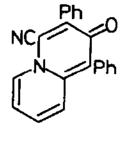
The primary cycloadducts **447** are not usually isolable when acetylenic dipolarophiles are used.[295,300,303–305] In these cases the aromatic indolizines **448** are usually formed either by dehydrogenation or by elimination of R^1—H (**447** → **448**).

Pyridinium-*N*-ylides **445** and pyridazinium-*N*-ylides **449** show very similar behaviour towards olefinic and acetylenic 1,3-dipolarophiles (Scheme 50).[306–312]

Cyclopropenes react normally with pyridinium-*N*-ylides **445** giving the primary cycloadducts **446**.[306,313] However, the reaction of cyclopropenones with pyridinium-*N*-ylides takes a different course. Pyridinium-*N*-dicyanomethylide **445** ($R^1 = R^2 = CN$) and diphenylcyclopropenone do not yield a stable cycloadduct **453** because this is transformed, by elimination of hydrogen cyanide and cleavage of the three-membered ring, into the stable product **454**.[314]



453



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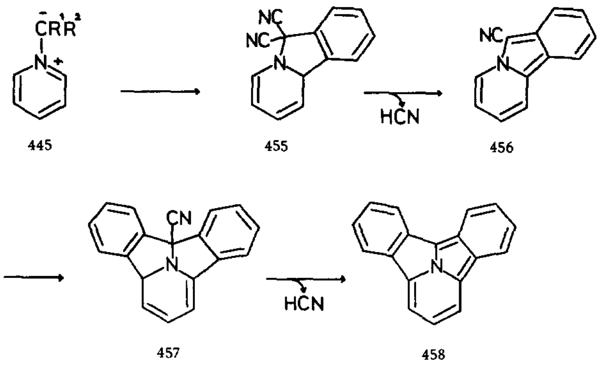
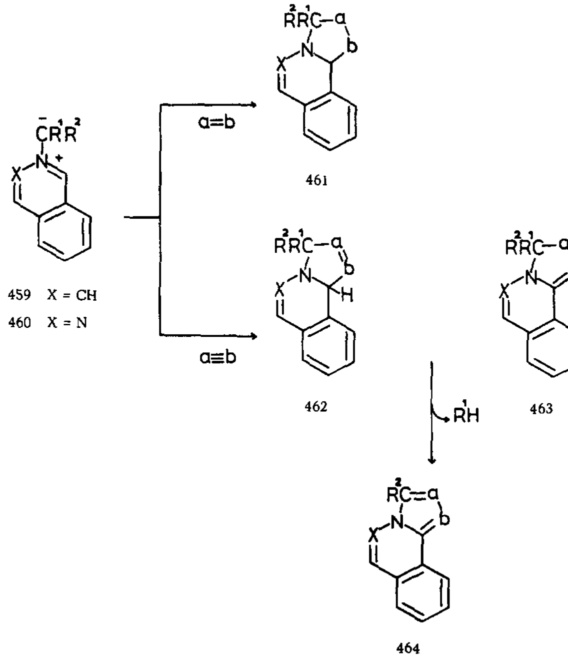


Scheme 51. Cycloaddition reaction of pyridinium-*N*-dicyanomethylide **445** ($R^1 = R^2 = CN$) with benzyne.[315]

The reaction between pyridinium-*N*-dicyanomethylide **445** ($R^1 = R^2 = CN$) and benzyne yields the novel [2,2,3]cyclazine **458** by a surprising sequence of reactions involving (i) cycloaddition with benzyne (**445** → **455**), (ii) elimination of hydrogen cyanide (**455** → **456**), (iii) cycloaddition with benzyne (**456** → **457**), and (iv) elimination of hydrogen cyanide (**457** → **458**) (Scheme 51).[315]

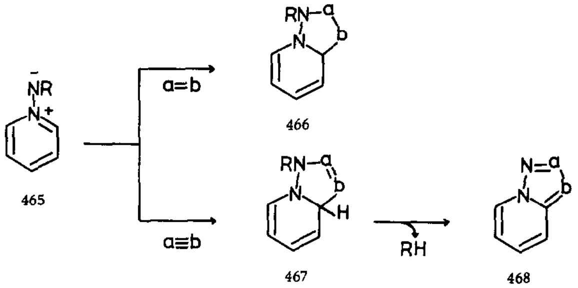
Isoquinolinium-*N*-ylides **459**,[316–322] phthalazinium-*N*-ylides **460**,[323–325] and benzo[*c*]-cinnolinium-*N*-ylides **472**[326–329] showed corresponding 1,3-dipolar cycloaddition reactions towards olefinic and acetylenic dipolarophiles (Scheme 52). Olefinic dipolarophiles gave 1 : 1 cycloadducts **461** which were usually sufficiently stable to be isolated, although in one case[318] aromatisation also occurred. Acetylenic dipolarophiles can give rise to three types of reaction product **462**, **463** and **464**. In the cases studied,[316–329] the formation of one or more of these three types of product is observed : the relation of the primary cycloadduct **462** to the other two products **463** and **464** is clear.

The literature on the 1,3-dipolar cycloaddition reactions of pyridinium-*N*-aminides **465** is extensive, but the topic has been well reviewed.[293,330,331] The cycloaddition reactions of pyridinium-*N*-aminides with olefinic and acetylenic dipolarophiles[330–334] (Scheme 53) correspond exactly with the cycloaddition reactions of pyridinium-*N*-ylides (Scheme 50). Pyridazinium-*N*-aminides,[307,310,311,335] quinolinium-*N*-aminides,[336] isoquinolinium-*N*-aminides,[318,336] phthalazinium-*N*-aminides,[337] quinoxalinium-*N*-aminides,[337,338] quinazolinium-*N*-aminides[337] and phenan-



Scheme 52. Cycloaddition reactions of isoquinolinium- and phthalazinium-*N*-ylides.[316–329]

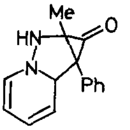
thridinium-*N*-aminides[339] also participate in a set of cycloaddition reactions which correspond exactly with those of pyridinium-*N*-aminides (Scheme 53). The cycloaddition reactions of pyridinium-*N*-aminide, quinolinium-*N*-aminide and isoquinolinium-*N*-aminide with dibenzoylacetylene have been used to provide intermediates in an ingenious synthesis of tricyclic and tetracyclic derivatives of the type A heteropentalene, thieno[3,4-*c*]pyrazole **398**.[270]



Scheme 53. Cycloaddition reactions of pyridinium-*N*-aminides.[330–334,340]

The 1,3-dipolar cycloaddition of pyridinium-*N*-aminide **465** (R = H) with nitriles (a ≡ b; a = RC, b = N) yields triazolo[1,5-*a*]pyridines **468** (a = RC, b = N)[340] by a pathway which is analogous to the cycloaddition of acetylenes (Scheme 53). This is one of the rare examples of a nitrile functioning as a 1,3-dipolarophile towards an electron octet-stabilised 1,3-dipole without an orthogonal double bond (azomethine imine).

The cycloaddition of diphenylcyclopropenone with pyridinium-*N*-dicyanomethylide **445** ($R^1 = R^2 = CN$) which yields the product **454**[314] is matched by the reaction between methylphenylcyclopropenone and pyridinium-*N*-aminide **465** (R = H). The cycloaddition is regiospecific. The primary cycloadduct **469** is not isolable because it is transformed into the isomer **470** which then dehydrogenates yielding the 3*H*-pyrido[1,2-*b*]pyridazinone **471**.[341]



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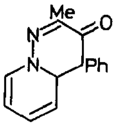

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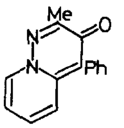
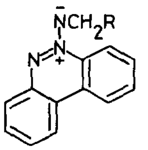


471

Benzo[*c*]cinnolinium *N*-alkylaminides **472** participate in an exothermic reaction with dimethyl acetylenedicarboxylate in dimethylformamide solution at room temperature yielding the product **473**.[342] This remarkable transformation (Scheme 54) involves 1,3-dipolar cycloaddition (**472** → **474**) followed by isomerisation of the intermediate 1,2,3-triazane **474**. The driving force for the isomerisation (**474** → **473**) (Scheme 54) is probably associated with the relief of the destabilisation produced by the lone pair–lone pair–lone pair interaction in the 1,2,3-triazane **474**. Lone pair–lone pair destabilisation



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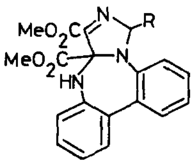

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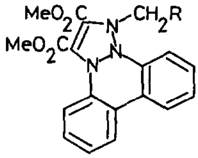
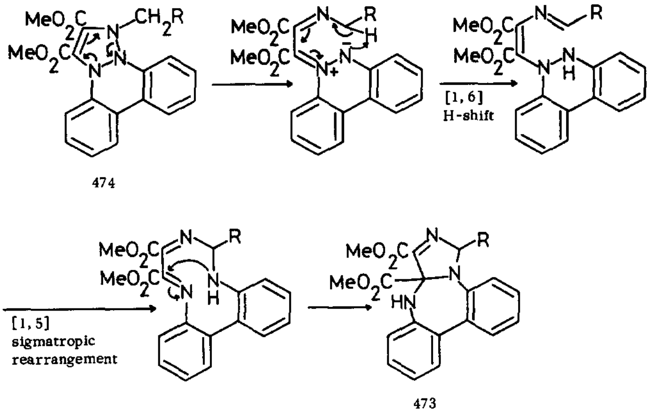


474



Scheme 54. Thermal rearrangement of the cycloadduct **474** formed from benzo[*c*]cinnolinium-*N*-alkylaminides **472** and dimethyl acetylenedicarboxylate.[342]

also probably assists the cleavage of the nitrogen–nitrogen bond in the [1,5] sigmatropic rearrangement of the 6-membered hydrazine which then leads to the 10-membered intermediate given in the mechanism proposed (Scheme 54).

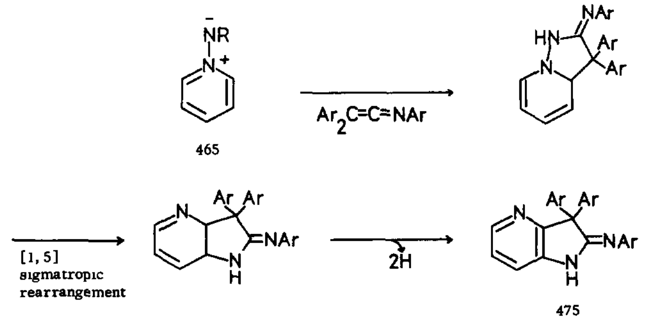
An example of a 1,3-cycloaddition reaction between pyridinium-*N*-aminides **465** and heterocumulenes has been reported (Scheme 55).[343] Triarylketene imines and pyridinium-*N*-aminides **465** (R = H) produce cycloadducts which then undergo [1,5] sigmatropic rearrangements associated with N—N bond cleavage (*cf* Scheme 54). This [1,5] sigmatropic rearrangement is then followed by dehydrogenation giving 1*H*-pyrrolo[3,2-*b*]pyridines **475** (Scheme 55).[343]

The *N*-aminides of quinoline and isoquinoline are in equilibrium with stable dimers which are derivatives of hexahydro-1,2,4,5-tetrazine.[330] The equilibrium between quinolinium-*N*-aminide and its dimer has been investigated by NMR.[344] The dimerisation of pyridinium-*N*-aminides **465** can be regarded as a cycloaddition in which the two C—N bonds associated with the 6-membered hexahydro-1,2,4,5-tetrazine ring in the dimer are formed consecutively in a non-concerted process.

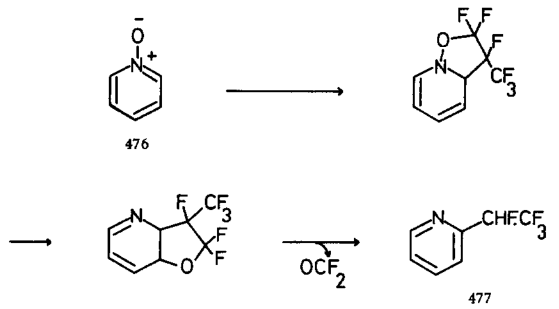
Pyridine *N*-oxide **476** does not normally participate as a 1,3-dipole in cycloaddition reactions with olefinic and acetylenic dipolarophiles.[9] However, pyridine *N*-oxide **476** does react with perfluoropropene (Scheme 56) yielding 2-(1,2,2,2-tetrafluoroethyl)pyridine **477** by a sequence involving (i) 1,3-dipolar cycloaddition, (ii) [1,5] sigmatropic rearrangement, (iii) elimination of carbonyl fluoride, and (iv) hydrogen migration.[345]

Pyridine *N*-oxide **476** reacts with benzyne (generated from anthranilic acid and isoamyl nitrite) yielding a mixture of 2-(2-hydroxyphenyl)pyridine **479** and 3-(2-hydroxyphenyl)pyridine **481**. These transformations can be interpreted (Scheme 57) as involving the common intermediate **478** which then undergoes either the direct rearrangement (**478** → **479**) or the sequential isomerisation (**478** → **480** → **481**) involving the intermediate spirocyclohexadienone (**480**).[346]

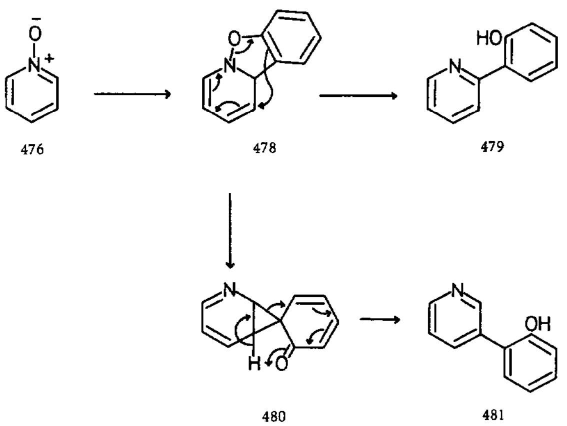
The reactions between pyridine *N*-oxides and aryl isocyanates have been extensively investigated.[347–352] Two general reaction pathways have been identified (Schemes 58 and 59). Heating pyridine *N*-oxide **476** with aryl isocyanates in dimethyl formamide (110°C; 7 hr) yielded the 2,3-



Scheme 55. Cycloaddition of pyridinium-*N*-aminides **465** (R = H) and triphenylketene imine.[343]



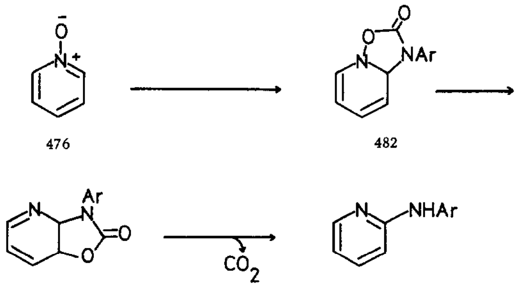
Scheme 56. Reaction of pyridine N-oxide **476** with perfluoropropene.[345]



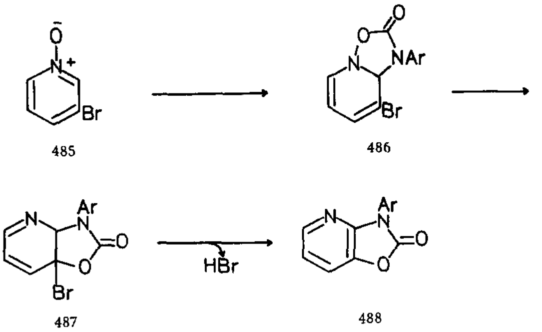
Scheme 57. Reaction of pyridine N-oxide **476** with benzyne.[346]

dihydropyridines **483** and the 2-anilinopyridines **484**. Prior to the X-ray crystallographic investigation,[350] no iron-clad experimental distinction could be made between the constitutions **482** and **483** for the isolable cycloadducts. However, this uncertainty was firmly resolved in a very careful investigation[350] and the following sequence of reactions was proposed (Scheme 58). The initial cycloadduct **482** was not isolable, but it underwent thermal isomerisation yielding the isolable 2,3-dihydropyridine **483** which could then eliminate carbon dioxide. The thermal isomerisation (**482** → **483**) could involve either a concerted [1,5] sigmatropic rearrangement or a non-concerted process involving N—O bond cleavage giving either a dipolar or diradical intermediate.

Support for the proposed reaction (Scheme 58) is provided by the isolation of the product **488** from 3-bromopyridine N-oxide **485** and aryl isocyanates[348,353] (Scheme 59). In these cases, the intermediate cycloadduct **487** eliminates hydrogen bromide yielding the stable product **488**.

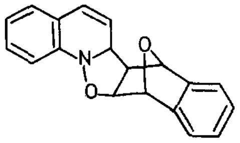


Scheme 58. Reaction of pyridine N-oxide **476** with aryl isocyanates.[347–352]



Scheme 59. Reaction of 3-bromopyridine *N*-oxide **485** with aryl isocyanates.[348,353]

Similar 1,3-dipolar cycloaddition reactions between *N*-oxides and aryl isocyanates have also been reported for pyrimidine *N*-oxide,[354] 3-bromoquinoline *N*-oxide[355] and 3-nitroquinoline *N*-oxide.[355] Quinoline *N*-oxide and 1,4-dihydro-1,4-epoxynaphthalene yield the cycloadduct **489.**[356] Quinoxaline *N*-oxide and olefinic dipolarophiles (dimethyl maleate and *N*-phenylmaleimide) yield the cycloadducts **490.**[357] Quinoxaline *N*,*N*-dioxide with *N*-phenylmaleimide and dimethyl acetylenedicarboxylate yield 2 : 1 cycloadducts **491.**[357]



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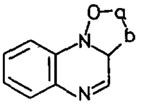

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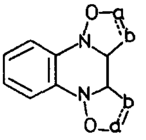
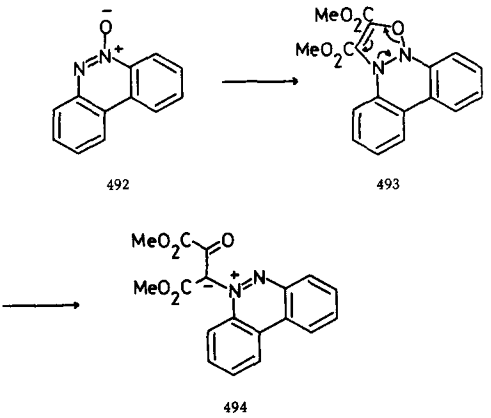


491

A striking difference has been observed between the thermal rearrangement of the dimethyl acetylenedicarboxylate cycloadduct **474** of benzo[*c*]cinnolinium-*N*-alkylaminide (Scheme 54)[342] and the dimethyl acetylenedicarboxylate cycloadduct **493** of benzo[*c*]cinnoline *N*-oxide **492** (Scheme 60).[358] Benzo[*c*]cinnoline *N*-oxide **492** and dimethyl acetylenedicarboxylate in nitrobenzene (190°C; 3 hr) yields the benzo[*c*]cinnolinium *N*-ylide **494** by the sequence (Scheme 60). A similar reaction is



Scheme 60. Cycloaddition reaction of benzo[*c*]cinnoline *N*-oxide **492** with dimethyl acetylenedicarboxylate.[358]

observed for phenanthridine *N*-oxide.[358] The remarkable differences between Scheme 54 and Scheme 60 clearly involve the additional opportunity for [1,6]*H*-shift (Scheme 54) provided by the *N*-alkyl group in a diradical or dipolar intermediate.

6. *Conjugated heterocyclic* N-*ylides and related compounds isoconjugate with odd non-alternant hydrocarbon anions*

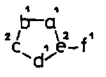
No cycloaddition reactions of any members of class 6 of heterocyclic mesomeric betaines have been reported.

7. *Conjugated heterocyclic* N-*ylides and related compounds isoconjugate with even alternant hydrocarbon dianions*

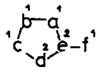
No cycloaddition reactions of any members of class 7 of heterocyclic mesomeric betaines have been reported.

8. *Conjugated heterocyclic* N-*ylides and related compounds isoconjugate with even non-alternant hydrocarbon dianions*

Many members of class 8 are known and they can be allocated either to type **A** (**496** and **498**) or to type **B** (**497** and **499**) systems. This division of heterocyclic *N*-ylides and related compounds into type **A** (**496** and **498**) and type **B** (**497** and **499**) corresponds in all respects with (i) the division of meso-ionic heterocycles into type **A** (**110**) and type **B** (**111**) (see p. 2250), and (ii) the classification of heteropentalenes into types **A**, **B**, **C** and **D** (Scheme 44). In the formulations **496** and **497**, the superscripts 1 and 2 indicate the number of p-electrons which are contributed by the atoms or groups (a, b, c, d, e and f) to the π-electron systems of the heterocycles. The formulations **496** and **497** correspond with the dipolar structures for type **A** (**498**) and type **B** (**499**) respectively. Representatives of type **A** (**500**–**502**) and type **B** (**503**–**505**) heterocyclic mesomeric betaines of class 8 are listed in Scheme 61.


496

Type A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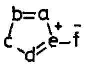
Type B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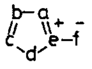
Type A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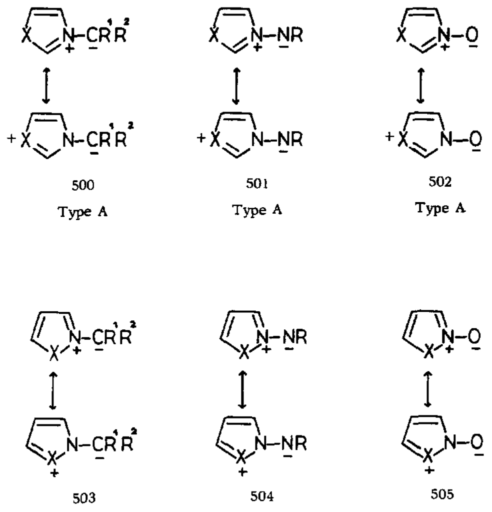
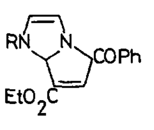
Type B



Scheme 61. Representatives of type **A** and type **B** heterocyclic mesomeric betaines of class 8.



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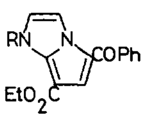
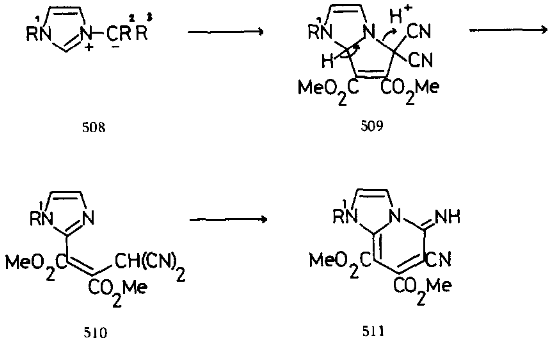


507

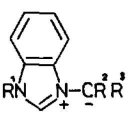
We now consider the cycloaddition reactions of type A and type B heterocyclic mesomeric betaines of class 8.

Imidazolium-*N*-ylides **500** (X = RN) belong to type A and they react with acetylenic dipolarophiles yielding intermediate cycloadducts which then either dehydrogenate or isomerise. Thus, the imidazolium-*N*-ylide **500** (X = NMe; R^1 = PhCO; R^2 = H) and ethyl propiolate yield the intermediate cycloadduct **506** (R = Me) which then gives the product **507** (R = Me).[98] On the other hand, the imidazolium-*N*-dicyanomethylide **508** (R^1 = Me, R^2 = R^3 = CN) and dimethyl acetylenedicarboxylate yield the intermediate cycloadduct **509** which, by a sequence of prototropic isomerisations followed by cyclisation, yields the product **511** (R^1 = Me) (Scheme 62).[98]



Scheme 62. Reaction of the imidazolium-dicyanomethylide **506** with dimethyl acetylenedicarboxylate.[98]

A number of cycloaddition reactions of benzimidazolium-*N*-ylides **512**,[359,360] benzimidazolium-*N*-aminides **513**[331,361–363] and benzimidazole *N*-oxides **514**[364] with dipolarophiles has been reported. All these reactions may be rationalised as involving an initial 1,3-dipolar cycloaddition.



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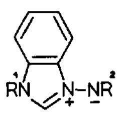

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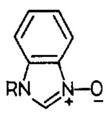
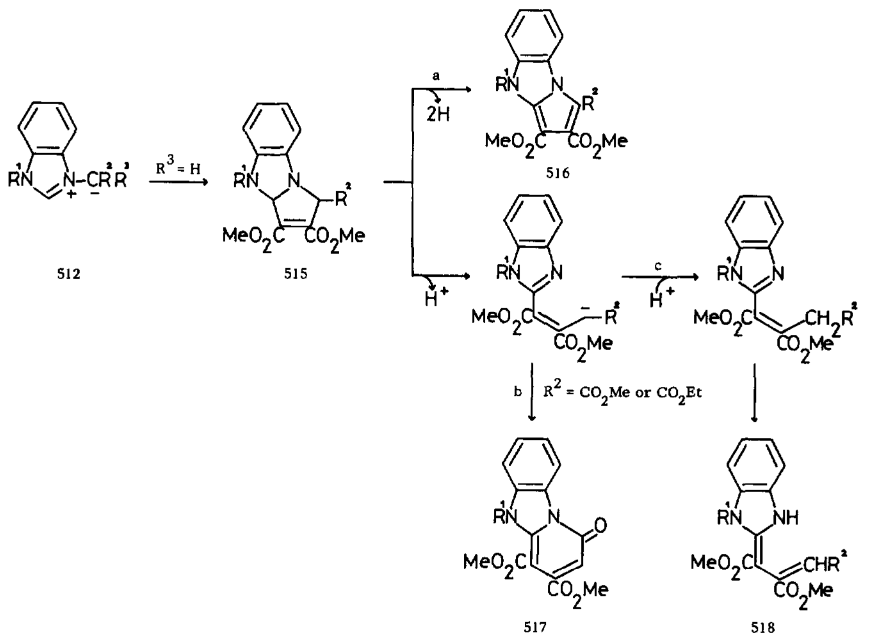


514

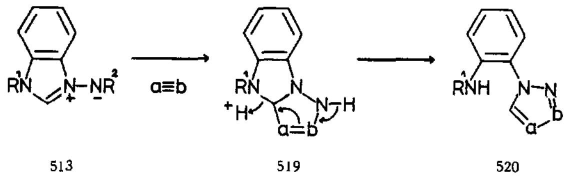
Three reaction pathways have been identified for the reaction of benzimidazolium-*N*-ylides **512** and dimethyl acetylenedicarboxylates. These pathways (a, b or c) all involve the formation of the cycloadduct **515** which may then participate in either reaction pathway a (**515** → **516**), reaction pathway b (**515** → **517**), or reaction pathway c (**515** → **518**) (Scheme 63).[359,360]

Benzimidazolium-*N*-aminides **513** (R^2 = H) participate in 1,3-dipolar cycloadditions with acetylenic dipolarophiles (a ≡ b) yielding the intermediate cycloadducts **519** which then isomerise yielding the products **520** (Scheme 64).[361,362]

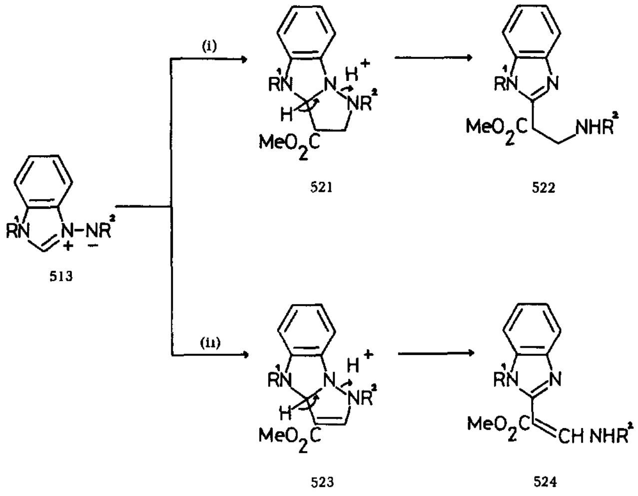
Carbonyl stabilised benzimidazolium-*N*-aminides **513** (R^2 = CO_2Me or COPh) also participate in 1,3-dipolar cycloadditions with methyl acrylate, acrylonitrile, fumaronitrile, and methyl propiolate.[363] The reactions observed with methyl acrylate and methyl propiolate are typical (Scheme 65). It is interesting to note that the transformations observed (Scheme 64) for the cycloadducts derived from benzimidazolium-*N*-aminides **513** (R^2 = H) are quite different from the transformations observed (Scheme 65) for the cycloadducts derived from benzimidazolium-*N*-aminides **513** (R^2 = CO_2Me or COPh). In the latter case (Scheme 65), the transformations of the intermediate cycloadducts **521** and **523** are determined by the consequences of N—N bond cleavage.



Scheme 63. Reaction of benzimidazolium-*N*-ylides with dimethyl acetylenedicarboxylate.[359,360]

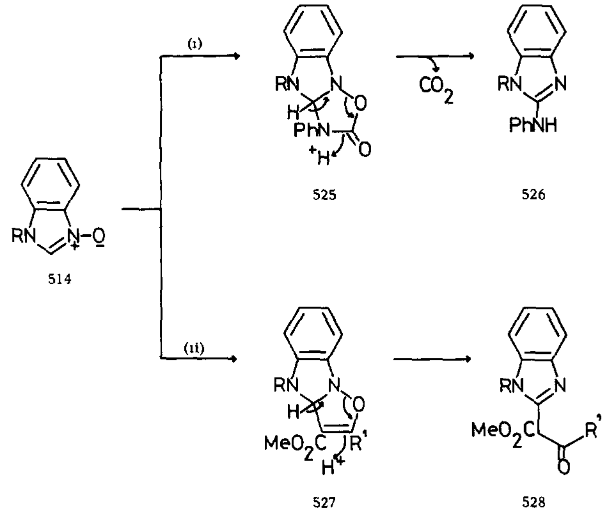


Scheme 64. Reaction of benzimidazolium-*N*-aminides **513** (R^2 = H) with acetylenic dipolarophiles.[361,362]



Reagents (i) methyl acrylate
(ii) methyl propiolate

Scheme 65. Reaction of benzimidazolium-*N*-aminides **513** ($R^2 = CO_2Me$ or COPh) with olefinic and acetylenic dipolarophiles.[363]



Reagents (i) phenyl isocyanate
(ii) methyl propiolate or dimethyl acetylenedicarboxylate

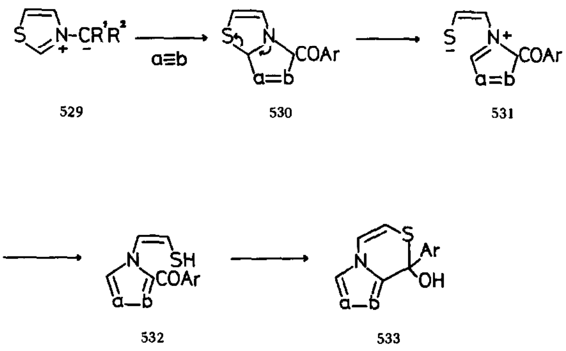
Scheme 66. Reaction of benzimidazole-*N*-oxide with heterocumulenes and acetylenic dipolarophiles.[364]

Benzimidazole *N*-oxide **514** participates in 1,3-dipolar cycloaddition reactions with heterocumulenes and acetylenic dipolarophiles (Scheme 66).[364] Phenyl isocyanate forms an intermediate cycloadduct **525** which then extrudes carbon dioxide yielding the 2-anilinobenzimidazole **526**. Methyl propiolate yields the intermediate cycloadduct **527** (R^1 = H) which is then transformed to the 2-substituted benzimidazole **528** (R^1 = H). Dimethyl acetylenedicarboxylate similarly yields the product **528** ($R^1 = CO_2Me$).[364]

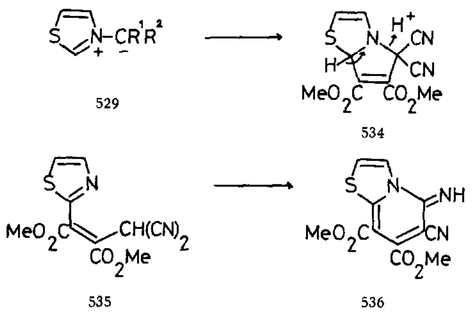
Thiazolium-*N*-ylides **500** (X = S) and thiazolium-*N*-aminides **501** (X = S) belong to type A and they also react with dipolarophiles. Thiazolium-*N*-ylides **529** (R^1 = H, R^2 = COPh) react with acetylenic dipolarophiles (methyl propiolate and dimethyl acetylenedicarboxylate) giving the intermediate cycloadducts **530** which are then transformed into the products **533** by the sequence (**530** → **531** → **532** → **533**) given in Scheme 67.[365] When methyl propiolate is used in this reaction, then the carbinol **533** undergoes a Michael addition with the reagent giving the corresponding 2:1 adduct.[365]

The thiazolium-*N*-dicyanomethylide **529** ($R^1 = R^2$ = CN) participates in a cycloaddition reaction with dimethyl acetylenedicarboxylate and the intermediate cycloadduct **534** is transformed into the product **536** by the sequence (**534** → **535** → **536**) (Scheme 68).[98] This transformation (**529** → **536**) corresponds exactly with the transformation (**508** → **511**) (Scheme 62).

The cycloadditions of thiazolium-*N*-ylides **500** (X = S) with *N*-phenyl maleimide[298] and dimethyl maleate[298] are normal, but the reactions with cyclopropenes are complicated.[366,367] The initial cycloadducts are not isolated from cyclopropenes, but additional reactions occur giving polycyclic cage products.[366,367]

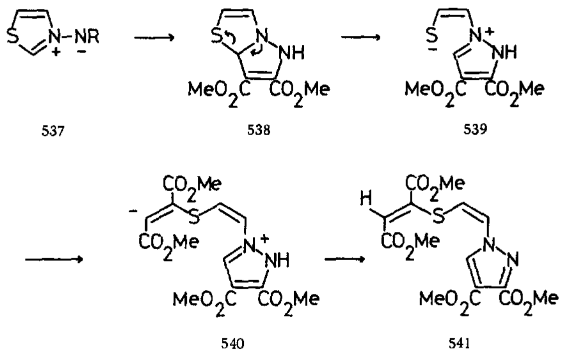


Scheme 67. Reaction of thiazolium-*N*-ylides with acetylenic dipolarophiles.[365]



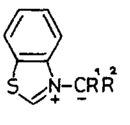
Scheme 68. Reaction of thiazolium-*N*-dicyanomethylide **529** ($R^1 = R^2 = CN$) with dimethyl acetylenedicarboxylate.[98]

The thiazolium-*N*-aminide **537** (R = H) participates in a cycloaddition reaction with dimethyl acetylenedicarboxylate yielding the 2 : 1 product **541** (Scheme 69).[368] The mechanism of the reaction sequence given in Scheme 69 is obviously closely related to that of Scheme 67.

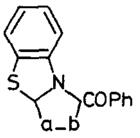


Scheme 69. Reaction of thiazolium-*N*-aminide **537** (R = H) with dimethyl acetylenedicarboxylate.[368]

The benzothiazolium-*N*-ylide **542** is a type **A** system and it reacts as expected with olefinic dipolarophiles (a=b) yielding the cycloadducts **543**.[369,370]



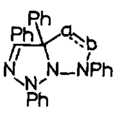
542



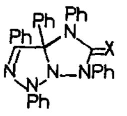
543

Only a few cases of cycloaddition reactions of type **B** heterocyclic mesomeric betaines of class 8 (Scheme 61) have been reported. Examples include the cycloaddition reactions of azolium-*N*-aminides **544**[371–373] and furazan *N*-oxides **135**.[374]

The 1,2,3-triazolium-*N*-aminides **544** (R = Ph) participate in cycloaddition reactions with olefinic and acetylenic dipolarophiles yielding the cycloadducts **545**.[371–373] Phenyl isocyanate and phenyl isothiocyanate yield the corresponding cycloadducts **546** and **547** respectively.

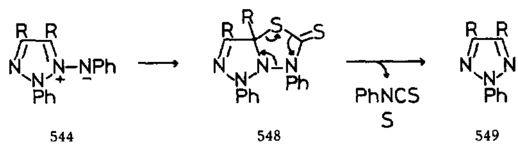


545



546 X = O

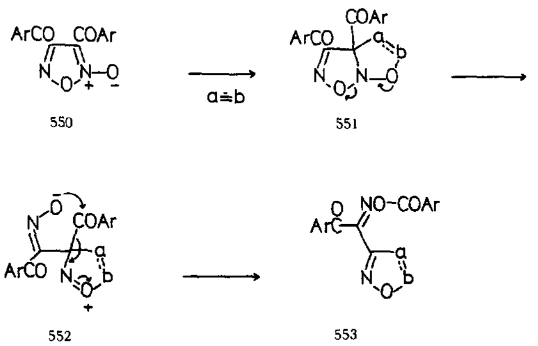
547 X = S



Scheme 70. Reaction of 1,2,3-triazole-*N*-aminides with carbon disulphide [371–373]

The cycloaddition reactions of the triazolium-*N*-aminides **544** (R = Me or Ph) with carbon disulphide take an interesting course because the intermediate cycloadduct **548** extrudes sulphur and phenyl isothiocyanate yielding the 1,2,3-triazole **549** (Scheme 70).[371–373]

The chemistry of furazan *N*-oxides **135** has been excellently reviewed.[374] Furazan *N*-oxides **550** participate in cycloaddition reactions with olefinic and acetylenic dipolarophiles and a particularly interesting molecular rearrangement of the initial cycloadduct **551** has been proposed (Scheme 71).[374]



Scheme 71. Reaction of 4,5-dibenzoylfurazan *N*-oxide with olefinic and acetylenic dipolarophiles.[374]

9. *Cross-conjugated heterocyclic mesomeric betaines isoconjugate with odd alternant hydrocarbon anions*

The membership of this class is very limited. No cycloaddition reactions of any members of class 9 of heterocyclic mesomeric betaines have been reported.

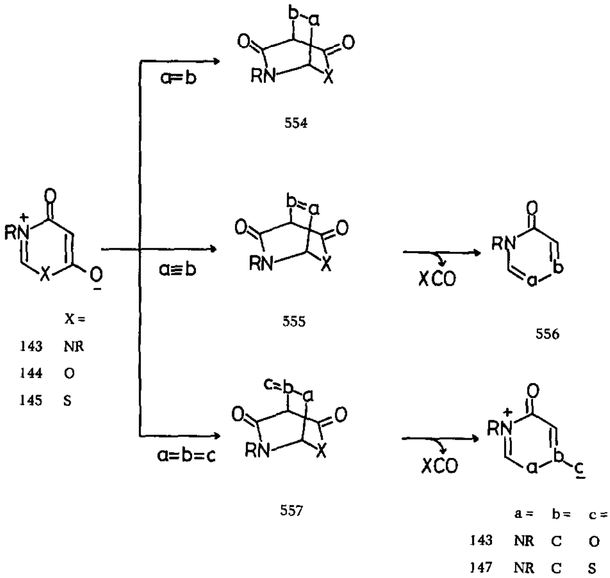
10. *Cross-conjugated heterocyclic mesomeric betaines isoconjugate with odd non-alternant hydrocarbon anions*

No member of this class has been described. No cycloaddition reactions of any members of class 10 of heterocyclic mesomeric betaines have been reported.

11. *Cross-conjugated heterocyclic mesomeric betaines isoconjugate with even alternant hydrocarbon dianions*

Recently considerable interest has developed in the synthesis and the chemistry of this class of cross-conjugated mesomeric betaines and the subject has been excellently reviewed by Friedrichsen *et al.*[375] and by Kappe.[376] However, the descriptions used for the heterocyclic mesomeric betaines belonging to class 11 as "6-membered meso-ionic heterocycles of the *m*-quinodimethane dianion type"[375] or "zwitterionic malonyl heterocycles"[376] are not acceptable and we strongly advocate (p. 2255) that their general description as cross-conjugated heterocyclic mesomeric betaines should be adopted. A striking contrast has been observed between the cycloaddition reactions of conjugated heterocyclic mesomeric betaines (classes 1–8) and cross-conjugated heterocyclic mesomeric betaines (classes 9–12). Whereas conjugated heterocyclic mesomeric betaines can function towards dipolarophiles as 1,3-dipolar systems, in contrast, cross-conjugated heterocyclic mesomeric betaines would be predicted to react towards dipolarophiles as 1,4-dipolar systems.[377] This prediction has been fully confirmed by recent studies of the cycloaddition reactions of the cross-conjugated heterocyclic mesomeric betaines which belong to class 11.

Cross-conjugated heterocyclic mesomeric betaines, isoconjugate with the *m*-quinodimethane dianion **34** (Scheme 5) which participate in dipolar cycloaddition reactions include 1,3-disubsti-



Scheme 72. Cycloaddition reactions of cross-conjugated heterocyclic mesomeric betaines **143**–**145**.[105,107,110,122,375,378,379]

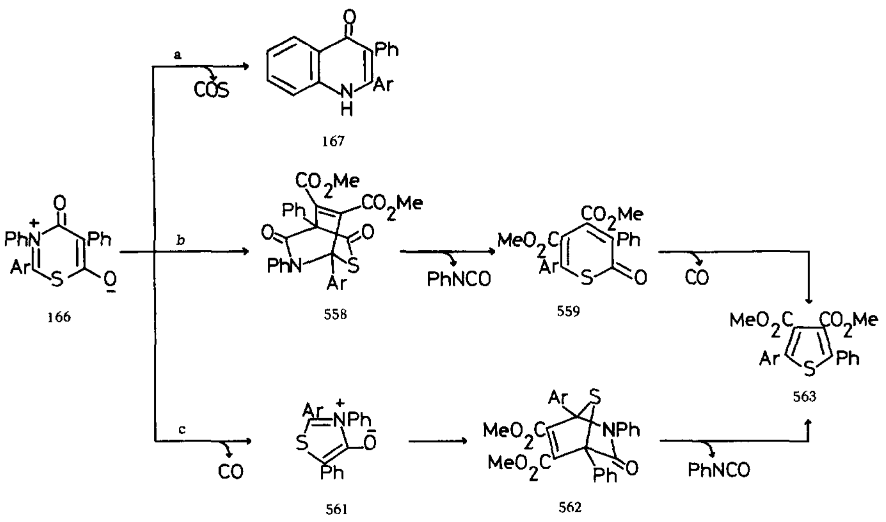
tuted-3,6-dihydro-6-oxopyrimidinium-4-olates **143**,[105,107,375,378,379] 3-substituted-4-oxo-4*H*-1,3-oxazinium-6-olates **144**[375] and 3-substituted-4-oxo-4*H*-1,3-thiazinium-6-olates **145**.[110,122] These cycloaddition reactions with alkenes, acetylenes and heterocumulenes are summarised in Scheme 72.

1,3-Disubstituted-3,6-dihydro-6-oxopyrimidinium-4-olates **143** react with olefinic dipolarophiles (maleic anhydride, maleimides and tetracyanoethylene) yielding the cycloadducts **554**.[107,375,378] Acetylenic dipolarophiles (dimethyl acetylenedicarboxylate[105,107] and benzyne[378]) also undergo 1,4-dipolar cycloaddition, but in these cases thermal elimination of phenyl isocyanate from the intermediate cycloadduct **555** may also be observed yielding α-pyridone derivatives **556**.[378] 1,2-Diphenyl-3-methyl-3,6-dihydro-6-oxopyrimidinium-4-olate (*cf* **143**; X = NMe) and dimethyl acetylenedicarboxylate in boiling acetone (48 hr) yield dimethyl 1-methyl-2-oxo-6-phenyl-1,6-dihydropyridine-4,5-dicarboxylate (*cf* **556**). Clearly the intermediate cycloadduct (*cf* **555**) in this reaction could have eliminated either phenyl isocyanate or methyl isocyanate, but only the extrusion of phenyl isocyanate is observed.[107]

1,3-Disubstituted-3,6-dihydro-6-oxopyrimidinium-4-olates **143** undergo 1,4-cycloaddition with singlet oxygen ($^1O_2$ generated chemically or photochemically) yielding stable peroxides **554** (a—b = O—O) in high yield (84–92%).[379]

Several interesting examples of the cycloaddition reactions of cross-conjugated heterocyclic mesomeric betaines with heterocumulenes have been reported (Scheme 72). Thus, 4-oxo-4*H*-1,3-oxazinium-6-olates **144** and aryl isothiocyanates yield 3,6-dihydro-6-oxopyrimidinium-4-thiolates **147**.[375] Similarly, 4-oxo-4*H*-1,3-thiazinium-6-olates **145** and aryl isocyanates yield 4,6-dihydro-6-oxopyrimidinium-4-olates **143**.[110] These interconversions (**144** → **147**) and (**145** → **143**) illustrate a general method for interconverting cross-conjugated heterocyclic mesomeric betaines which involves the cycloadducts **557** as intermediates. A similar sequence has been proposed[375] for the formation of 6-hydroxypyrimid-4-ones from 3,6-dihydro-6-oxo-pyrimidinium-4-olates **143** and isocyanic acid.

The reaction of 2,3,5-triaryl-4-oxo-4*H*-1,3-thiazinium-6-olates **166** with dimethyl acetylenedicarboxylate in boiling xylene (3 hr) yields the quinolone **167** and the thiophene **563** (Scheme 73).[122] The mechanism for the formation of the quinolone (**166** → **167**; pathway a) involving intramolecular charge neutralisation of the cross-conjugated mesomeric betaine has been discussed (Scheme 7). Two mechanisms (Scheme 73; pathways b or c) have been envisaged[122] for the formation of the thiophene **563**. Pathway b involves (i) cycloaddition (**166** → **558**), (ii) extrusion of phenyl isocyanate (**558** → **559**), and (iii) extrusion of carbon monoxide (**559** → **563**). Pathway c involves (i) elimination of carbon monoxide yielding the type A meso-ionic 1,3-thiazolium-4-olate **561**, (ii) cycloaddition (**561** → **562**), (iii) extrusion of phenyl isocyanate. The two mechanisms (pathways b and c) considered[122] for the formation of the thiophene **563** both involve unusual eliminations of carbon

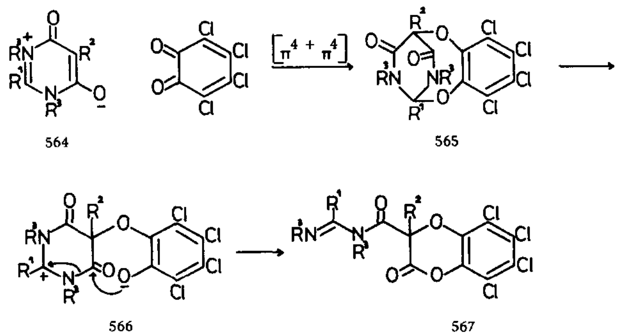


Scheme 73. The reaction of the cross-conjugated heterocyclic mesomeric betaine **166** with dimethyl acetylenedicarboxylate.[122]

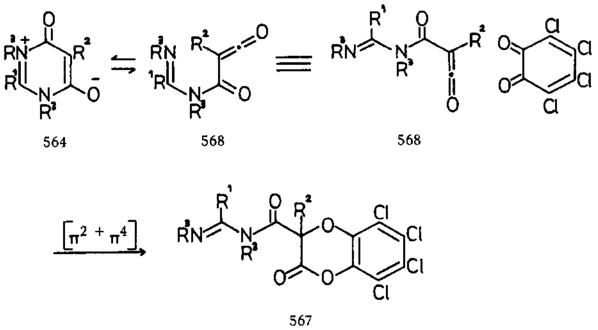
monoxide: this requires further experimental scrutiny. Furthermore, when the cross-conjugated mesomeric betaine **166** was heated in xylene or acetonitrile in the absence of dimethyl acetylenedicarboxylate, then only the quinolone **167** was formed: the type **A** meso-ionic 1,3-thiazolium-4-olate **561** was not detected.[122]

The cycloaddition reactions of cross-conjugated heterocyclic mesomeric betaines with tetrachloro-1,2-benzoquinone have been carefully examined by Friedrichsen[119,134,375] and two general types of cycloaddition reaction have been identified (Schemes 74 and 76).

1,3-Disubstituted-3,6-dihydro-6-oxopyrimidinium-4-olates **564** (*cf* **143**) and tetrachloro-1,2-benzoquinone in benzene or acetonitrile solution at room temperature yield the products **567**. The constitution of the product **567** has been firmly established by X-ray crystallography.[134] Two mechanisms for this transformation can be envisaged (Schemes 74 and 75). The mechanism which is reported[134] is that given in Scheme 74. Friedrichsen *et al.*[134] propose that the cycloadduct **565** is initially formed by a $[_{\pi}4 + _{\pi}4]$ cycloaddition which is then transformed by a dipolar intermediate **566** into the product **567**. The alternative possibility that this reaction could involve cycloaddition to open chain valence tautomers has been considered, but rejected: it is stated that "these tautomers are not involved in this cycloaddition".[375] We do not share this view and, just as type **A**[2,4] and type **B** meso-ionic heterocycles (**9** → **360**) and (**359** → **361**) (p. 2284)[253–255] participate in cycloaddition reactions involving their covalent valence tautomers, so we suggest that the products **567** are formed directly in a $[_{\pi}2 + _{\pi}4]$ cycloaddition involving the ketenoid valence tautomer **568** as the $_{\pi}2$-component and tetrachloro-1,2-benzoquinone as the $_{\pi}4$-component. We favour the mechanism (Scheme 75) in which intramolecular charge neutralisation of the cross-conjugated mesomeric betaine **564** produces the ketene **568** which is then trapped by the tetrachloro-1,2-benzoquinone. This is the first type of



Scheme 74. The reaction of the cross-conjugated heterocyclic mesomeric betaine **564** with tetrachloro-*o*-benzoquinone.[134]

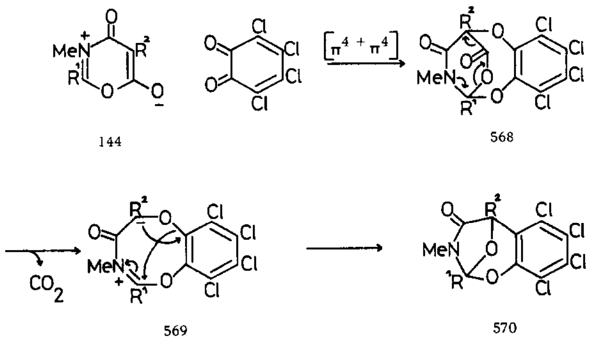


Scheme 75. The reaction of the cross-conjugated heterocyclic mesomeric betaine **564** with tetrachloro-1,2-benzoquinone.

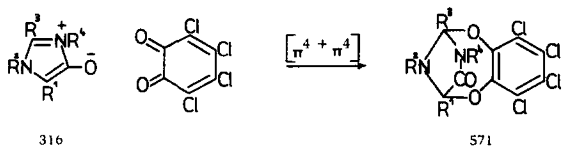
cycloaddition reaction shown by cross-conjugated mesomeric betaines towards tetrachloro-1,2-benzoquinone.

The second type of reaction between tetrachloro-1,2-benzoquinone and cross-conjugated mesomeric betaines of class 11 is illustrated by the cycloaddition reactions of 3-substituted 4-oxo-4*H*-1,3-oxazinium-6-olates **144**[119] (Scheme 76). The reaction between tetrachloro-1,2-benzoquinone and 4-oxo-4*H*-1,3-oxazinium-6-olates **144** occurs in high yield in methylene chloride at room temperature yielding the products **570** whose constitutions have been firmly established by X-ray crystallography.[119] The mechanism proposed[375] for this transformation (Scheme 76) involves the formation of the cycloadduct **568**, which then fragments giving carbon dioxide and a dipolar intermediate **569**, which then gives the product **570** (Scheme 76).[119,375] Although the constitution of the product is firmly established, the mechanism proposed[119,375] for its formation is so unusual that we have considered alternatives. The proposed mechanism (Scheme 76) involves an intramolecular nucleophilic displacement at an aromatic carbon atom **569** (arrows). This reaction could be regarded as a relative of the Smiles rearrangement, but this is a rather distant analogy. Furthermore, the Smiles rearrangement is normally associated with substrates in which the stabilisation of anionoid intermediates can be acceptably rationalised. Our reasons for preferring an alternative (Scheme 85) to the proposed mechanism (Scheme 76) are now presented.

Precedent for the $[_{\pi}4 + {}_{\pi}4]$ cycloaddition reaction (Scheme 76) was judged by Friedrichsen to have been provided by his earlier studies[380,381] on the cycloaddition reactions of the type A meso-ionic heterocycles, 1,3-diazolium-4-olates **316** (Scheme 77),[381] 1,3-oxazolium-4-olates **257** (Scheme 78),[381] 1,3-oxazolium-5-olates **104** (Schemes 79 and 80)[380] and bicyclic 4-acyl-1,3-oxazolium-5-olates **580**,[383] with tetrachloro-1,2-benzoquinone. The mechanisms proposed (Schemes 77, 78 and 80)[380,381] for all the cycloaddition reactions of type A meso-ionic heterocycles involve a concerted $[_{\pi}4 + {}_{\pi}4]$ cycloaddition reaction[375] with tetrachloro-1,2-benzoquinone as a common mechanistic feature. If the possibility of antarafacial participation by one of the $_{\pi}4$-components is initially excluded then we are left with the fact that a concerted thermal $[_4\pi_s + {}_4\pi_s]$ cycloaddition reaction is symmetry forbidden. In contrast, the concerted excited state $[_{\pi}4_s + {}_{\pi}4_s]$ pathway is symmetry allowed, so this pathway could be operating in a number of known photochemical cycloaddition reactions. However, there is the usual need for caution in adopting the conclusion that such photochemical reactions are



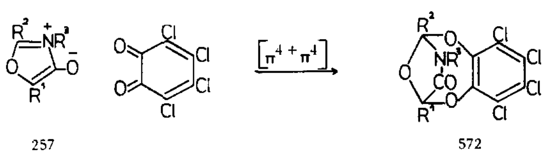
Scheme 76. Proposed mechanism for the reaction of the cross-conjugated heterocyclic mesomeric betaine **144** with tetrachloro-1,2-benzoquinone.[119,375]



Scheme 77. Proposed mechanism for the reaction of 1,3-diazolium-4-olates **316** with tetrachloro-1,2-benzoquinone.[381]

concerted. There is, in our view, a similar need for caution in postulating thermal $[_{\pi}4+_{\pi}4]$ processes. We have therefore examined alternatives (Schemes 82–85) to the mechanisms which have been proposed[119,134,375] on the basis of putative $[_{\pi}4+_{\pi}4]$ processes for these thermal reactions.

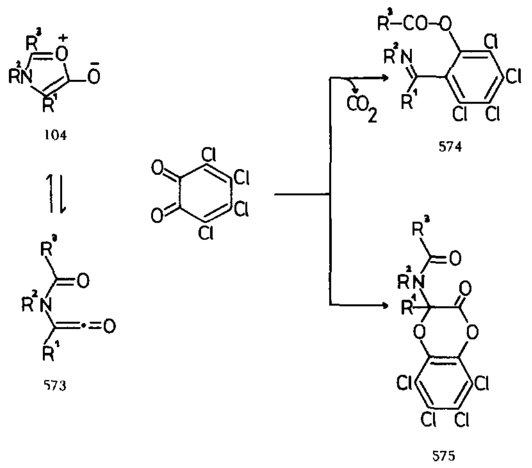
1,3-Diazolium-4-olates **316** and tetrachloro-1,2-benzoquinone react very rapidly (10–20 min) in solution (methylene chloride, benzene, or methanol) yielding cycloadducts **571** in high yield (95–99%). The constitution of one of these adducts **571** ($R^1 = R^2 = R^3 = Ph, R^4 = Me$) was firmly established by an X-ray crystal structure[381] and it was considered that the cycloaddition was a concerted $[_{\pi}4+_{\pi}4]$ process (Scheme 77).[381] An alternative mechanism is discussed later (Scheme 82).



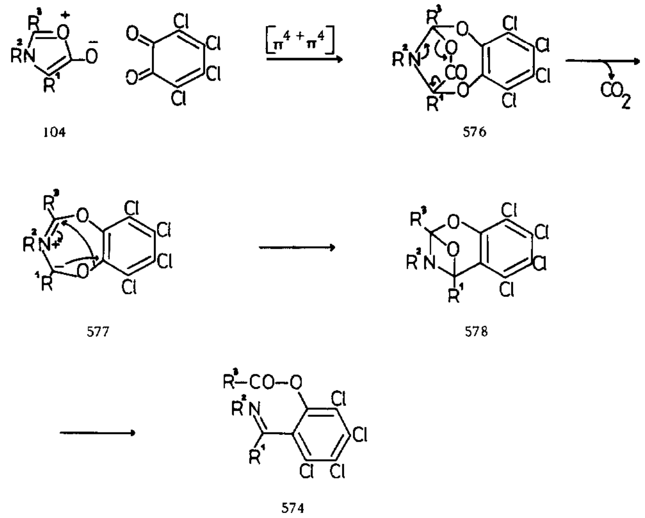
Scheme 78. Proposed mechanism for the reaction of 1,3-oxazolium-4-olates **257** with tetrachloro-1,2-benzoquinone.[381]

One example of the cycloaddition reaction between the 1,3-oxazolium-4-olate **257** ($R^1 = p$-nitrophenyl, $R^2 = Ph$, $R^3 = Me$) and tetrachloro-1,2-benzoquinone has been reported[381] (Scheme 78). The reaction was carried out in dichloromethane at room temperature (15 min) and gave the product **572** in high yield (98%). Again it was proposed that this reaction involved a concerted $[_{\pi}4+_{\pi}4]$ process (Scheme 78),[381] but an alternative mechanism analogous to that given in Scheme 82 merits consideration.

1,3-Oxazolium-5-olates **104** react rapidly (10–30 min) with tetrachloro-1,2-benzoquinone in solution (dichloromethane, methyl cyanide or benzene) at room temperature and usually yield the cycloadducts **575** (Scheme 79). We consider that this reaction (**104** → **575**) involves the acceptable $[_{\pi}4+_{\pi}2]$ cycloaddition reaction between the ketenoid valence tautomer **573** and tetrachloro-1,2-benzoquinone (Scheme 79). This view is not supported by Friedrichsen *et al.*,[380] who state that "there is evidence for the assumption that ketenes are not involved in these reactions as intermediates". However, no alternative mechanism for the reaction (**104** → **575**) is proposed by these investigators.



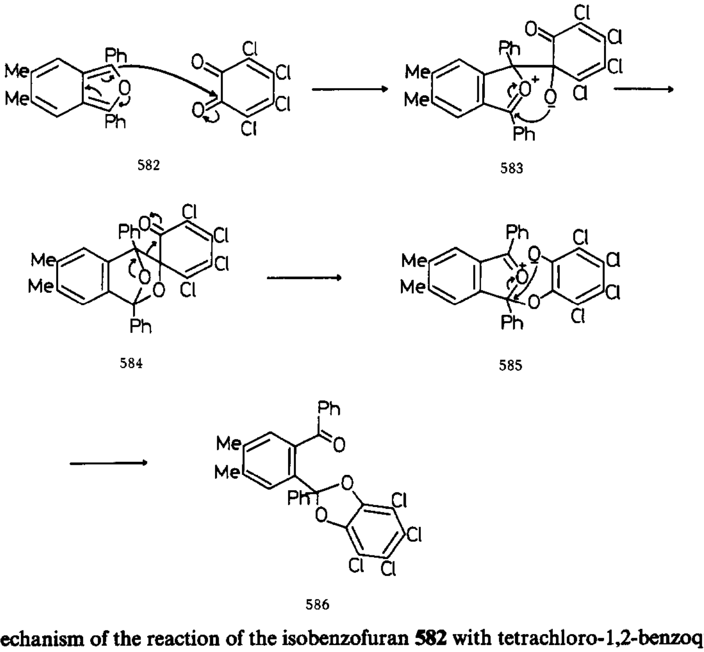
Scheme 79. Cycloaddition reactions of 1,3-oxazolium-5-olates **104** with tetrachloro-1,2-benzoquinone.[380]



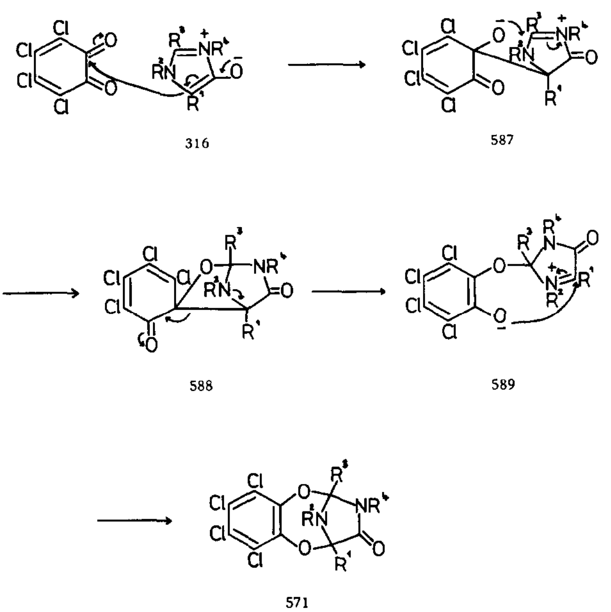
Scheme 80. Proposed mechanism for the reaction of 1,3-oxazolium-5-olates **104** with tetrachloro-1,2-benzoquinone.[380]

A remarkable duality of reaction pathway (Scheme 79; **104** → **574** and **104** → **575**) has been observed[380] in the reaction of certain 1,3-oxazolium-5-olates **104** with tetrachloro-1,2-benzoquinone. The 1,3-oxazolium-5-olate **104** (R^1 = CONHPh, R^2 = Me, R^3 = Ph) in methyl cyanide (room temp, 15 min) yields one product **575** (R^1 = CONHPh, R^2 = Me, R^3 = Ph; 94%), whereas the same reactants in benzene (room temp, 10 min) yield two products **575** (R^1 = CONHPh, R^2 = Me, R^3 = Ph; 49%) and **574** (R^1 = CONHPh, R^2 = Me, R^3 = Ph; 48%). This dependence of product ratio upon reaction solvent must surely be regarded as an influence of solvent upon the valence tautomerism **104** $\rightleftharpoons$ **573**. Similarly, the 1,3-oxazolium-5-olate **104** (R^1 = CONHCOPh, R^2 = Me, R^3 = Ph) in dichloromethane (room temp, 60 hr) yields two products **575** (R^1 = CONHCOPh, R^2 = Me, R^3 = Ph; 49%) and **574** (R^1 = CONHCOPh, R^2 = Me, R^3 = Ph; 39%).

The transformation **104** → **574** must be associated with elimination of carbon dioxide and the mechanism proposed[380] for this transformation is reproduced in Scheme 80. This mechanism (Scheme 80)[380] corresponds exactly with the mechanism (Scheme 76) proposed[119,373] for the reaction of the cross-conjugated heterocyclic mesomeric betaine **144** with tetrachloro-1,2-benzoquinone. Our criticisms of Scheme 76 given earlier can be levelled with equal vigour against Scheme 80, but in



Scheme 81. Mechanism of the reaction of the isobenzofuran **582** with tetrachloro-1,2-benzoquinone.[382]



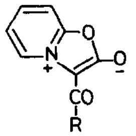
Scheme 82. Alternative mechanism for the reaction of 1,3-diazolium-4-olates **316** with tetrachloro-1,2-benzoquinone.

addition the generation **577** (arrows) of the 4-membered ring in the intermediate **578** poses an additional problem. It is proposed (Scheme 80)[380] that the isolated product **574** is formed by cleavage of the intermediate **578**. An alternative mechanism for the transformation (**104** → **574**) is given later (Scheme 83).

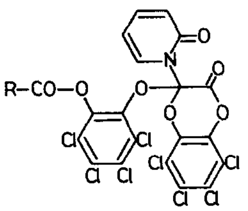
We consider that cogent evidence against the concerted $[_{\pi}4+_{\pi}4]$ cycloaddition reaction postulated in Schemes 74, 76–78 and 80 is provided by the careful study of the reaction between the isobenzofuran **582** and tetrachloro-1,2-benzoquinone in chloroform (room temp, 12 hr).[382] This yields the keto-acetal **586** (88%) and the mechanism proposed (Scheme 81) is based upon the high reactivity to be expected between the electron-rich isobenzofuran **582** and the highly electrophilic tetrachloro-1,2-benzoquinone. A corresponding high nucleophilic reactivity can be expected for the 1,3-dipolar systems of type A meso-ionic heterocycles and the 1,4-dipolar systems of cross-conjugated heterocyclic mesomeric betaines. We propose that the mechanisms reproduced in Schemes 74, 76, 77 and 80 should be replaced by the mechanisms presented in the Schemes 75, 85, 82 and 83 respectively. Scheme 78 can be replaced by an equivalent of Scheme 82.

The replacement of the $[_{\pi}4+_{\pi}4]$ cycloaddition reaction of Scheme 77 by the more complex mechanistic sequence in Scheme 82 is at first sight rather surprising, but the high nucleophilic reactivity of many type A meso-ionic heterocycles towards electrophiles is well documented. The reaction **316** (arrows) and subsequent transformations of the intermediates **587** (arrows), **588** (arrows), and **589** (arrows) are entirely acceptable. The $[_{\pi}4+_{\pi}4]$ cycloaddition (Scheme 78) can be replaced by an analogous sequence (Scheme 82).

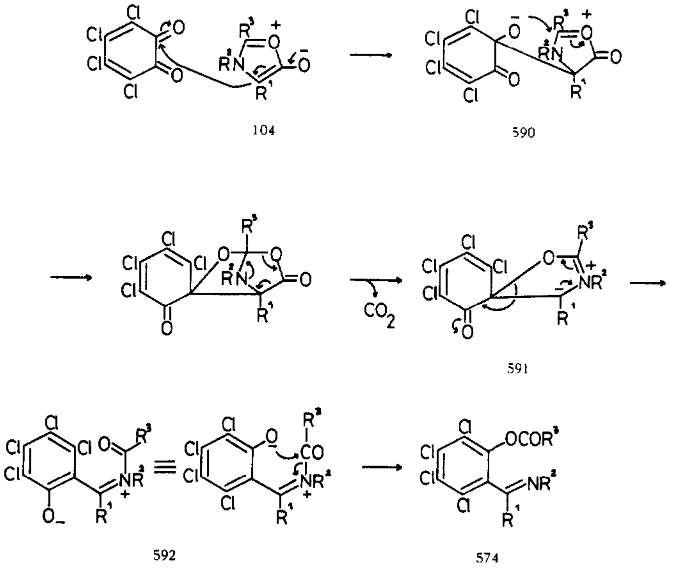
Our reservations about Scheme 80 are dismissed by Scheme 83. This accounts for the very interesting transformation (**104** → **574**). The elimination of carbon dioxide by fragmentation of the intermediate lactone giving the 1,3-dipole **591** has ample precedent (Scheme 28; **274** → **275**) and the *N*,*O*-acyl migration **592** (arrows) is well established.



580



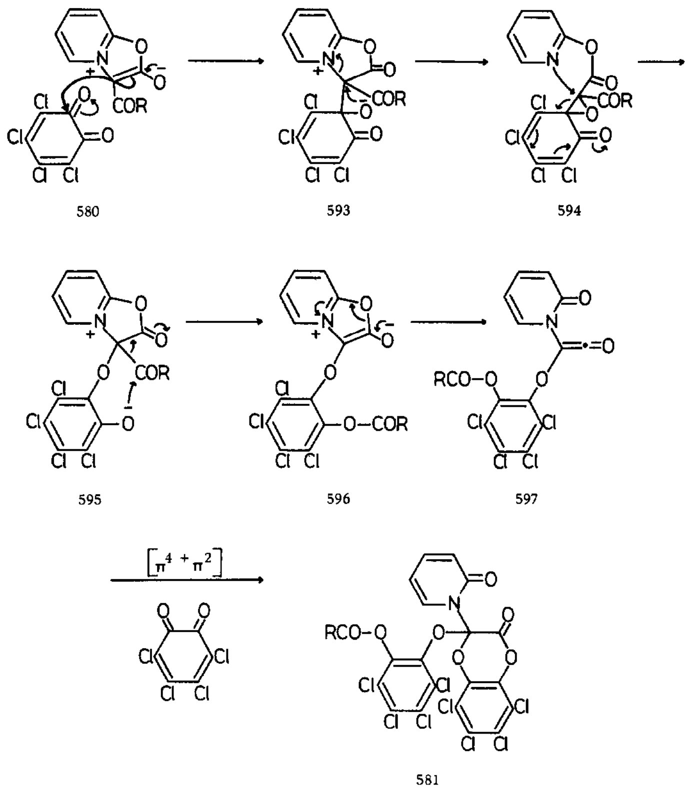
581



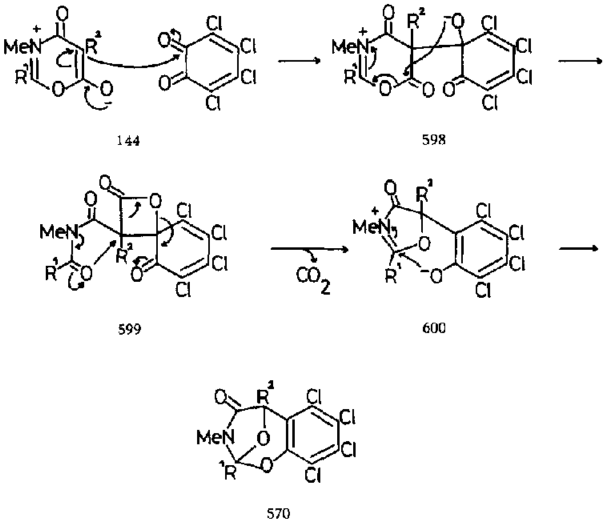
Scheme 83. Alternative mechanism for the reaction of 1,3-oxazolium-5-olates **104** with tetrachloro-1,2-benzoquinone.

The remarkable reaction[380] between the bicyclic 4-acyl-1,3-oxazolium-5-olates **580**[383] and tetrachloro-1,2-benzoquinone in toluene (100°C; 3–4 hr) yielding the 2 : 1 cycloadducts **581** provide a suitable challenge to the general principles of our mechanistic proposals for the reaction of heterocyclic mesomeric betaines with tetrachloro-1,2-benzoquinone. A mechanism for the transformation (**580** → **581**) is presented in Scheme 84.

Scheme 84 utilises two types of reactivity which we believe to be characteristic of tetrachloro-1,2-benzoquinone: (i) its reactivity as an electrophile towards the 1,3-dipolar systems of conjugated



Scheme 84. Mechanism for the reaction of bicyclic 4-acyl-1,3-oxazolium-5-olates **580** with tetrachloro-1,2-benzoquinone.

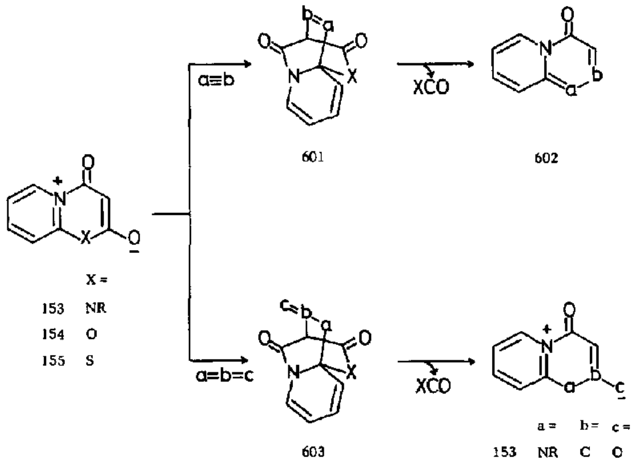


Scheme 85. Alternative mechanism for the reaction of the cross-conjugated heterocyclic mesomeric betaine **144** with tetrachloro-1,2-benzoquinone.

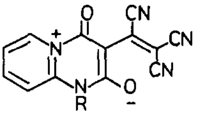
mesomeric betaines and (ii) its reactivity as the ${}_\pi 4$-participant in $[{}_\pi 4 + {}_\pi 2]$ cycloaddition reactions with ketenes. The first type of reactivity of tetrachloro-1,2-benzoquinone can obviously be extended to include its reactivity as an electrophile towards the 1,4-dipolar systems of cross-conjugated heterocyclic mesomeric betaines: this reactivity is illustrated by Scheme 85. The transformation (**144** → **570**) also involves elimination of carbon dioxide and this is acceptably accommodated by the fragmentation of the intermediate β-lactone **599** (arrows). Scheme 85 replaces Scheme 76.

Bicyclic cross-conjugated heterocyclic mesomeric betaines **153**–**155** behave as 1,4-dipoles towards acetylenic dipolarophiles (dimethyl acetylenedicarboxylate) and heterocumulenes (phenyl isocyanate)[110,120,131] (Scheme 86). Under the rather vigorous reaction conditions (boiling xylene or boiling phenyl isocyanate) the intermediate cycloadducts **601** and **603** were not isolated. The product from cycloaddition reaction with dimethyl acetylenedicarboxylate was the 4*H*-quinolizin-4-one **602**. The transformations (**154** → **153**) and (**155** → **153**) provide a method for the interconversion of bicyclic cross-conjugated mesomeric betaines (Scheme 86).[110,129]

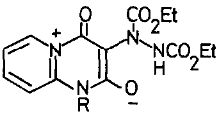
Support for the view that the 1,4-dipolar cycloaddition reactions (Scheme 86) of the bicyclic cross-conjugated heterocyclic mesomeric betaines **153**–**155** involves a two-step reaction in which the betaine behaves as a nucleophile towards the electrophilic dipolarophile is provided by the following results. The cross-conjugated mesomeric betaine **153** yields the product **604** with tetracyanoethylene, and the product **605** with diethyl azodicarboxylate.[131]



Scheme 86. Cycloaddition reactions of bicyclic cross-conjugated heterocyclic mesomeric betaines **153**–**155**.[110,120,131]



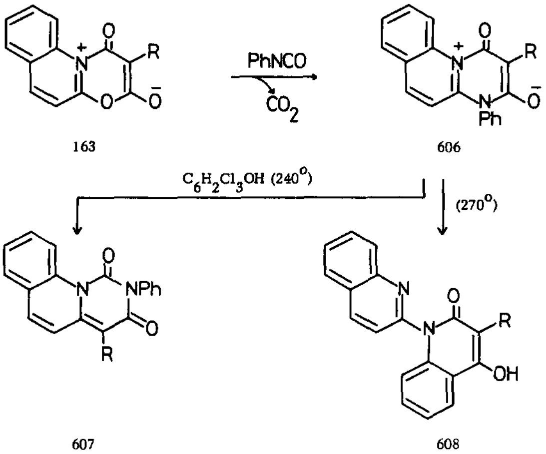
604



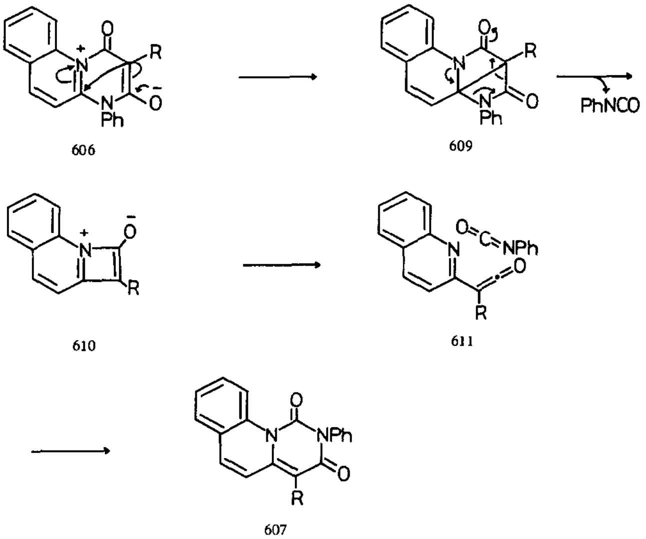
605

An analogous reaction (Scheme 86; **154** → **153**) has been used to transform the tricyclic cross-conjugated mesomeric betaine **163** into the corresponding tricyclic cross-conjugated 6-oxopyrimidinium-4-olate **606** (Scheme 87). This compound **606** undergoes two fascinating thermal rearrangements. When heated in 2,4,6-trichlorophenol (240°C; 40 min), **606** yields the isomer **607**, whereas when **606** is heated alone (270°C; 40 min) or in boiling diphenyl ether (60 min) it yields a different isomer **608**.[384] The mechanisms proposed[384] for these isomerisations (**606** → **607**) (Scheme 88) and (**606** → **608**) (Scheme 89) provide excellent examples of the principles of reaction mechanism enunciated in this section.

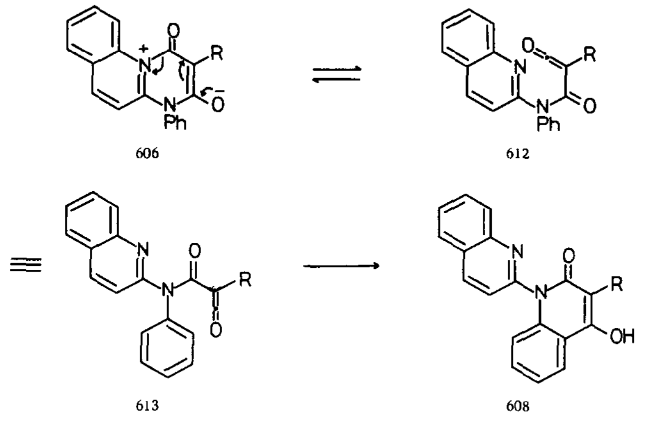
The extensive investigations by Kappe[105,110,120,375,376,378,384] provide excellent support for the proposal that intramolecular charge neutralisation is a general reaction which is a common feature of



Scheme 87. The formation and thermal rearrangements of the tricyclic cross-conjugated heterocyclic mesomeric betaine **606**.[120,384]

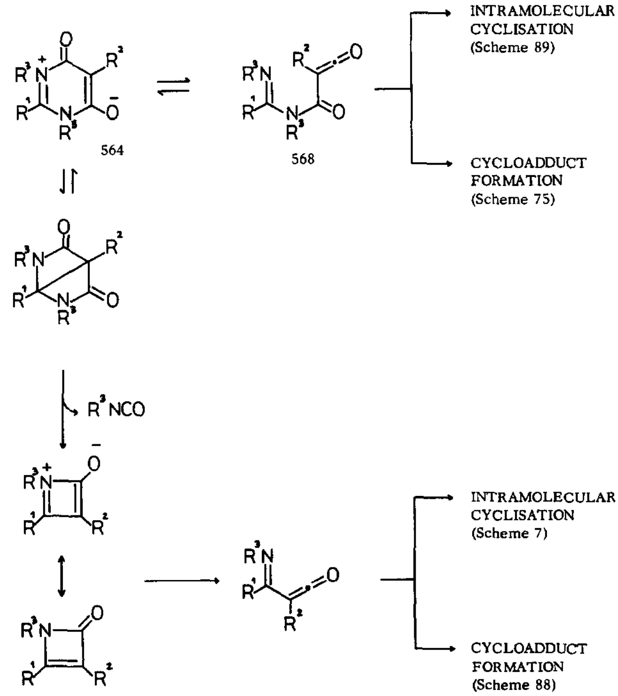


Scheme 88. Mechanism of the thermal isomerisation (**606** → **607**).[384]



Scheme 89. Mechanism of the thermal rearrangement (**606** → **608**).[384]

different types of reaction which are exhibited by cross-conjugated heterocyclic mesomeric betaines belonging to class 11. Two general types of reaction can be recognised (Scheme 90). Intramolecular charge neutralisation of the first type is associated with the equilibrium, which is established thermally, between 6-oxopyrimidinium-4-olates **564** and its ketenoid valence tautomer **568**. This equilibrium (**606** ⇌ **612**) is involved in the thermal rearrangement (**606** → **608**) (Scheme 89). A similar equilibrium (**564** ⇌ **568**) is also involved in the cycloaddition reaction of the 6-oxopyrimidinium-4-olate **564** with tetrachloro-1,2-benzoquinone (Scheme 75). Intramolecular charge neutralisation of the second type yields the bicyclic valence tautomer which, after elimination of the isocyanate (R^3NCO) and electrocyclic ring-opening, yields a second ketenoid intermediate (Scheme 90). Intramolecular cyclisation of this ketene intermediate is involved in the thermal transformation (**165** → **167**) (Scheme 7). The same ketene intermediate (generated by the elimination of carbonyl sulphide) also undergoes intramolecular cyclisation in the thermal transformation (**166** → **167**) (Scheme 7). An example of cycloadduct formation by this type of ketene intermediate is provided by its role as an intermediate **611** in the thermal isomerisation (**606** → **607**) (Scheme 88).



Scheme 90. The role of ketene intermediates in the four general types of reaction exhibited by cross-conjugated heterocyclic mesomeric betaines of class 11

12. *Cross-conjugated heterocyclic mesomeric betaines isoconjugate with even non-alternant hydrocarbon dianions*

Recently there has been great interest in the synthesis and chemistry of this class, but no cycloaddition reactions of any members of class 12 of heterocyclic mesomeric betaines have been reported.

13. *Pseudo-cross-conjugated heterocyclic mesomeric betaines isoconjugate with odd alternant hydrocarbon anions*

The membership of this class is very limited. No cycloaddition reactions of any members of class 13 of heterocyclic mesomeric betaines have been reported.

14. *Pseudo-cross-conjugated heterocyclic mesomeric betaines isoconjugate with odd non-alternant hydrocarbon anions*

The membership of this class is very limited. No cycloaddition reactions of any members of class 14 of heterocyclic mesomeric betaines have been reported.

15. *Pseudo-cross-conjugated heterocyclic mesomeric betaines isoconjugate with even alternant hydrocarbon dianions*

No member of this class has been described. No cycloaddition reactions of any members of class 15 of heterocyclic mesomeric betaines have been reported.

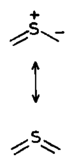
16. *Pseudo-cross-conjugated heterocyclic mesomeric betaines isoconjugate with even non-alternant hydrocarbon dianions*

No member of this class has been described. No cycloaddition reactions of any members of class 16 of heterocyclic mesomeric betaines have been reported.

VI. STRUCTURE AND BONDING IN CONJUGATED HETEROCYCLIC MESOMERIC BETAINES CONTAINING SULPHUR

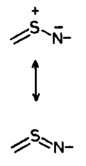
Consideration of the structure of heterocyclic mesomeric betaines containing sulphur has produced a number of interesting cases where the compounds can be represented either by dipolar structures or by covalent structures involving tetracovalent sulphur. Bonding in this valence state, S(IV), necessarily involves participation by the 3d-orbitals of the sulphur atoms. Examples include 1,2,3-thiadiazolium-4-olates (**614** or **615**),[385] 1,3,2,4-dithiadiazolium-5-olates (**616** or **617**),[386] thiopyrylium-3-olates (**52** or **618**),[35] 1,5-dithia-2,4,6,8-tetrazocines (**103** or **619**),[79] 1,3-thiazolium-4-olates (**620** or **621**),[387] thieno[3,4-*c*]thiophenes (**396** or **622**),[18] thieno[3,4-*c*]isothiazoles (**401** or **623**)[388] and naphtho[1,8-*cd*] [1,2,6]thiadiazines (**624** or **625**)[389] (Scheme 91).

Consideration of the dipole types (Scheme 18) shows that only the 1,3-dipoles **188** (X = S) and **189** (X = S) can be mesomerically associated with canonical forms involving tetracovalent sulphur. Therefore, if a heterocycle can be represented either by a covalent formula involving tetracovalent sulphur or by a dipolar representation associated with the dipole types **188** (X = S) or **189** (X = S), then the dipolar representation contains a 1,3-dipolar residue which is normally associated with conjugated mesomeric betaines (Scheme 18). The dipole types **188** (X = S) and **189** (X = S) are associated with thiocarbonyl ylides **626**, thiocarbonyl imines **627** and thionitroso imines **628**.



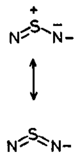
Thiocarbonyl ylide

626



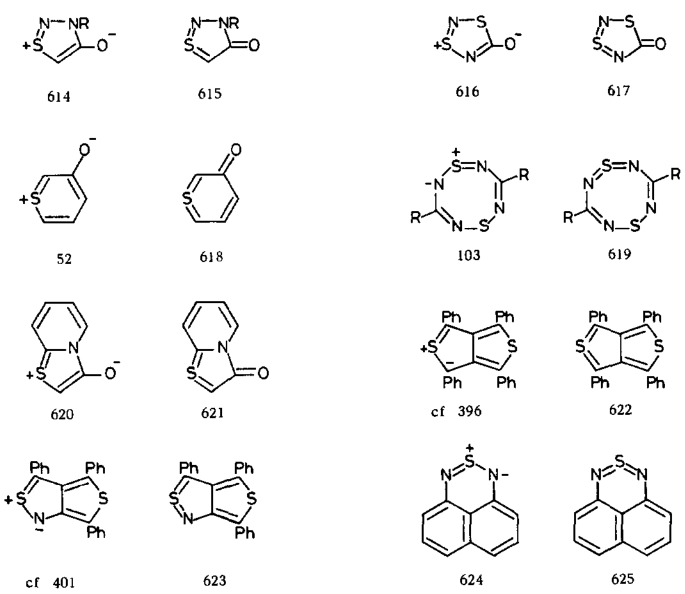
Thiocarbonyl imine

627



Thionitroso imine

628



Scheme 91. Dipolar and covalent formulations of conjugated heterocyclic mesomeric betaines containing sulphur.

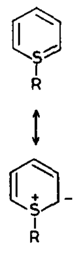
The association of these 1,3-dipole types with the conjugated heterocyclic mesomeric betaines listed in Scheme 91 is as follows:

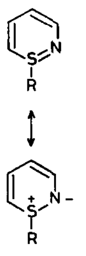
Thiocarbonyl ylide (**626**)—**52**, **620**, **396**;
Thiocarbonyl imine (**627**)—**614**, **401**;
Thionitroso imine (**628**)—**616**, **103**, **624**.

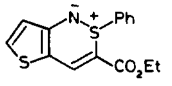
We now consider the following question. Are covalent structures involving tetracovalent sulphur necessary for an accurate description of the structure of sulphur-containing conjugated mesomeric betaines? Based upon the recent investigations by Gleiter, the answer is a firm negative.

Gleiter in a powerful contribution of spectroscopic and theoretical methods has explored the need to invoke 3d-orbital participation by sulphur in a number of conjugated heterocyclic mesomeric betaines. The spectroscopic techniques involve the determination of the electronic and photoelectron spectra of the neutral molecules as well as the study of the electron spin resonance spectra of the derived radical-anions and radical-cations. The theoretical methods are based upon molecular orbital models utilising perturbation theory. The compounds which have been examined include tetraphenylthieno[3,4-*c*]thiophene (*cf* **396**),[390] triphenylthieno[3,4-*c*]isothiazole (*cf* **401**),[388] naphtho[1,8-*cd*][1,2,6]thiadiazine **624**[391,392] as well as some inorganic monocyclic and bicyclic sulphur–nitrogen compounds.[393] Gleiter concludes that bonding involving participation by the 3d-orbitals of sulphur need not be invoked in the structures of these compounds. It follows that the structures of the heterocycles depicted in Scheme 91 are satisfactorily represented by the indicated dipolar structures.

It must be emphasised that similar considerations do not apply to thiabenzenes **629** and azathiabenzenes **630**. Although these compounds can be represented by structures involving


629


630


631

tetracovalent sulphur, the important point is that thiabenzenes **629** and azathiabenzenes **630** are not mesomeric betaines because the positive charge is localised on the sulphur atom and is not associated with a π-electron system. The view[394] that they must be regarded as cyclic sulphonium ylides is correct. This view is certainly supported by the X-ray crystal structure of the sulphimide **631** which demonstrates that the sulphur is pyramidal and only the negative charge is delocalised.[394]

VII. THE MATRIX CLASSIFICATION OF HETEROCYCLIC MESOMERIC BETAINES AND ITS EXTENSION

The classification of heterocyclic mesomeric betaines proposed in Section III can be summarised in the form of a matrix diagram (Scheme 92). Sixteen different classes are available for the classification of the very large number of known heterocyclic mesomeric betaines which are isoconjugate with hydrocarbon mono-anions and dianions.

The great advantage of this classification is that it does provide, for the first time, a structural basis for understanding the chemistry of heterocyclic mesomeric betaines. Scheme 92 also emphasises gaps in our knowledge: certain classes of mesomeric betaines are represented by large numbers of known heterocyclic types, whereas other classes are either sparsely populated (Section III, 2, 3, 6, 9, 12, 13 and 14) or are not, as yet, associated with known examples (Section III, 10, 15 and 16).

There are no exceptions to the classification (Scheme 92) of heterocyclic mesomeric betaines when they are isoconjugate with hydrocarbon mono-anions and dianions. A commendable feature of this classification is that it can be extended to include the relatively small number of known heterocyclic mesomeric betaines which are isoconjugate with hydrocarbon trianions.

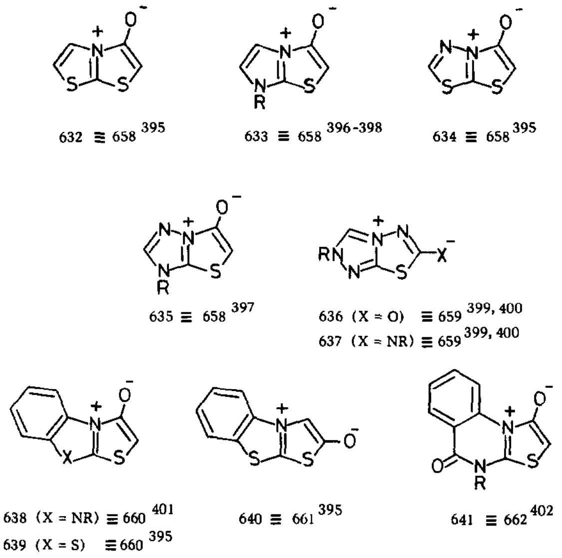
Known examples include the conjugated heterocyclic mesomeric betaines (Scheme 93) and the cross-conjugated heterocyclic mesomeric betaines (Scheme 94). The isoconjugate relation of both groups of heterocycles (Schemes 93 and 94) to the odd non-alternant hydrocarbon trianions listed in Scheme 95 is clear. The same method used throughout Section III is used in Schemes 93 and 94 to indicate isoconjugate relations with the trianions listed in Scheme 95: equivalence signs between formula numbers indicate isoconjugate relations. Scheme 95 refers only to odd non-alternant systems and so far as we are aware no heterocyclic mesomeric betaines have yet been synthesised which are isoconjugate with odd alternant hydrocarbon trianions. The possibility of extending the classification to include isoconjugates of hydrocarbon tetra-anions and even higher poly-anions can be envisaged, but the production of heterocycles containing the required number of suitably located heteroatoms could present synthetic problems.

The conjugated mesomeric betaines (Scheme 93) have all been described [395–402] as meso-ionic heterocycles. With the exception of the compounds **636** and **637**, this is a correct use of the term meso-ionic (Section I) because these compounds (Scheme 93) are derivatives of type **A** meso-ionic heterocycles. The conjugated mesomeric betaines (Scheme 93) are derivatives of 1,3-thiazolium-4-olate **632, 633, 634, 635, 638, 639** and **641** and 1,3-thiazolium-5-olate **640**. It is interesting to discover that the compounds **636** and **637** are not derivatives of either type **A** or type **B** meso-ionic heterocycles, so they should not be described as meso-ionic.

With one exception **653**,[411] all the cross-conjugated heterocyclic mesomeric betaines listed in Scheme 94 have also been described as meso-ionic heterocycles. This is an incorrect use of the term

		ISOCONJUGATE EQUIVALENTS			
		Odd Alternant Hydrocarbon Anions	Odd Non-alternant Hydrocarbon Anions	Even Alternant Hydrocarbon Dianions	Even Non-alternant Hydrocarbon Dianions
CONJUGATED HETEROCYCLIC SYSTEMS	Conjugated Mesomeric Betaines	MANY	FEW	TWO	MANY
	Conjugated Heterocyclic N-Ylides and Related Compounds	MANY	TWO	MANY	MANY
CROSS-CONJUGATED HETEROCYCLIC SYSTEMS	Cross-conjugated Mesomeric Betaines	TWO	NONE	MANY	FEW
	Pseudo-cross-conjugated Mesomeric Betaines	TWO	ONE	NONE	NONE

Scheme 92. Known representatives (Section III, 1–16) of the sixteen possible classes of heterocyclic mesomeric betaines isoconjugate with hydrocarbon anions and dianions.


632 ≡ 658^{395}

633 ≡ 658$^{396-398}$

634 ≡ 658^{395}

635 ≡ 658^{397}

636 (X = O) ≡ 659$^{399, 400}$

637 (X = NR) ≡ 659$^{399, 400}$

638 (X = NR) ≡ 660^{401}

639 (X = S) ≡ 660^{395}

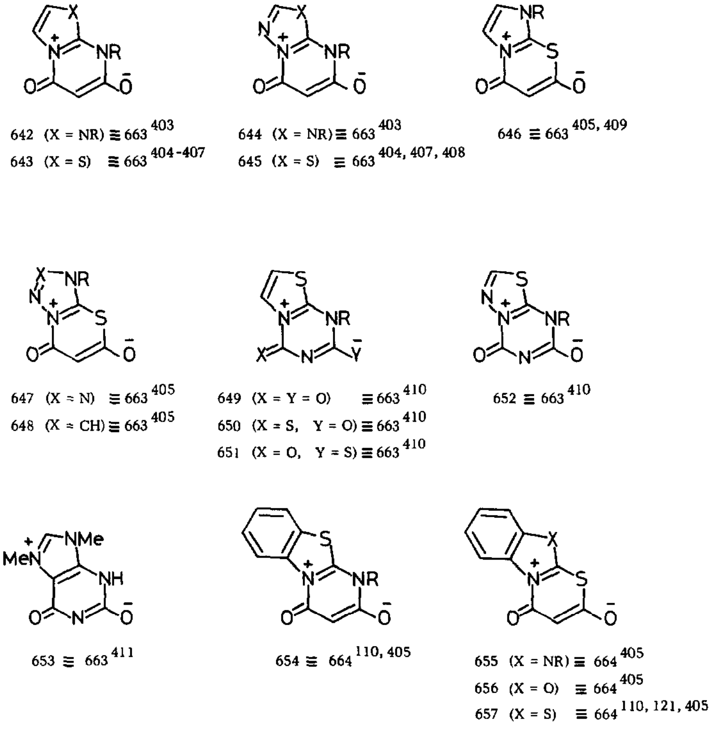
640 ≡ 661^{395}

641 ≡ 662^{402}

Scheme 93. Conjugated mesomeric betaines isoconjugate with odd non-alternant hydrocarbon trianions.

meso-ionic and it is our earnest plea that in future such heterocycles will just be called cross-conjugated heterocyclic mesomeric betaines. The exception is the uric acid derivative **653** and it is interesting to note that its true nature as a cross-conjugated system was clearly appreciated by Bredereck *et al.* in 1959 who named it "xanthinium betaine".[411]

The cross-conjugated mesomeric betaine **665** belonging to the type **646** is transformed into the isomer **667** by heating (220°C; 1 min).[405] This thermal isomerisation involves intramolecular charge neutralisation **665** (arrows), thus generating the intermediate ketene **666**, which then cyclises to the product **667**. The mechanism (Scheme 96) is yet another example of the role of ketene intermediates (Scheme 90) in the thermal transformations of cross-conjugated heterocyclic mesomeric betaines.


642 (X = NR) ≡ 663^{403}

643 (X = S) ≡ 663$^{404-407}$

644 (X = NR) ≡ 663^{403}

645 (X = S) ≡ 663$^{404, 407, 408}$

646 ≡ 663$^{405, 409}$

647 (X = N) ≡ 663^{405}

648 (X = CH) ≡ 663^{405}

649 (X = Y = O) ≡ 663^{410}

650 (X = S, Y = O) ≡ 663^{410}

651 (X = O, Y = S) ≡ 663^{410}

652 ≡ 663^{410}

653 ≡ 663^{411}

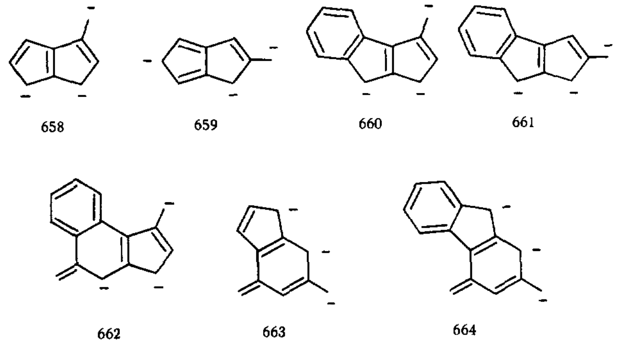
654 ≡ 664$^{110, 405}$

655 (X = NR) ≡ 664^{405}

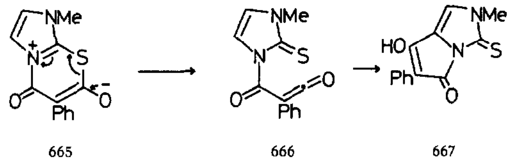
656 (X = O) ≡ 664^{405}

657 (X = S) ≡ 664$^{110, 121, 405}$

Scheme 94. Cross-conjugated mesomeric betaines isoconjugate with odd non-alternant hydrocarbon trianions.

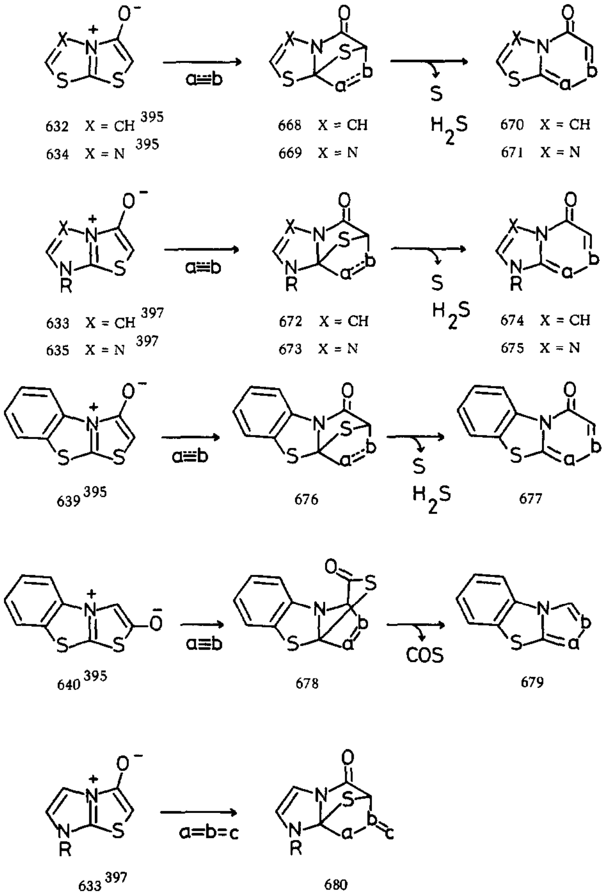


Scheme 95. Odd non-alternant hydrocarbon trianions.

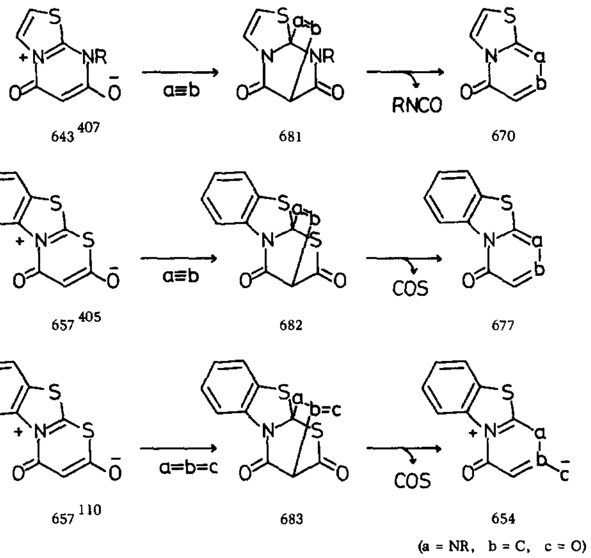


Scheme 96. Thermal isomerisation of the cross-conjugated heterocyclic mesomeric betaine **665**.[405]

The principles on which our classification of heterocyclic mesomeric betaines rests are given satisfying support by the revealing distinction between the 1,3-dipolar cycloadditions shown by the conjugated heterocyclic mesomeric betaines (Scheme 97) and the 1,4-dipolar cycloadditions shown by the cross-conjugated heterocyclic mesomeric betaines (Scheme 98).



Scheme 97. Cycloaddition reactions of conjugated heterocyclic mesomeric betaines isoconjugate with odd non-alternant hydrocarbon trianions.



Scheme 98. Cycloaddition reactions of cross-conjugated heterocyclic mesomeric betaines isoconjugate with odd non-alternant hydrocarbon trianions.

The conjugated heterocyclic mesomeric betaines **632**, **633**, **634**, **635**, **639** and **640** isoconjugate with odd non-alternant hydrocarbon trianions (Scheme 93) participate in 1,3-dipolar cycloaddition reactions (Scheme 97) with electron-deficient acetylenes (a≡b) and with electron-deficient alkenes (a═b). The electron-deficient acetylenes include dimethyl acetylenedicarboxylate, dibenzoylacetylene and hexafluoro-2-butyne. The electron-deficient alkenes include ethyl acrylate, acrylonitrile, maleic anhydride, fumaronitrile, *N*-ethylmaleimide and *N*-phenylmaleimide. The cycloaddition reactions are usually carried out in boiling benzene or boiling toluene and under these reaction conditions the cycloadducts are not usually isolated. The cycloadducts from acetylenic dipolarophiles either extrude sulphur or eliminate carbon oxysulphide yielding α-pyridones. The cycloadducts from olefinic dipolarophiles eliminate hydrogen sulphide yielding the same α-pyridones.

In one case **635**,[397] this conjugated mesomeric betaine was not isolable but it could be trapped by its generation in the presence of dipolarophiles. Subsequent extrusion of sulphur or elimination of hydrogen sulphide yielded the corresponding α-pyridone **675**.

A remarkable reaction[397] occurs between imidazo[2,1-*b*]thiazolium-3-olates **633** and heterocumulenes (a═b═c) (Scheme 97). Thus, alkyl or aryl isocyanates yield the corresponding cycloadducts **680** which are stable and are formed in essentially quantitative yield.

Although the cycloaddition reactions of the cross-conjugated mesomeric betaines (Scheme 94) are rather limited, they nevertheless conform to a general pattern of 1,4-dipolar cycloaddition (Scheme 98). The thiazolo[3,2-*a*]pyrimidinium-7-one-5-olate **643** and dimethyl acetylenedicarboxylate in boiling chloroform yield the corresponding α-pyridone **670** by elimination of the alkyl isocyanate from the intermediate cycloadduct **681**.[407] Benzothiazolothiazinium-olates **657** and dimethyl acetylenedicarboxylate also yield α-pyridones **677** by elimination of carbon oxysulphide from the intermediate cycloadduct. Similarly, benzothiazolothiazinium-olates **657** and the heterocumulene, phenyl isocyanate, also yield an adduct **683** which then eliminates carbon oxysulphide giving the cross-conjugated mesomeric betaine **654** (R = Ph).[110]

VIII. CONCLUSION

As an epilogue, it is gratifying that the true nature of meso-ionic heterocycles has at last become clear. Meso-ionic heterocycles constitute a very small component of the total array of heterocyclic mesomeric betaines. This use of the term meso-ionic has found wide general acceptance, but the need for maintaining the restriction of the use of the term meso-ionic so that it is applied only to the 5-membered meso-ionic heterocycles of type **A** and type **B** is obvious. The indiscriminate extension of the use of the term meso-ionic to describe other heterocyclic mesomeric betaines is unnecessary and confusing. We believe that it is much better to use existing terminology to classify heterocyclic mesomeric betaines as has been adopted throughout this Report.

Following the introduction of the term meso-ionic by Baker and Ollis in 1949, it was proposed by them in 1955 that the dipolar formulation of meso-ionic heterocycles should be indicated by a positive sign within a circle and a negative sign associated with the exocyclic substituent.[22] This representation of meso-ionic heterocycles has been widely used, but now it is recognised that meso-ionic heterocycles form a small component of the very large array of heterocyclic mesomeric betaines, then it is obvious that a special formulation for 5-membered meso-ionic heterocycles is no longer necessary or desirable. It is now proposed that the circle symbol should no longer be used in the structural representation of meso-ionic heterocycles. Henceforth all heterocyclic mesomeric betaines should be represented by appropriately selected dipolar structures. This proposal has been followed throughout this Report and this has clear advantages when possible modes of dipolar cycloaddition are under consideration.

The recognition, proposed explicitly in this Report, that all mesomeric betaines are either acyclic mesomeric betaines or heterocyclic mesomeric betaines, has produced an important result. Our extension of Huisgen's original classification of acyclic mesomeric betaines[2] to include all (acyclic and heterocyclic) mesomeric betaines is fundamentally sound, but this extension generates the need to have a satisfactory classification of all heterocyclic mesomeric betaines. The classification now proposed provides an acceptable basis for correlating the chemical reactions of the very large number of known heterocyclic mesomeric betaines. The classification is general and applies not only to the known heterocyclic mesomeric betaines but also to all the many fascinating new types of heterocyclic mesomeric betaines which await recognition and synthesis.

Acknowledgements—We thank May and Baker Limited and the Science and Engineering Research Council for the award of a CASE Studentship (S.P.S.) and Glaxo Group Research for the award of a Postdoctoral Fellowship (S.P.S.).

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