

18 Heterocyclic Chemistry

Part (ii) Heteroaromatic Compounds

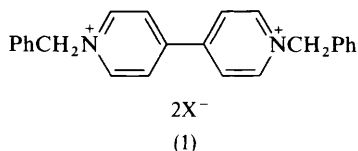
By M. H. PALMER

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The arrangement of the heteroaromatic section this year is to concentrate on major topics rather than widespread coverage of synthetic methods. Thus a higher proportion of material of a physical-organic nature is included.

1 Ground-state Properties of the Ring Systems

Molecular Structure.—There is now more interest than formerly in accurate *X*-ray analysis of simple heterocycles; this is important to theoretical studies of the bonding in such molecules, but much work still remains to be done on systems where microwave studies are presently impracticable. For both 4-cyanopyridine¹ and pyridine *N*-oxide,² the geometric features are very similar to pyridine itself, but for the 4,4'-bis-quaternary salt (1), the ring is marginally



larger than in neutral pyridines and perhaps slightly more similar to that of benzene.³ The microwave spectrum of thiazole yields a structure very close to that expected by superposition of thiophen and 1,3,4-thiadiazole.⁴ The crystal structure of sulphathiazole shows the heterocyclic ring to be non-planar, the thiazoline tautomer to be present, and the 4,5-bond to be purely olefinic.⁵ Substituents, *e.g.* *t*-butyl, can markedly effect ring geometry, and 4,5-di-*t*-butyl-imidazole has a singularly long 4,5-bond for a formal double bond; the external

¹ M. Laing, N. Sparrow, and P. Somerville, *Acta Cryst.*, 1971, **B27**, 1986.

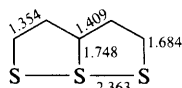
² D. Ulku, B. P. Huddle, and L. C. Morrow, *Acta Cryst.*, 1971, **B27**, 432.

³ J. H. Russell and S. C. Wallwork, *Acta Cryst.*, 1971, **B27**, 2473.

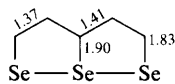
⁴ L. Nygaard, E. Asmussen, J. H. Høg, R. C. Maheshwari, C. H. Nielson, I. B. Petersen, J. Rastrup-Andersen, and G. O. Sorensen, *J. Mol. Structure*, 1971, **8**, 225.

⁵ G. J. Kruger and G. Gafner, *Acta Cryst.*, 1971, **B27**, 326.

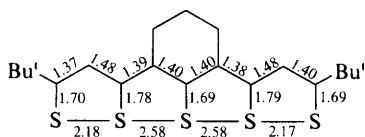
angles between the *t*-butyl groups are markedly distorted;^{6a} a similar feature is present in the 2,3-bond of 2,3-di-*t*-butylquinazoline.^{6b} In the carbocyclic ring of the latter and of a 1,2-benzothiazole derivative,⁷ the short ($\alpha\beta$) and long ($\beta\beta$) bonds are evident, as in naphthalene. The N—C bonds of 8-hydroxyquinoline *N*-oxide⁸ are very long, and again the structure is like that of naphthalene. This is also particularly true of various thiathiophthens (1,6,6a-trithiapentalenes) where the parent compound has been redetermined⁹ and a number of substituted systems have been investigated.¹⁰ Results of some of the key types are given here [compounds (2),⁹ (3),⁹ (4),¹¹ and (5),¹² bond lengths in Å].



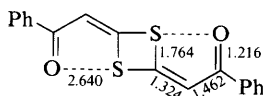
(2)



(3)



(4)



(5)

Among molecules with related structures, compounds with nitrogen and oxygen in the rings¹³ again demonstrate the slight differences in bond lengths. It seems to be generally agreed that these systems do exhibit bonding between classically non-bonded atoms. From the theoretical standpoint the rigid geometry makes this inevitable, *i.e.* within the molecular orbital framework all electrons are attracted to all nuclei, and the only question is how much electron density lies along a plane through the nuclear centres. *X*-ray electron spectroscopy (ESCA) shows differences in environment at sulphur atoms in some thiathiophthens, but, as in the *X*-ray-diffraction data, care in interpretation is necessary since some of these features can possibly be related to molecular orientation in the crystal.¹¹

Among other condensed-ring compounds the bond lengths of molecule (6) are very similar to those resulting from fusion of a benzene ring with thiophen;

⁶ G. J. Visser and A. Vos, *Acta Cryst.*, (a) 1971, **B27**, 1802, (b) 1971, **B27**, 1793.

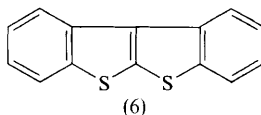
⁷ A. C. Bonamartini, M. Nardelli, C. Palmieri, and C. Pellizzari, *Acta Cryst.*, 1971, **B27**, 1775.

⁸ R. Desiderato, J. C. Terry, G. R. Freeman, and H. A. Levy, *Acta Cryst.*, 1971, **B27**, 2443.

⁹ A. Hordvik and K. Julshamn, *Acta Chem. Scand.*, 1971, **25**, 1895, 2507.

¹⁰ A. Hordvik, *Acta Chem. Scand.*, 1971, **25**, 1583, 1822; A. Hordvik and K. Julshamn, *ibid.*, p. 1835; R. Kristensen and J. Sletten, *ibid.*, p. 2366; T. R. Lynch, I. P. Mellor, and S. C. Nyburg, *Acta Cryst.*, 1971, **B27**, 1958; I. P. Mellor and S. C. Nyburg, *ibid.*, p. 1954; J. Sletten, *Acta Chem. Scand.*, 1971, **25**, 3577.

¹¹ D. T. Clark, D. Kilcast, and D. H. Reid, *Chem. Comm.*, 1971, 638.



the bis-sulphone has more aliphatic bond lengths in the centre rings.¹² Above 0 °C *N*-methylazepine yields two dimers; the higher melting has a *trans*-piperazine system.¹⁴ The detailed crystal structures of a *trans*-corrin¹⁵ and corrole¹⁶ have been published; they are very similar to that of porphyrin published some time ago, except that the $\beta\beta$ -bonds are longer and the $\alpha\beta$ -bonds shorter than in the latter.

Electronic Structure.—Within the hierarchy of molecular orbital calculations, empirical (Hückel and its variants such as the ω -technique), semi-empirical (CNDO, INDO, MINDO, *etc.*), and non-empirical ('*ab initio*'), the first category is now redundant. CNDO self-consistent field calculations lead to charge distributions which vary with the method of analysis,¹⁷ but seem very plausible, and often match those of non-empirical calculations. In the latter case, ground-state properties such as ionization potential,¹⁹ dipole moments,^{18,19} and often electronic spectra are being interpreted in detail.^{18–20} A useful review of the field not cited earlier has been published.²¹ CNDO calculations of reacting systems are practicable, and in one such case²² various stable π -complexes were calculated for the interaction of hydrogen fluoride and benzene or pyridine. Rapid development of this approach is expected.

Determination of the magnetic-susceptibility anisotropy for 2- and 4-pyranone shows that the experimental figure can be entirely accounted for in terms of local group contributions, and that the molecules are thus non-aromatic.²³ This contrasts with the results for benzene, furan, *etc.*, where aromaticity is inferred. The low barriers to inversion calculated for phospholes, but larger for their benzo-derivatives, have been interpreted in terms of $(3p-2p)\pi$ delocalization, and thus aromaticity.²⁴

¹² I. Goldberg, U. Shmueli, *Acta Cryst.*, 1971, **B27**, 2164, 2173.

¹³ P. L. Johnson, K. I. G. Reid, and I. C. Paul, *J. Chem. Soc. (B)*, 1971, 946; K. I. G. Reid and I. C. Paul, *ibid.*, p. 952; F. Leung and S. C. Nyburg, *Canad. J. Chem.*, 1971, **49**, 167.

¹⁴ S. Gottlicher and G. Habermehl, *Chem. Ber.*, 1971, **104**, 524.

¹⁵ J. D. Dunitz and E. F. Meyer, *Helv. Chim. Acta*, 1971, **54**, 77.

¹⁶ H. R. Harrison, O. J. R. Hodder, and D. C. Hodgkin, *J. Chem. Soc. (B)*, 1971, 640.

¹⁷ D. D. Shillady, F. P. Billingsley, and J. E. Bloor, *Theor. Chim. Acta*, 1971, **21**, 1.

¹⁸ M. H. Palmer and A. J. Gaskell, *Theor. Chim. Acta*, 1971, **23**, 52; P. Siegbahn, *Chem. Phys. Letters*, 1971, **8**, 245.

¹⁹ D. T. Clark and D. M. J. Lilley, *Chem. Phys. Letters*, 1971, **9**, 234.

²⁰ M. Hackmeyer and J. H. Whitten, *J. Chem. Phys.*, 1971, **54**, 3739.

²¹ 'Quantum Aspects of Heterocyclic Compounds in Chemistry and Biochemistry,' ed. E. D. Bergmann and B. Pullman, Israel Academy of Sciences and Humanities, Academic Press, New York, 1970, vol. 2.

²² W. Jakubetz and P. Schuster, *Tetrahedron*, 1971, **27**, 101.

²³ R. C. Benson, C. L. Norris, W. H. Flygare, and P. Beak, *J. Amer. Chem. Soc.*, 1971, **93**, 5591.

²⁴ W. Egan, R. Tang, G. Zon, and K. Mislow, *J. Amer. Chem. Soc.*, 1971, **93**, 6205.

N.M.R. and Aromaticity.—Careful analysis of the ^1H n.m.r. spectrum of benzo-thiophen shows the similarity to naphthalene and similar diamagnetic ring currents.²⁵ The effects of geometry on coupling constants in five-membered rings have been correlated,²⁶ and two lines are obtained from the correlation of $^3J_{(\text{H,H})}$ with $^2J_{(^{13}\text{C,H})}$, which has been interpreted in terms of an aromatic series and olefinic series.²⁷ The ^{13}C n.m.r. shifts of various 5,6-fused heterocycles with one or more nitrogen atoms and their anions and cations can be correlated reasonably well with those calculated by the CNDO procedure and average excitation energy approach.²⁸ The ^{15}N magnetic resonance of pyridine²⁹ and ^{14}N of both pyridine and other azines³⁰ have been obtained; the ^{14}N shifts show a nearly linear correlation with calculated π -electron density, but this may be an oversimplification, since for *N*-methylpyridinium salts other effects dominate the ^{14}N shifts.³¹ An extensive survey of the ^1H chemical shifts of azines, their *N*-oxides, and protonated species has been given.³² The site of substituents in monocyclic heteroaromatics is usually fairly unambiguous, but extensive compilations of coupling constants which may be useful in this respect have been given for pyridines³³ and chloromethylthiophens;³⁴ the former set have been correlated with CNDO calculated values. Interaction of pyridine³⁵ and pyrazine³⁶ with silyl chlorides leads to the dihydro-derivatives (7) and (8), neither of which is stable to air or, from the ^1H n.m.r. evidence, aromatic. In contrast, the long-awaited synthesis of isobenzofuran (9), by pyrolysis of two Diels–Alder adducts (10) and (11),³⁷ shows this compound to have ^1H chemical shifts (those in CDCl_3 shown) consistent with a diamagnetic ring current and hence aromaticity [*cf.* (12)].



(7) $\text{X} = \text{SiCl}_3$, $\text{Y} = \text{CHSiCl}_3$

(8) $\text{X} = \text{Y} = \text{NSiMe}_3$

²⁵ K. D. Bartle, D. W. Jones, and R. S. Matthews, *Tetrahedron*, 1971, **27**, 5177.

²⁶ R. J. Abraham, K. Parry, and W. A. Thomas, *J. Chem. Soc. (B)*, 1971, 446.

²⁷ D. M. McKinnon and T. Schaefer, *Canad. J. Chem.*, 1971, **49**, 89.

²⁸ R. J. Pugmire, M. J. Robins, D. M. Grant, and R. K. Robins, *J. Amer. Chem. Soc.*, 1971, **93**, 1887; R. J. Pugmire and D. M. Grant, *ibid.*, p. 1880.

²⁹ R. L. Lichter and J. D. Roberts, *J. Amer. Chem. Soc.*, 1971, **93**, 5218.

³⁰ M. Witanowski, L. Stefanik, H. Januszewski, and G. A. Webb, *Tetrahedron*, 1971, **27**, 3129.

³¹ F. W. Wehrli, W. Giger, and W. Simon, *Helv. Chim. Acta*, 1971, **54**, 229; W. Giger, P. Schauwecker, and W. Simon, *ibid.*, p. 2488.

³² P. Hamm and W. von Philipsborn, *Helv. Chim. Acta*, 1971, **54**, 2363.

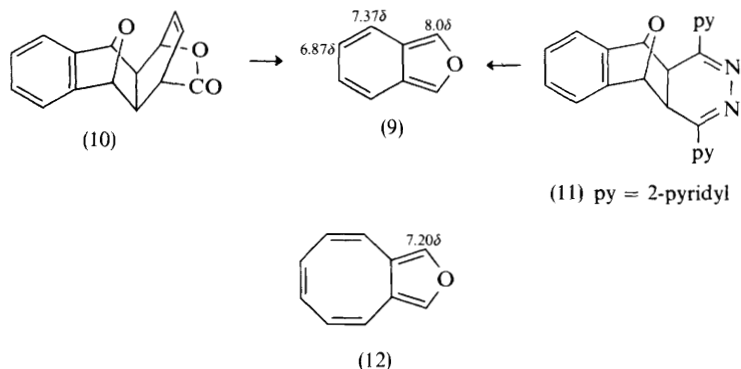
³³ J. P. Dore, M. L. Martin, S. Barnier, and M. Blain, *Org. Magn. Resonance*, 1971, **3**, 661.

³⁴ T. Sone and K. Takahashi, *Org. Magn. Resonance*, 1971, **3**, 527.

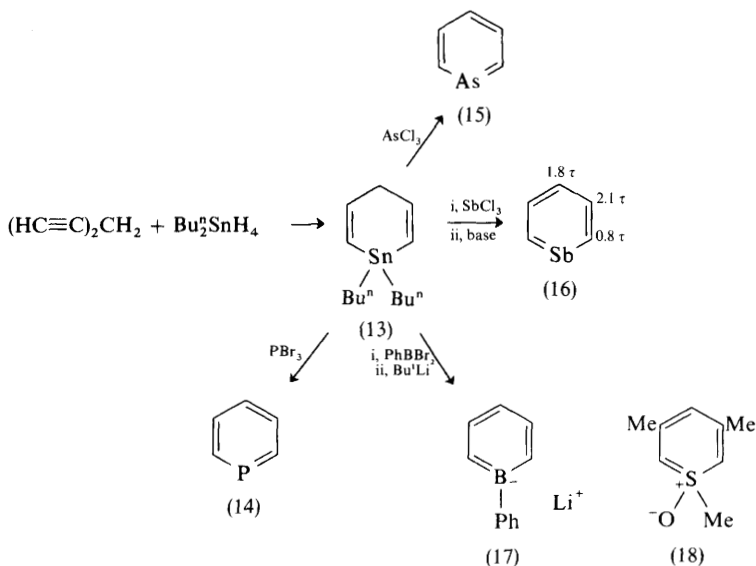
³⁵ D. Kummer and H. Koster, *Angew. Chem. Internat. Edn.*, 1971, **10**, 412.

³⁶ R. A. Sulzbach and A. F. M. Iqbal, *Angew. Chem. Internat. Edn.*, 1971, **10**, 127.

³⁷ D. Wege, *Tetrahedron Letters*, 1971, 2337; R. N. Warrener, *J. Amer. Chem. Soc.*, 1971, **93**, 2346.



The year 1971 has seen the synthesis of several other interesting ring systems. Selenium dioxide oxidation of semicarbazones gives 1,2,3-selenadiazoles,³⁸ the parent compound of which has 4-H and 5-H chemical shifts (neat liquid) at 6.66 and 7.47 δ , respectively. The Group Vb homologues of pyridine, phosphazene (14), arsa- (15), and stiba-benzenes (16), have all been prepared from 1,1-di-n-butyl-1,4-dihydrostannabenzene (13);³⁹ full details of the proton resonance have not been given, but all absorb in the 'aromatic region'. The α -protons at lowest field are well separated from the others, and have progressively higher values of the coupling constant $J_{(2,3)}$. The same starting material (13) yields

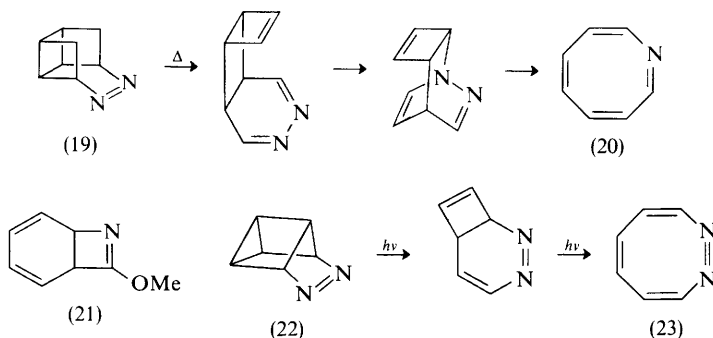


³⁸ I. Lalezari, A. Shafiee, and M. Yalpani, *J. Org. Chem.*, 1971, **36**, 2836.

³⁹ A. J. Ashe, *J. Amer. Chem. Soc.*, 1971, **93**, 3293, 6690.

the 1-phenylborabenzene anion (17).⁴⁰ This compound shows the heterocyclic protons at 3.05 τ (2,6-H), 2.6 τ (3,5-H), and 3.66 τ (4-H), which, considering that there must be some electron donation from the boron atom (*i.e.* an upfield shift), is strongly indicative of a diamagnetic ring current. The proton resonance of the ring protons in thiabenzene 1-oxide (18) is at very high field,⁴¹ and the corresponding ¹³C shifts (109, 50, and 89 p.p.m. from CS₂ for α -, β -, and γ -carbon, respectively) are also at very high field compared with those of benzene (65 p.p.m.) or thiophene (68 and 66 p.p.m.). The proton coupling $J_{(2,6)} = 4.4$ Hz must be one of the highest *meta* constants in proton resonance.

Coupling of two thiapyrylium ions *via* the radical, followed by oxidation, yields the 4,4'-bisthiapyrylium salts whose proton resonance lies only slightly downfield of that of the monocation.⁴² Azocine (20), prepared by vacuum pyrolysis of diazabasketene (19),⁴³ resinifies above -50°C , but the 2-methoxy-derivatives are rather more stable.⁴⁴ The latter have invariant ¹H n.m.r. spectra from -75 to $+185^\circ\text{C}$, and show no evidence of the bicyclic system (21), except in their reactivity. U.v. irradiation of the tetracyclo-compound (22) gives the 1,2-diazocine (23), which shows singlets at 6.08 and 6.93 δ (4:2 ratio).⁴⁵ As expected, none of these 8 π -electron rings show diamagnetic ring currents. Although this is also the case with the 10 or 14 π -electron benzo-derivatives (24)⁴⁶ and (25),⁴⁷ the 2-methoxydiazocine dianion, obtained by reduction with potassium in THF, absorbs downfield of the neutral compound, rather than upfield as might have been expected from the negative charge. This does appear to be evidence of a diamagnetic ring current.⁴⁸



⁴⁰ A. J. Ashe and P. Shu, *J. Amer. Chem. Soc.*, 1971, **93**, 1804.

⁴¹ A. G. Hortmann and R. L. Harris, *J. Amer. Chem. Soc.*, 1971, **93**, 2471.

⁴² Z. Yoshida, S. Yoneda, T. Sugimoto, and O. Kikukawa, *Tetrahedron Letters*, 1971, 3999.

⁴³ D. W. McNeil, M. C. Kent, E. Hedaya, P. F. D'Angelo, and P. O. Schissel, *J. Amer. Chem. Soc.*, 1971, **93**, 3817.

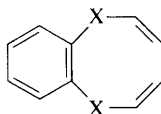
⁴⁴ L. A. Paquette, T. Kakihana, J. F. Hansen, and J. C. Phillips, *J. Amer. Chem. Soc.*, 1971, **93**, 152.

⁴⁵ B. M. Trost and R. M. Cory, *J. Amer. Chem. Soc.*, 1971, **93**, 5573.

⁴⁶ H. J. Shue and F. W. Fowler, *Tetrahedron Letters*, 1971, 2437.

⁴⁷ D. L. Coffen, Y. C. Poon, and M. L. Lee, *J. Amer. Chem. Soc.*, 1971, **93**, 4627.

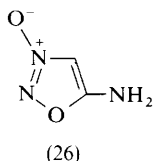
⁴⁸ L. A. Paquette, J. F. Hansen, and T. Kakihana, *J. Amer. Chem. Soc.*, 1971, **93**, 168.



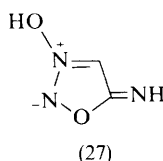
(24) X = NMe

(25) X = S

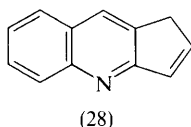
Tautomeric Equilibria and Conformations.—A distinction can be made by n.m.r. between the spectra of the *7H*- and *9H*-tautomers of xanthenes, and the 1- and 3-methyl derivatives appear to be the *7H*-tautomers.⁴⁹ The protonation of purines⁵¹ and of *N*-methylcarbazole⁵⁰ has been studied by n.m.r. A similar study of the tautomerism of 'dihydroxythiophens' shows the 2,3-, 2,4-, and 3,4-series to be the 3-hydroxy- and 4-hydroxy-3-thiolen-2-ones, and 3-hydroxy-2-thiolen-4-ones, respectively.⁵² The 4-hydroxyisoxazole tautomer is preferred over the cyclic oxime form.⁵³ The nitrosation of hydroxyaminoacetonitriles yields cyclic compounds which are better represented as 5-amino-1,2,3-oxadiazole *N*-oxides (26) rather than the sydnoneimine (27), since in contrast to the latter they do not form salts with acid.⁵⁴ Although largely in the *1H*- (28) and *3H*-forms, the purple colour of cyclopenta[*b*]quinoline arises from the estimated 0.1 % of the *4H*-tautomer (29).⁵⁵



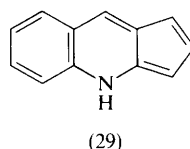
(26)



(27)



(28)



(29)

Various groups have studied the conformation of furan, pyrrole, and thiophen aldehydes and ketones by n.m.r. spectra. The nuclear Overhauser effect,⁵⁶

⁴⁹ D. Lichtenberg, F. Bergmann, and Z. Niemann, *J. Chem. Soc. (C)*, 1971, 1676.

⁵⁰ H. J. Chen, L. E. Hakka, R. L. Hinman, A. J. Kresge, and E. B. Whipple, *J. Amer. Chem. Soc.*, 1971, **93**, 5102.

⁵¹ R. Wagner and W. von Philipsborn, *Helv. Chim. Acta*, 1971, **54**, 1543.

⁵² J. Z. Mortensen, B. Hedegaard, and S. O. Lawesson, *Tetrahedron*, 1971, **27**, 3839.

⁵³ G. Bianchi, M. J. Cook, and A. R. Katritzky, *Tetrahedron*, 1971, **27**, 6133.

⁵⁴ M. Gotz and K. Grozinger, *Tetrahedron* 1971, **27**, 4449.

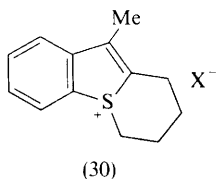
⁵⁵ J. J. Eisch and F. J. Gadek, *J. Org. Chem.*, 1971, **37**, 2065.

⁵⁶ S. Combrisson, B. Roques, P. Rigny, and J. J. Basselier, *Canad. J. Chem.*, 1971, **49**, 904; B. Roques, C. Jaurequeberry, M. C. Fournie-Zaluski, and S. Combrisson, *Tetrahedron Letters*, 1971, 2693.

long-range coupling,⁵⁷ and low-temperature studies⁵⁸ are valuable here. An attempt to use nematic-phase measurements, normally good for measuring inter-proton distances, *e.g.* for thiophen,⁵⁹ was successful with a thiophen dialdehyde but not for the furan analogue,⁶⁰ where a negative distance was calculated between two hydrogen atoms!

2 Quaternary Salts and *N*-Oxides

Alkylation of a range of 2-(4-dimethylaminophenyl)pyridines often leads to kinetically controlled attack on the exocyclic nitrogen, but the thermodynamically favoured products are quaternary salts.⁶¹ A similar thermal reversal occurs with 5-phenyltetrazoles, where the quaternary salts are only stable at low temperatures.⁶² The relative rates of methylation at N-4 of 2-substituted-pyrazines and 3-substituted-pyridines are constant.⁶³ The electron densities at N-1 and N-2 in cinnolines are equal, and the proportion of methylated compounds is controlled by steric effects;⁶⁴ there have been further studies of the methylation of cinnolin-4-ones.⁶⁵ An unusual cycloalkylation is the formation of (30) from 2-(4-iodobutyl)-3-methylbenzothiophen.⁶⁶ The *N*-oxide of pentachloropyridine,



where the basicity is low, can be prepared from the azine by treatment with peracetic acid mixture in the presence of concentrated sulphuric acid; apparently the peracid is protonated and hence more reactive.⁶⁷ The differential solvent-induced n.m.r. shifts can be used to determine the site of *N*-oxidation in substituted pyrazines;⁶⁸ 3-methoxy- and 3-unsubstituted-1,2,4-triazines give 1-oxides, whereas the 3-amino-compounds give 2-oxides.⁶⁹

⁵⁷ B. Roques and M. C. Fournie-Zaluski, *Org. Magn. Resonance*, 1971, **3**, 305.

⁵⁸ K.-I. Dahlqvist and A.-B. Hornfeldt, *Tetrahedron Letters*, 1971, 3837.

⁵⁹ J.-M. Dereppe, J.-P. Morisse, and M. van Meerssche, *Org. Magn. Resonance*, 1971, **3**, 583.

⁶⁰ T. N. Huckley, *Tetrahedron Letters*, 1971, 3497.

⁶¹ G. Y. Paris, D. L. Garmaise, and J. Komlossy, *J. Heterocyclic Chem.*, 1971, **8**, 169.

⁶² T. Isida, S. Kozima, K. Nabika, and K. Sisido, *J. Org. Chem.*, 1971, **36**, 3807.

⁶³ L. W. Deady and J. A. Zoltewicz, *J. Amer. Chem. Soc.*, 1971, **93**, 5475.

⁶⁴ M. H. Palmer and P. S. McIntyre, *Tetrahedron*, 1971, **27**, 2913, 2921.

⁶⁵ D. E. Ames, H. R. Ansari, A. D. G. France, A. C. Lovesey, B. Novitt, and R. Simpson, *J. Chem. Soc. (C)*, 1971, 3088.

⁶⁶ J. A. Cotruvo and I. Degani, *Chem. Comm.*, 1971, 436.

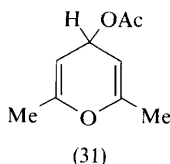
⁶⁷ G. E. Chivers and H. Suschitzky, *J. Chem. Soc. (C)*, 1971, 2867.

⁶⁸ W. W. Paudler and S. A. Humphrey, *Org. Magn. Resonance*, 1971, **3**, 217.

⁶⁹ W. W. Paudler and T. K. Chen, *J. Org. Chem.*, 1971, **36**, 787.

3 Aromatic Substitution

Hydrogen–deuterium exchange using deuterioacetic acid occurs in the 2-methyl and 3-positions of 2,6-di-methylpyrylium salts, but not in the 4-position. This is ascribed to formation of the acetate (31) and ring-opened species.⁷⁰ The partial rate factors for nitration of 4-phenylpyridine show all positions to be strongly



deactivated with respect to benzene; this is largely a field effect.⁷¹ The rates of nitration in quinoline, quinolin-4-one, and cinnolin-4-one have been determined.⁷² The hydrogen–deuterium exchange in quinoline, isoquinoline, and their *N*-oxides takes place on the protonated molecules except for the 2-H and 3-H of quinoline.⁷³

The rates of exchange in deuterioacetic acid for both the 2- and 3-positions of *N*-methylpyrrole are higher than for the parent ring, but the effect is most marked at the 2-position.⁷⁴ The partial rate factors for acetylation of furan (F) and thiophen (T) have been obtained; furan is more selective at the α -position,⁷⁵ and comparison with the corresponding benzo-derivatives (BF/BT) leads to the following order of reactivity: $\alpha\text{-F} \gg \alpha\text{-T} \gg \alpha\text{-BF} \approx \beta\text{-BT} > \alpha\text{-BT} \approx \beta\text{-BF} > \beta\text{-F} \approx \beta\text{-T}$.⁷⁶ The rates of both H–D exchange and nitration in 3,5-dimethylisoxazole, -isothiazole, and 1,3,5-trimethylpyrazole show that the first of these reacts as the free base and the others as the conjugate acid.⁷⁷ The rates of H–D exchange in the ring positions of various azaindenes correlate well with SCF π -electron calculations, but apparently not with the corresponding π -localization energies; further studies of the latter type which include all valence electrons seem desirable.⁷⁸

Reduction of pyridines with lithium aluminium hydride followed by direct treatment of the reduced salt with alkyl halide or bromine gives 3-substituted-pyridines in high yield.⁷⁹ Oxidation of 3-substituted-*N*-methyl quaternary salts by ferricyanide gives more of the 6- than the 2-pyridinone when the substituent

⁷⁰ D. Farcasiu, A. Vasilescu, and A. T. Balaban, *Tetrahedron*, 1971, **27**, 681.

⁷¹ F. De Sarbo and J. H. Ridd, *J. Chem. Soc. (B)*, 1971, 712.

⁷² D. H. G. Crout, J. R. Penton, and K. Schofield, *J. Chem. Soc. (B)*, 1971, 1254; R. B. Moodie, J. R. Penton, and K. Schofield, *ibid.*, p. 1493.

⁷³ U. Bressel, A. R. Katritzky, and J. R. Lea, *J. Chem. Soc. (B)*, 1971, **4**, 11.

⁷⁴ G. P. Bean, *Chem. Comm.*, 1971, 421.

⁷⁵ G. Ciranni and S. Clementi, *Tetrahedron Letters*, 1971, 3833; S. Clementi, P. Linda, and M. Vergoni, *Tetrahedron*, 1971, **27**, 4667.

⁷⁶ S. Clementi, P. Linda, and G. Marino, *J. Chem. Soc. (B)*, 1971, 79.

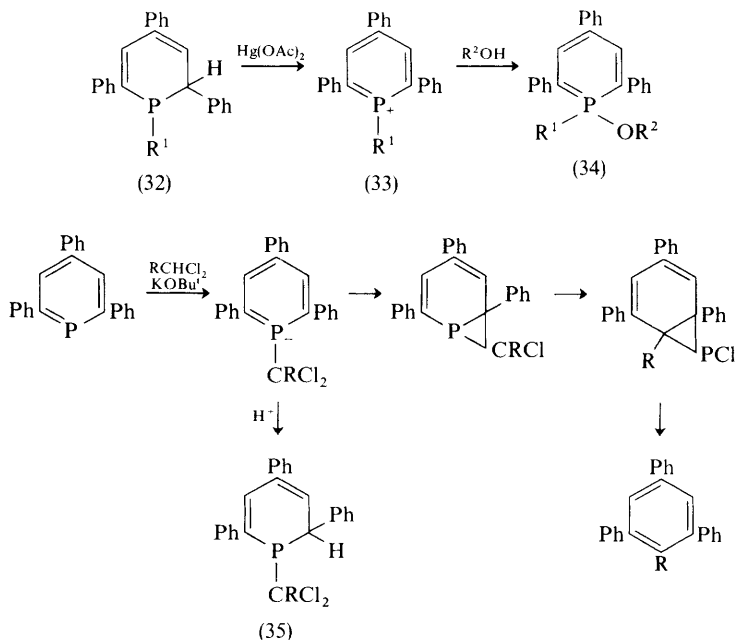
⁷⁷ A. G. Burton, P. P. Forsythe, C. D. Johnson, and A. R. Katritzky, *J. Chem. Soc. (B)*, 1971, 2365.

⁷⁸ W. Engewald, M. Muhlstadt, and C. Weiss, *Tetrahedron*, 1971, **27**, 851, 4171.

⁷⁹ C. S. Giam and S. D. Abbott, *J. Amer. Chem. Soc.*, 1971, **93**, 1294.

is electron withdrawing.⁸⁰ It seems that the rate-determining step in these reactions is formation of the ferricyanide complex rather than cleavage of the C—H bond.⁸¹ Direct alkylation of pyridine with an alkyl-lithium gives high yields of 2- and 2,6-substituted compounds, even with *t*-butyl-lithium.⁸² The product from pyridine *N*-oxide and Grignard reagents is apparently acyclic.⁸³

Addition of lithium alkyls to 2,4,6-triphenylphosphabenzene gives 1,2-dihydro-derivatives (32), which on oxidation lead to the quaternary salts (33) and then the 1-alkyl-1-alkoxyphosphabenzenes (34) on treatment with alcohols.⁸⁴ *gem*-Dihalides and base give benzene derivatives *via* a 1,2-addition sequence (Scheme 1), which can be interrupted to yield (35) by the addition of an acid.⁸⁵ 1-Substituted-phospholes lose the substituent on treatment with alkali metals; the solutions give e.s.r. signals from the intermediate radical-anion; re-alkylation is readily achieved.⁸⁶



Scheme 1

⁸⁰ H. Mohrle and H. Weber, *Chem. Ber.*, 1971, **104**, 1478.

⁸¹ R. A. Abramovitch and A. R. Vinutha, *J. Chem. Soc., (B)*, 1971, 131.

⁸² R. F. Francis, J. T. Wisener, and J. M. Paul, *Chem. Comm.*, 1971, 1420; F. V. Scalzi and N. F. Golob, *J. Org. Chem.*, 1971, **36**, 2541.

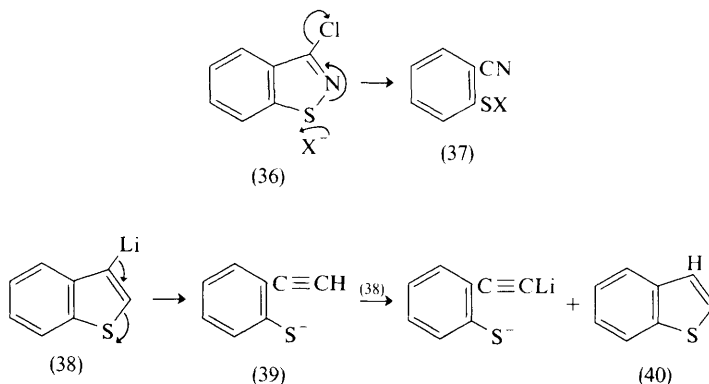
⁸³ T. J. van Bergen and R. M. Kellog, *J. Org. Chem.*, 1971, **36**, 1705.

⁸⁴ G. Märkl and A. Merz, *Tetrahedron Letters*, 1971, 1215; G. Märkl, A. Merz, and H. Rausch, *ibid.*, p. 2989.

⁸⁵ G. Märkl and A. Merz, *Tetrahedron Letters*, 1971, 1269.

⁸⁶ D. Kilcast and C. Thomson, *Tetrahedron*, 1971, **27**, 5705; E. H. Bray, I. Caplier, and R. Saussez, *ibid.*, p. 5523.

Although 3-chloro-1,2-benzisothiazole reacts normally with ethanolic sodium ethoxide, with sodium cyanide in acetone (or carbanions) the reaction yields aryl thiocyanates (37) (or sulphides) by attack on sulphur (36).⁸⁷ There is some similarity in the spontaneous cleavage of 3-lithiobenzo[*b*]thiophen and the metal–hydrogen exchange accompanying it⁸⁸ [(38)–(40)], or the spontaneous cleavage of 5-lithio-1-methyltetrazole to methyl cyanamide.⁸⁹



The rates of displacement of a fluorine atom are greater than those of chlorine for a variety of displacements by methoxide ion or piperidine.⁹⁰ Thus, in benzo-1,2,3-thiadiazoles, although the 6-position is normally the most reactive, fluorine in other positions is selectively replaced rather than a 6-chloro-substituent.⁹¹ The positional order of reactivity of halogenothiazoles to methoxide ions is $5 > 2 > 4$, but with a rate range of 30. The 4- or 5-reactivity does not involve hetarynes since the 5-phenyl-4-chloro-compound has similar reactivity to the compounds without a substituent.⁹² The chemistry of hetarynes has been reviewed,⁹³ and there has been further discussion of their significance in reactions of halogenopyridines.⁹⁴ 3-Bromothiophenes can be conveniently prepared from the 2-bromo-compound by rearrangement in the presence of potassium amide.⁹⁵ Benzyne adds across the 1,4-positions of phosphabenzene.⁹⁶

Further replacements of fluorine in perfluoroheteroaromatics have been reported; the order of reactivity for α -substitution by hydrogen chloride in

⁸⁷ D. E. L. Carrington, K. Clarke, and R. M. Scowston, *J. Chem. Soc.*, (C), 1971, 3262, 3903.

⁸⁸ R. P. Dickenson and B. Iddon, *J. Chem. Soc.* (C), 1971, 3447.

⁸⁹ R. Raap, *Canad. J. Chem.*, 1971, **49**, 2139.

⁹⁰ G. B. Bressaw, I. Giardi, G. Illuminati, P. Linda, and G. Sleiter, *J. Chem. Soc.* (B), 1971, 225.

⁹¹ J. H. Davies, E. Haddock, P. Kirby, and S. B. Webb, *J. Chem. Soc.* (C), 1971, 2843.

⁹² M. Bosco, L. Forlani, P. E. Todesco, and L. Troisi, *Chem. Comm.*, 1971, 1093.

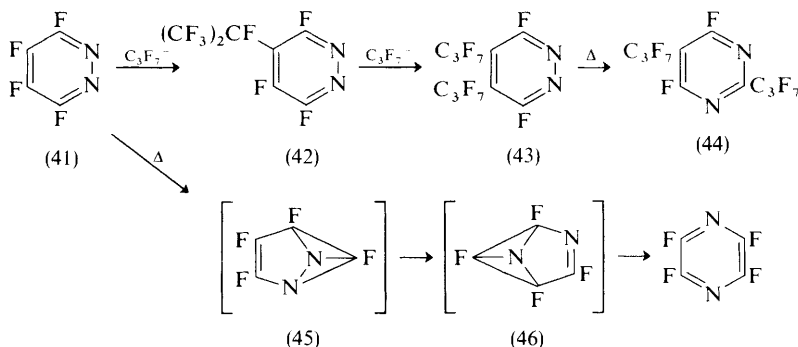
⁹³ T. Kauffman and R. Wirthwein, *Angew. Chem. Internat. Edn.*, 1971, **10**, 20.

⁹⁴ H. N. M. van der Lans, H. J. den Hertog, and A. van Veldhuizen, *Tetrahedron Letters*, 1971, 1875; J. A. Zoltewicz and A. A. Sale, *J. Org. Chem.*, 1971, **36**, 1455.

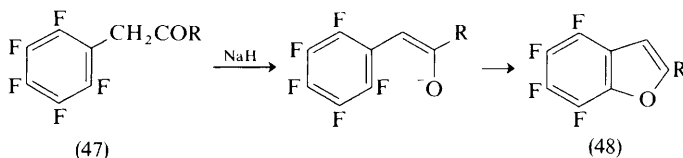
⁹⁵ M. G. Reinecke, H. W. Adickes, and C. Pyun, *J. Org. Chem.*, 1971, **36**, 2690.

⁹⁶ G. Märkl, F. Lieb, and C. Martin, *Tetrahedron Letters*, 1971, 1249.

sulpholane is quinoline \gg isoquinoline $>$ pyridine.⁹⁷ The reaction of hexafluoropropene with fluorides and tetrafluoro-pyridazine or -pyrimidine leads to 4,5- or 4,6-substitution respectively; the perfluoropropyl group is better able to absorb the resulting negative charge at the addition stage than the nitrogen atoms.⁹⁸ Brief treatment of these perfluorinated aromatics at 580 °C or above leads to rearrangement⁹⁹ of the pyridazines to the pyrimidines (44) plus a smaller amount of the corresponding pyrazines (Scheme 2). These changes are interpreted in terms of the diazabenzvalene derivatives (45) and (46). An unusual type of cyclization with elimination of a fluoride ion is given in (47) \rightarrow (48).¹⁰⁰



Scheme 2



4 Oxidation Reactions

Examples of anodic oxidation applied to furans and thiophenes in the presence of various nucleophiles have been given, for example (49) \rightarrow (50) where $X = O$ or S .¹⁰¹ Perylum and thiapyrylium ions and furans¹⁰² react in the triplet

⁹⁷ R. D. Chambers, M. Hole, W. K. R. Musgrave, and J. G. Thorpe, *J. Chem. Soc.*, (C), 1971, 61.

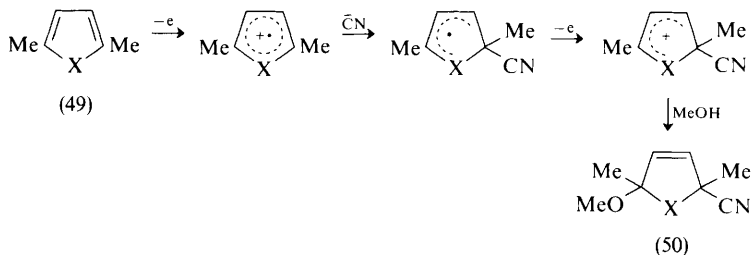
⁹⁸ R. D. Chambers, Y. A. Cheburkov, J. A. H. MacBride, and W. K. R. Musgrave, *J. Chem. Soc.* (C), 1971, 532; C. J. Drayton, W. T. Flowers, and R. N. Haszeldine, *ibid.*, p. 2750.

⁹⁹ R. D. Chambers, J. A. H. MacBride, and W. K. R. Musgrave, *J. Chem. Soc.* (C), 1971, 3384.

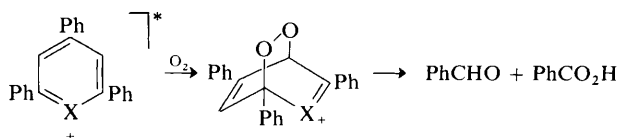
¹⁰⁰ G. M. Brook, W. K. R. Musgrave, and T. R. Thomas, *J. Chem. Soc.* (C), 1971, 3596.

¹⁰¹ K. Yoshida and T. Fueno, *J. Org. Chem.*, 1971, **36**, 1523; K. Yoshida, T. Saeki, and T. Fueno, *ibid.*, p. 3673.

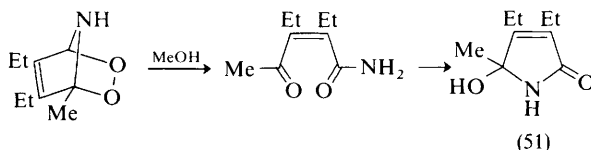
¹⁰² T. Tsuchiya, H. Arai, and H. Igeta, *Tetrahedron Letters*, 1971, 2579.



excited state with ground-state oxygen (Scheme 3), but their ground-state molecules do not react with singlet excited oxygen,¹⁰³ a result showing the electrophilic nature of singlet oxygen. Conversely, pyrroles¹⁰⁴ do react with singlet oxygen, giving various products, *e.g.* (51).



Scheme 3



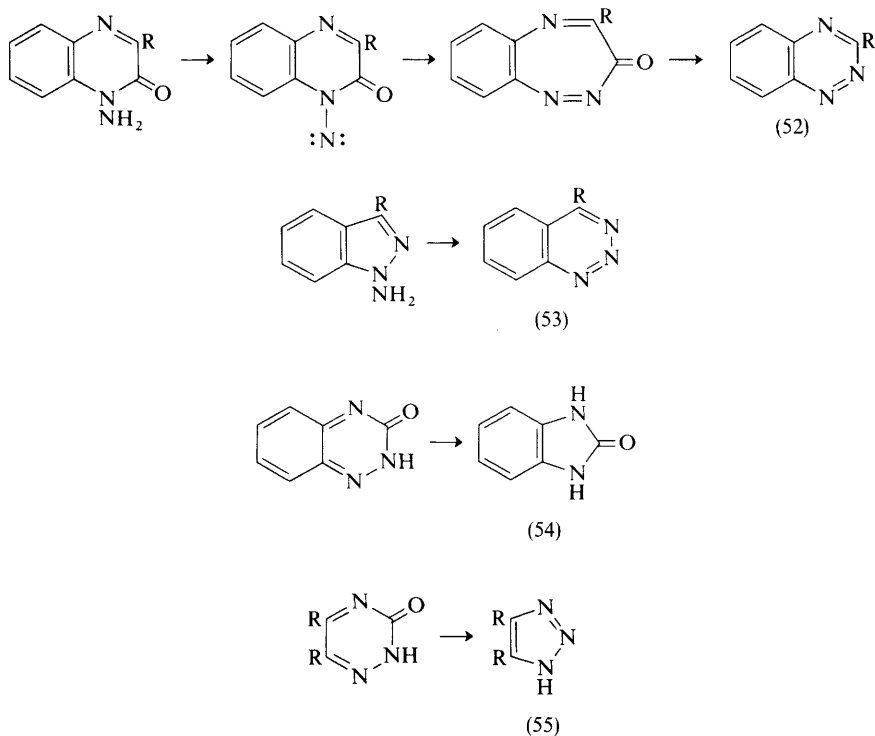
In an important series of publications, Rees has described the formation and oxidation of *N*-aminoheterocycles. Reaction of the azine with hydroxylamine-*O*-sulphonic acid or chloramine followed by treatment with lead tetra-acetate gives the nitrene, which forces the loss of an adjacent carbonyl group and recyclization to the 1,2-diaza-system. Thus quinoxalin-2-ones and indazoles give benzo-1,2,4- (52) and -1,2,3-triazines (53), respectively (Scheme 4).¹⁰⁵ The 1,2,4-triazine-3-ones, in contrast, failed to give observable *N*-amino-derivatives, but gave the ring-contracted species (54) and (55).¹⁰⁶ The cinnolin-3-one and benzo-triazin-4-ones gave normal *N*-amino-derivatives, which on oxidation yielded nitrogen and ring-contracted products; the latter series showed intermediate

¹⁰³ Z. Yoshida, T. Sugimoto, and S. Yoneda, *Tetrahedron Letters*, 1971, 4259.

¹⁰⁴ G. B. Quistad and D. A. Lightner, *Tetrahedron Letters*, 1971, 4417; *Chem. Comm.*, 1971, 1099.

¹⁰⁵ B. Adger, C. W. Rees, A. A. Sale, and R. C. Storr, *Chem. Comm.*, 1971, 695; D. J. C. Adams, S. Broadbury, D. C. Howell, M. Keating, C. W. Rees, and R. C. Storr, *ibid.*, p. 828.

¹⁰⁶ C. W. Rees and A. A. Sale, *Chem. Comm.*, 1971, (a), 531, (b) 532.



Scheme 4

formation of benzocyclopropanone.^{106b,107} In a related reaction, oxidation of arylhydrazones gave the nitrile rather than the diazoalkane or *sym*-tetrazine.¹⁰⁸ Other amine oxidations lead to benzo[*c*]cinnoline-*N*-imine¹⁰⁹ and benzo-1,2,3-triazines¹¹⁰ from 2,2'-diaminobiphenyl and *o*-aminophenyl ketone hydrazones. In contrast, the oxidation of 1-aminoimidazo[1,2-*a*]pyridinium ions gave the corresponding azo-compound, perhaps showing the electrophilic nature of the nitrene.¹¹¹

5 Reduction

The only processes calling for comment are the polarographic reduction¹¹² of 2-methoxyazocines directly to the dianion without evidence of the intermediate

¹⁰⁷ J. Adamson, D. L. Forster, T. L. Gilchrist, and C. W. Rees, *J. Chem. Soc. (C)*, 1971, 981.

¹⁰⁸ D. B. Mobbs and H. Suschitzky, *Tetrahedron Letters*, 1971, 361.

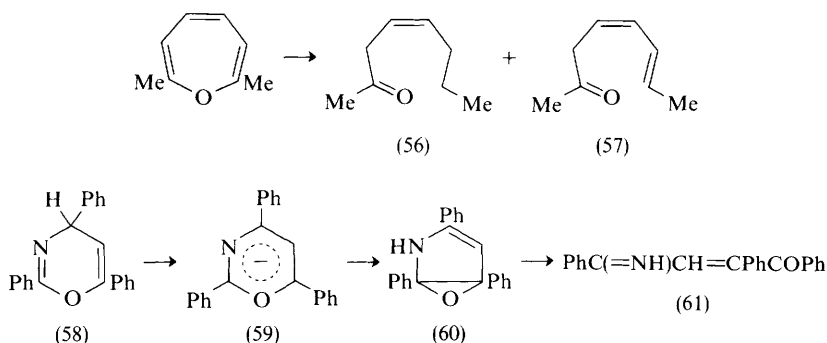
¹⁰⁹ S. E. Gail, C. W. Rees, and R. C. Storr, *Chem. Comm.*, 1971, 1545.

¹¹⁰ S. Bradbury, M. Keating, C. W. Rees, and R. C. Storr, *Chem. Comm.*, 1971, 827.

¹¹¹ E. E. Glover and M. Yorke, *J. Chem. Soc. (C)*, 1971, 3280.

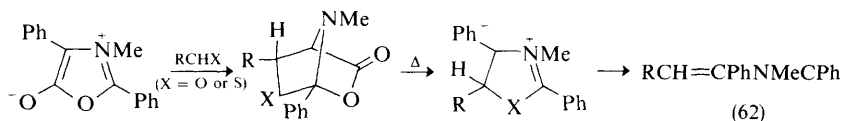
¹¹² L. B. Anderson, J. F. Hansen, T. Kakihana, and L. A. Paquette, *J. Amer. Chem. Soc.*, 1971, **93**, 161.

radical-anion, a contrast to cyclo-octatetraene where the two stages are visible. This is interpreted as the first electron addition yielding a planar ring which is much more readily reduced (to a 10π -electron system) than the neutral compound. In Hückel terms the lowest vacant orbital of oxepin is antibonding, and this correlates with the observation that the alkali-metal reduction of the 2,7-dimethyl compound leads to ring opening, giving (56) and (57).¹¹³ In a similar way, reaction of the 4*H*-1,3-oxazine (58) with butyl-lithium yields an 8π -electron ring which rearranges to yield (60) and (61) *via* the identified species (59).¹¹⁴



6 Photochemical Reactions and Valency Isomerism

Photolysis of various mesoionic compounds related to the sydnone gives carbon dioxide and a three-atom fragment from the ring which can be trapped by acetylene dicarboxylic esters. Thus 3-arylsydnone gives pyrazoles,¹¹⁵ *via* the nitrilimine, and 4-aryl-1,3,2-oxathiazolinium 5-oxides yield isothiazoles *via* the nitrile sulphide.¹¹⁶ A thermal reaction on the addition product of aldehydes or thioaldehydes to oxazolium 5-oxides also leads to loss of carbon dioxide (Scheme 5) and the formation of open-chain compounds (62).¹¹⁷



Scheme 5

¹¹³ L. A. Paquette and T. McCreadie, *J. Org. Chem.*, 1971, **36**, 1402.

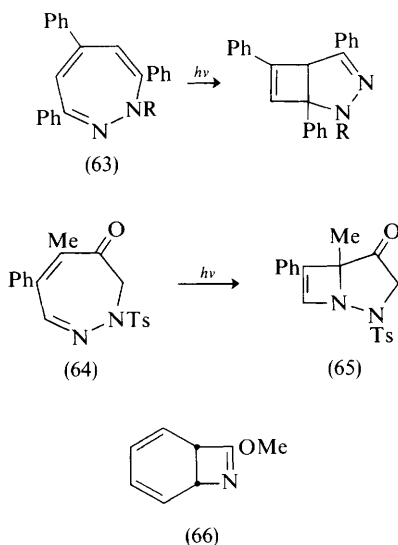
¹¹⁴ R. R. Schmidt, *Angew. Chem. Internat. Edn.*, 1971, **10**, 572.

¹¹⁵ H. Gotthardt and F. Reiter, *Tetrahedron Letters*, 1971, 2749; M. Marky, H. J. Hansen, and H. Schmidt, *Helv. Chim. Acta*, 1971, **54**, 1275; C. S. Angadiyavar and M. V. George, *J. Org. Chem.*, 1971, **36**, 1589.

¹¹⁶ H. Gotthardt, *Tetrahedron Letters*, 1971, 1277, 1281.

¹¹⁷ R. Huisgen, E. Funke, H. Gotthardt, and H.-L. Panke, *Chem. Ber.*, 1971, **104**, 1532; E. Funke, R. Huisgen, and F. C. Schaefer, *Chem. Ber.*, 1971, **104**, 1550.

Cyclohexa-2,5-dien-1,4-diols can lead to either phenols or oxepins, and suitable substituents such as *t*-butyl can force formation of the latter.¹¹⁸ The synthesis of various oxepins and their Diels–Alder reactions through the benzene oxide form have been described.¹¹⁹ 2,2,2-Trifluoroethanol is claimed to be unique in promoting nitrene (from nitrosobenzene) addition to benzene;¹²⁰ the direction of nitrene insertion in *p*-disubstituted-benzenes is subject to marked steric effects.¹²¹ Carbon–carbon is preferred to nitrogen–carbon bond formation in the photochemical cyclization of 1,2-diazepines (63),¹²² but the latter occurs in the 6-ones (64) to yield (65).¹²³ 2-Methoxyazocines react in the form (66).^{44,124}



The photochemical rearrangement of 2-deuterioquinoline *N*-oxide yields 3-deuterioquinolin-2-one and indolecarbaldehyde derivatives,¹²⁵ whereas the related isotogen rearrangement [(67) \rightarrow (70)] goes *via* epoxide-like intermediates (68) and (69), since ethanol fails to intercept the quinoid intermediate (71).¹²⁶

¹¹⁸ A. Rieker, *Angew. Chem. Internat. Edn.*, 1971, **10**, 425; S. Berger, G. Henes, and A. Rieker, *Tetrahedron Letters*, 1971, 1257.

¹¹⁹ W. Eberbach, M. Perroud-Arguelles, H. Achenbach, E. Drucky, and H. Prinzbach, *Helv. Chim. Acta*, 1971, **54**, 2579.

¹²⁰ R. J. Sundberg and R. H. Smith, *Tetrahedron Letters*, 1971, 267.

¹²¹ J. M. Photis, *J. Heterocyclic Chem.*, 1971, **8**, 167, 729.

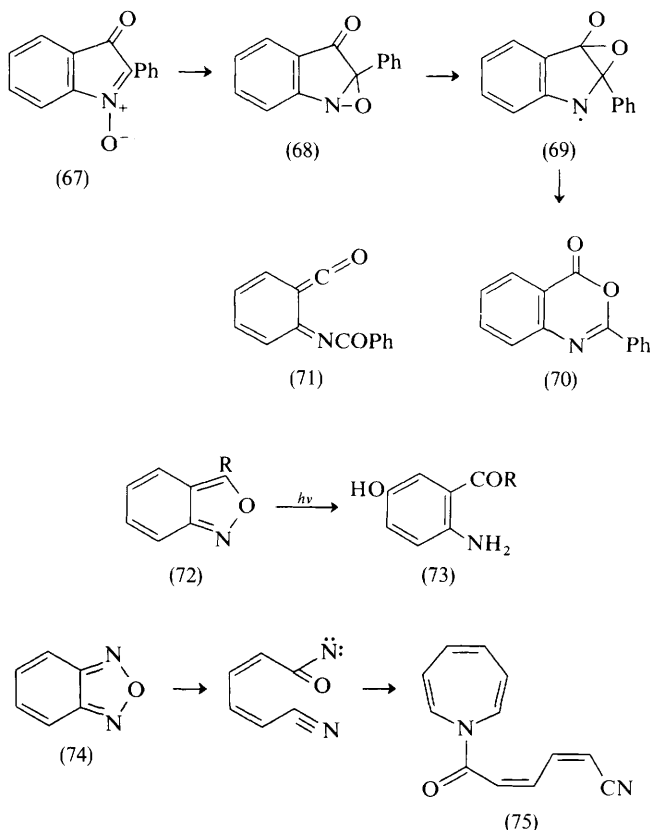
¹²² G. Kan, M. T. Thomas, and V. Snieckus, *Chem. Comm.*, 1971, 1022; J. Streith, J. P. Luttringer, and M. Nastasi, *J. Org. Chem.*, 1971, **36**, 2962.

¹²³ J. A. Moore, E. J. Volker, and C. M. Kopay, *J. Org. Chem.*, 1971, **36**, 2676.

¹²⁴ L. A. Paquette and T. Kakiham, *J. Amer. Chem. Soc.*, 1971, **93**, 174; L. A. Paquette, *Angew. Chem. Internat. Edn.*, 1971, **10**, 11.

¹²⁵ O. Buchardt, K. B. Tomer, and V. Madsen, *Tetrahedron Letters*, 1971, 1311.

¹²⁶ D. R. Eckroth and R. H. Squire, *J. Org. Chem.*, 1971, **36**, 224.



Such intermediates are, however, involved in the cleavage of anthranils (72) to *o*-aminoacetophenones (73),¹²⁷ and furazans (74) to azepines (75).¹²⁸ Whereas an e.s.r. signal is obtained from the aryl nitrene from the photolysis of 2-azidoacetophenone to (76) and (77), under similar conditions no signal is obtained from 3-methylantranil, where only (76) is obtained.¹²⁹ Bicyclic products (78) arising from quinoid species such as (71) have been isolated from other photolytic reactions.¹³⁰ Photochemical hydroxyalkylation of azines continues to be studied,¹³¹ as does the reverse reaction.¹³²

¹²⁷ E. Giovannini, J. Rosales, and B. de Souza, *Helv. Chim. Acta*, 1971, **54**, 2111.

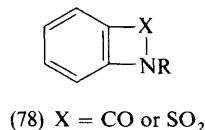
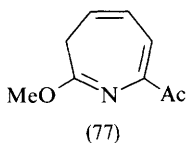
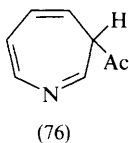
¹²⁸ M. Georgarakis, H. J. Rosenkranz, and H. Schmid, *Helv. Chim. Acta*, 1971, **54**, 819.

¹²⁹ M. A. Berwick, *J. Amer. Chem. Soc.*, 1971, **93**, 5780.

¹³⁰ R. A. Olofson, R. K. Vander Meer, and S. Stournas, *J. Amer. Chem. Soc.*, 1971, **93**, 1543; M. S. Ao and E. M. Burgess, *ibid.*, p. 5298.

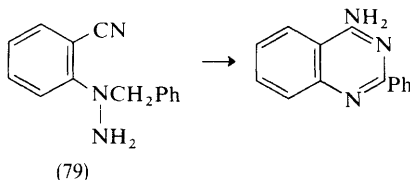
¹³¹ M. Natsume and M. Wada, *Tetrahedron Letters*, 1971, 4503; T. J. Van Bergen and R. M. Kellogg, *J. Org. Chem.*, 1971, **36**, 978; R. A. F. Deeleman, H. C. van der Plas, A. Koudijs, and P. S. Darwinkle-Risseuw, *Tetrahedron Letters*, 1971, 4159.

¹³² D. Elad, I. Rosenthal, J. Saloman, and J. Sperling, *Chem. Comm.*, 1971, 49.



7 Ring Synthesis

As always, there has been extensive work in this field, so any choice must appear arbitrary. Here it is restricted almost entirely to the most common ring systems. The condensation of aldehydes and ammonium salts leads to 1,2-dihydropyridines, not the 2,3-isomers;¹³³ the ready synthesis of 3-aminoacrolein and its conversion into 3-alkylpyridines and pyrimidines has been noted.¹³⁴ Further simple syntheses of 1,2,4-triazines and diaryl-1,3,5-triazinones have been given.¹³⁵ The cyclization of acetals in the Pomeranz–Fritsch isoquinoline synthesis, and in indole synthesis, can be facilitated by the use of boron trifluoride–trifluoroacetic anhydride as catalyst.¹³⁶ The reaction of 2-aminopyridine and β -ketoesters with polyphosphoric acid ethyl ester gives pyrido[1,2-*a*]pyrimidin-4-ones rather than 1,8-naphthyridines.¹³⁷ The group $[\text{Me}_2\text{N}-\text{CR}=\text{CR}-\text{CR}=\text{NMe}_2]^+ \text{X}^-$ can be readily cyclized to pyrimidines by reaction with amidines.¹³⁸ Quinazolines rather than indazoles are obtained from (79).¹³⁹ Two reactions related to the formation of isoxazoles and pyrazoles from dianions are the synthesis of 2-unsubstituted-oxazoles from metallated isonitriles (80)¹⁴⁰ and pyrazoles from trimetallated hydrazones (81).¹⁴¹ High yields of furans are obtained from propargylsulphonium salts and aliphatic ketones.¹⁴² Simple syntheses of 3,2-borazaropyridines (83)¹⁴³ via the thiophenes (82), and 5,1,3,4-boratriazaroles (84)¹⁴⁴ from amidrazones, show these compounds to be fairly stable to air,



¹³³ G. Krow, E. Michener, and K. C. Ramey, *Tetrahedron Letters*, 1971, 3653.

¹³⁴ E. Britmaier, *Angew. Chem. Internat. Edn.*, 1971, **10**, 268; E. Britmaier and S. Gassenmann, *Chem. Ber.*, 1971, **104**, 665.

¹³⁵ T. V. Saraswathi and V. R. Srinivasan, *Tetrahedron Letters*, 1971, 2315; B. Singh and J. C. Collins, *Chem. Comm.*, 1971, 498.

¹³⁶ M. J. Bevis, E. J. Forbes, N. N. Naik, and B. C. Uff, *Tetrahedron*, 1971, **27**, 1253.

¹³⁷ K. Bowden and T. H. Brown, *J. Chem. Soc. (C)*, 1971, 2163.

¹³⁸ R. M. Wagner and C. Jutz, *Chem. Ber.*, 1971, **104**, 2975.

¹³⁹ N. Finch and H. W. Gschwend, *J. Org. Chem.*, 1971, **36**, 1463.

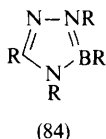
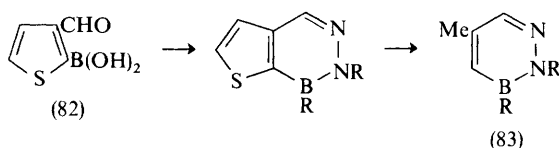
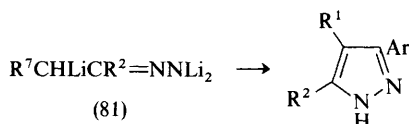
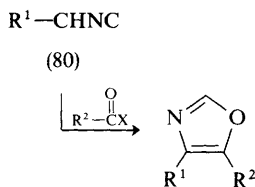
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except for those where R = Me. Among large ring compounds the synthesis of 1,2,5,6,9,12-hexa-aza-¹⁴⁵ and 1,2,4,5,8,9,11,12-octa-aza-[12]annulene¹⁴⁶ derivatives are of interest, and a series of porphin-like molecules containing sulphur and oxygen in place of one or more nitrogen atoms has been described.¹⁴⁷ Ethoxycarbonylnitrene inserts in the *meso*-ring 4,5-bond of porphyrins.¹⁴⁸

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