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Advances in the Chemistry of 1,2-Azoles

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Data obtained during 1960-1977 on the physical, physicochemical, and chemical properties of 1,2-azoles are surveyed. For the first time such data are subjected to comparative discussion to reveal common features and differences in properties. A list of 304 references is included.

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I. INTRODUCTION

1,2-Azoles include pyrazole, isoxazole, and isothiazole. Their derivatives have long found practical application: it is sufficient to mention the medicinal products—antipyretics of the pyrazolone series[1], sulphanilamides, and semi-synthetic penicillins containing the isoxazole ring[2]. During recent years isoxazole derivatives have come to be widely used in organic synthesis to obtain various heterocycles, peptides, steroids, and other naturally occurring compounds[3,4].

The chemistry of each of the 1,2-azoles has been considered in detail in a series of reviews published during the past 15 years—three on pyrazoles[1,5,6], five on isoxazoles[2-4,7,8], and two on the "youngest" class, the isothiazoles[9,10]—but they contain no comparative analysis of the properties of 1,2-azoles. Such comparison has been made in the books by Katritzky and Lagowski[11] and by Paquette[12], although the very condensed treatment results in a fragmentary description, which is accompanied also by inaccuracies and simple errors[12].

The nature of the heteroatom distinguishing one 1,2-azole from another not only determines the character of the bond between this atom and the nitrogen atom, of course, but also influences the properties of the molecule as a whole. The present Review has been written with the aim of revealing common and distinguishing features in the physical and chemical properties of heteroaromatic 1,2-azoles: it contains neither methods of preparation of azoles nor the properties of their hydrogenated derivatives. Considerable difficulties in compiling the Review arose from the need for selection from the ~800 publications on the properties of 1,2-azoles that have by now appeared (Autumn 1977). In order to avoid greatly increasing the length of the Review, references are given to existing reviews and attention is directed to information from publications not mentioned in them, as well as the most important fundamental work that has appeared since 1960.

II. ELECTRONIC STRUCTURE WITH PHYSICAL AND PHYSICOCHEMICAL PROPERTIES

1. Quantum-chemical Calculations and Molecular Geometry

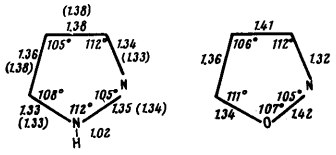
The simple LCAO-MO method has been used in the Hückel approximation to calculate molecular diagrams for pyrazole[13,14], isoxazole[15,16], and isothiazole[17]. The calculations showed that all the 1,2-azoles possess 6π-electron shells, and are therefore heteroaromatic systems. Since different values were used by different workers for the Coulombic and resonance integrals, only qualitative comparison of their molecular diagrams is possible. In all the 1,2-azoles the excess π-electron density is concentrated on the "pyridine" nitrogen and the $C_{(4)}$ atoms, while the second heteroatom bears a positive charge. The π-electron charges on the $C_{(3)}$ and $C_{(5)}$ atoms are either positive or negative depending on the heterocycle and on the parameters α and β. The highest bond orders have been found for the $C_{(3)}-N$ and $C_{(4)}-C_{(5)}$ bonds, and the lowest order for the bond between the heteroatoms. Calculations have also been made by the Pariser–Parr–Pople (PPP)[18,19] and other semi-empirical methods[20]. Especially noteworthy are the calculations which Witanowski et al.[18] made on all three 1,2-azoles by the same method.

More accurate results have been obtained by taking the σ electrons into account[21]. During the 1970s improved methods of calculation, including CNDO/2 have been used to elucidate the electronic structures of pyrazole and isoxazole[22], alkylpyrazoles[23], and phenylisothiazoles[24].

Many experimental characteristics of 1,2-azoles correlate well with quantities calculated by quantum-chemical methods. Thus the LCAO-MO method has yielded values agreeing with experiment for dipole moments[16,25], $\pi \rightarrow \pi^*$ transition frequencies in absorption spectra[14,19], and quadrupole interaction constants in the gas phase[25]. The PPP method gives good results for calculating the first ionisation potential[19] and the π-electron density on the nitrogen atoms[18]; and the CNDO/2 method for determining the total electron density on the "pyridine" nitrogen atom[23] and the carbon atoms[22,26], as follows from determinations of basicity and the hydrogen-1 and carbon-13 chemical shifts. Thus, as for other systems, no single method of quantum chemistry can be recommended for predicting all experimental results.

The literature contains much information on bond lengths and angles in the pyrazole ring, less on the parameters of the isoxazole ring, and hardly any on those of the isothiazole ring[280]. Such data have usually been obtained by X-ray diffraction[27,28] (see diagram); the parentheses in the diagram enclose bond lengths determined for pyrazole by neutron diffraction[29]. A striking feature of the parameters given in the diagram for the pyrazole ring in the crystalline state is the equalisation of carbon–nitrogen and carbon–carbon bond lengths, which indicates smoothing of the difference between "pyridine" and "pyrrole" nitrogen atoms and a high degree

of delocalisation of π bonds. Nevertheless, it has been firmly established that the hydrogen atom forming the nitrogen–hydrogen bond is attached solely to $N_{(1)}$.[29] The nitrogen–carbon bond lengths are close to the length 1.35 Å of the corresponding bond in pyridine; the carbon–carbon bonds in pyrazole are shorter than those in benzene (1.395 Å); and the nitrogen–nitrogen bond is shorter than the sum of the covalent radii of the nitrogen atoms (1.40 Å). All these data are evidence of the stability of the pyrazole molecule, which is confirmed by the chemical reactions of the heterocycle. For the variation in the bond lengths of the ring in the vapour state see Ref. 30.



Bond lengths (in Å) and angles in 1,2-azoles.

Since unsubstituted isoxazole is a liquid, X-ray diffraction has been applied to its crystalline derivatives[28,31], the results of which have given the mean bond lengths and angles indicated in the diagram for the ring. The nitrogen–oxygen bond is noteworthy, for its length (1.42 Å) exceeds considerably the sum (1.36 Å) of the covalent radii. This is clear evidence of the "looseness" and chemical instability of the bond, in good agreement with the chemical behaviour of isoxazole and its derivatives. On the other hand, the $C_{(5)}-O$ bond is shorter than in furan (1.37 Å). The three remaining bonds are similar in their parameters to the corresponding bonds in pyrazole. In contrast to the latter the largest angles in the isoxazole ring (111–112°) are the $N-C_{(3)}-C_{(4)}$ and $C_{(4)}-C_{(5)}-O$ angles. For variation in bond lengths in the rings of arylazoles see Refs. 32 and 33.

2. Basicity and Ionisation Potentials

1,2-Azoles are Hammett bases[34,35], weaker than pyridine. The pK_a values fall in the sequence from pyrazole through isothioazole to isoxazole (respectively +2.5,[36] −0.5,[35] and −3.0[35]), probably as a consequence of increasing polarisation of the bond between the heteroatoms. Isoxazole derivatives are the weakest bases among all 1,2- and 1,3-azoles, with negative pK_a values[35,37–39]. Their basicities have been determined spectrophotometrically: the potentiometric method used previously would give incorrect results.

French chemists have examined the pK_a values for 90 pyrazoles, and found linear relations of the type $pK_a^{calc} = pK_a^0 + \Sigma\Delta pK_m^n$, where pK_a^0 is the value for the pyrazole ring in which the carbon atoms are unsubstituted, while ΔpK_m^n is the effect of a substituent m at position n, which is more correctly characterised by the Hammett σ_{meta} constant[36]. The resulting equations describe the basicity of derivatives of pyrazole and of 1-methyl- and 1-*p*-nitrophenyl-pyrazoles. More complicated correlations have been revealed between basicity and substituent constants in the isoxazole series[37,39].

Pyrazoles in which the nitrogen atoms are unsubstituted are at the same time also weak acids. The acidity of pyrazole itself is extremely slight ($pK_a' \simeq 14$).[40] It is increased by factors of 10^4 when a nitro-group is introduced into the 4 position[41].

The ionisation constants of hydroxy- and amino-derivatives of 1,2-azoles, as well as those of azolecarboxylic acids[42,43], suggest that the azole rings (with the exception of pyrazole at position 4) tend to attract electrons more strongly than does the benzene ring.

The π_3- and n-ionisation potentials of 1,2-azoles and pyridine increase in the sequence[44,45]

pyridine < pyrazole < isothiazole < isoxazole

The N potentials provide an approximate measure of the basicity of these heterocycles, which diminishes in the same sequence.

3. Dipole Moments

A large quantity of data have now accumulated on the dipole moments of pyrazole and isoxazole derivatives: most of the work has been reviewed in Ref. 46. Dipole moments of unsubstituted azoles have been determined from measurements of the dielectric constant in benzene solution[46–48] and from the microwave spectra of the vapours[49–51]; similar results were obtained by the two methods. Special attention must be paid to the necessity of working with dilute solutions of N–H pyrazoles[47,52], owing to the occurrence of association in concentrated solutions. The dipole moments of 1,2-azoles increase on passing from pyrazole to isoxazole, also as a consequence of enhancement of the polarisation of the bond between the nitrogen atom and the other heteroatom. A method proposed recently for calculating dipole moments of azoles gives results that are extremely close to experimental values[53].

Several studies have been made on the influence of substituents on the dipole moments of pyrazole and isoxazole derivatives[48,52,54]. Substituents at position 5 in the ring of isoxazole and 1-methylpyrazole exert a strong influence; a phenyl group has a $+M$ effect in both rings[48,52]. In 1-phenylpyrazole strong $+M$ effects are observed from substituents (amino, chloro, bromo) at positions 3 and 5[54] and from a nitro-group at the *para*-position of the benzene ring[52]. Interesting deductions have been made from the dipole moments (experimental and calculated) of di- and tri-substituted pyrazoles and isoxazoles: a correlation coefficient of 0.982 has been found[48] for 4-substituted 3,5-dimethylisoxazoles between the dipole moment of the group and the Hammett σ_{meta} constants of the substituent. Results for the dipole moments of 4-substituted 3,5-dimethyl(or diphenyl)pyrazoles suggest that structures having a fixed nitrogen–hydrogen bond are present in solution[54].

4. Ultraviolet and Infrared Spectra

The ultraviolet spectra of 1,2-azoles, like those of other five-membered heteroaromatic compounds, contain only absorption bands corresponding to $\pi \rightarrow \pi^*$ transitions[55]. The presence of absorption corresponding to $n \rightarrow \pi^*$ transitions in the spectra of pyrazoles has been a matter of controversy[55,56].

Pyrazole and isoxazole possess similar ultraviolet spectra, but the presence of the sulphur atom in isothiazole leads to absorption at longer wavelengths, as with

other sulphur-containing heterocycles. Most data are available on the spectra of pyrazoles among 1,2-azole derivatives; noteworthy work was done by Grandberg[57] and especially by French chemists, who studied and classified the ultraviolet spectra of 170 pyrazole derivatives[56]. Considerably less work has been done on derivatives of the other 1,2-azoles; mention must be made of a study on the spectra of nitroisoxazoles[58], and also papers on the ultraviolet spectra of substituted isothioazoles[59-61]. The influence of substituents in heterocycles on the position and the intensity of absorption can readily be traced from the ultraviolet spectra. A 4-methyl group causes a bathochromic shift in λ_{max} by 8–9 nm;[56,59,61] the opposite relation—a hypsochromic shift—is observed in the spectra of 3-methylisoxazoles and 5-methylpyrazoles. Such shifts are far larger when acceptor substituents (nitrophenyl groups) are attached to nitrogen in the pyrazoles[56]. Auxochromes (halogen, alkyl, amino) present in a pyrazole ring cause a slight bathochromic shift in λmax; pyrazoles containing chromophoric groups (carbonyl, aryl, nitroso, nitro) absorb at far longer wavelengths (242–282 nm) than occurs in the benzene series[57]. An analogous band in the spectra of alkyl-4-nitroisoxazoles was attributed to conjugation between the nitro-group and the heterocyclic ring[58].

Certain conclusions on conjugation in phenylated azole systems can be drawn from a detailed analysis[16,62] of the ultraviolet spectra of *C*-phenyl derivatives of isoxazole and pyrazole supplemented by spectral data on phenylisothiazoles[59]. In 3- and 4-phenylisoxazoles and in 4- and 5-phenylisothiazoles the benzene ring is conjugated with multiple bonds in the heterocycles. Yet 3-phenylpyrazoles (whether or not *N*-substituted), 3-phenylisothiazole, and 5-phenylisoxazole are single conjugated systems, an effect which is more strongly developed than in biphenyl. Hypsochromic shifts in the spectra of arylpyrazoles observed on passing from mono- to 1,5-di-substituted rings are attributed to diminished conjugation in *C*- and *N*-arylpyrazoles owing to disturbance of coplanarity between the benzene and heterocyclic rings as a consequence of steric interaction between $N_{(1)}$- and $C_{(5)}$-substituents[56,57]. Depolarisation of the Rayleigh scattering indicates[63] that the angle between the planes of the rings in the preferred conformation of 1-phenylpyrazole is 11°; any substituent at position 5 increases the angle and diminishes conjugation. Grandberg et al. studied the fluorescence of 300 pyrazole derivatives[64], and used the spectra to determine the angle between the planes of the rings in 5-substituted 1-phenylpyrazoles[65]. Spectrophotometry has also been employed to investigate steric effects in 4-phenylpyrazoles[66] and 3(5)-arylisoxazole-4-carboxylic acids[67].

The infrared spectra of unsubstituted 1,2-azoles have by now been quite fully studied[68-73]. In the range 1200 to 1600 cm^{-1} three or four characteristic frequencies of each ring are fairly close to frequencies of the other, although simultaneous consideration of the frequencies permits accurate identification of the heterocycle. Absorption in the region of carbon–hydrogen stretching vibrations (3100 cm^{-1}) of variable intensity, which is observed in unsubstituted azoles, may be greatly strengthened in aryl derivatives[74-76].

Systematic investigations have been made also on the infrared spectra of derivatives of isoxazole[42,69,77-79], pyrazole[80], and isothiazole[61,81,82]. From the results general conclusions have been reached on the influence of the number and nature of substituents on the characteristic frequencies of the rings. For example, the raising of the frequency to 1630–1640 cm^{-1} in the spectra of trisubstituted isoxazoles indicates steric interaction between the substituents; in phenylisoxazoles the coplanarity of the rings is disturbed[69].

Raman spectra have been obtained for 1,2-azoles[71-73] and several of their derivatives[73,81,82]. At the present time hardly any use is made of these spectra for solving structural problems or identifying azoles.

5. Nuclear Magnetic and Quadrupole Resonance Spectra

The rapid development of nuclear magnetic resonance spectroscopy during the 1960s led to the appearance of a large number of papers containing results for 1,2-azoles and their derivatives. These related mainly to ^{1}H n.m.r. spectra of pyrazoles[83-85], isoxazoles[86], and isothiazoles[87], but magnetic spectra were also published for resonance on carbon-13[26,88-90] and nitrogen-14[18] nuclei. In the ^{1}H n.m.r. spectra of 1,2-azoles the signals due to 4-protons appear in the highest fields, whereas those due to the two remaining protons of each heterocycle, located in the immediate vicinity of the electronegative heteroatoms, are displaced down field. Certain difficulties arise in assigning signals from the 3- and 5-protons, especially in pyrazole derivatives. The signals of 3-protons in isoxazoles and isothiazoles are broadened owing to incomplete removal of spin–spin interaction between nitrogen and 3-hydrogen atoms as a consequence of quadrupole relaxation of the nitrogen-14 nucleus[91]. The broadening of the 3-hydrogen signal served as a reference in interpreting the 1H n.m.r. spectra of 4-arylisothiazoles, in which the chemical shifts of the 5-protons may be smaller than those of the 3-protons (on the δ scale)[92]. Assignment of the 3- and 5-proton signals in pyrazole derivatives necessitated the preparation of isomers whose structure had been rigorously established, as in the work of Habraken[66,93]. Under the influence of acceptor substituents the signals due to 3- and 5-protons in the ^{1}H n.m.r. spectra of isothiazoles and especially of pyrazoles may change places: the signals due to 5-protons appear down field[84,85,94,95]. Detailed and systematic studies have been made of this inversion[84,95]. The effects of solvents differing in polarity were used to assign the proton signals: dipolar aprotic solvents exert a very strong influence[84,96], and may shift 5-proton signals down field[84].

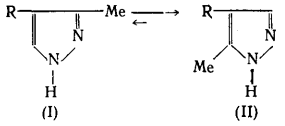
Study of the ^{1}H n.m.r. spectra of arylisoxazoles revealed a linear dependence of the chemical shift of the 4-proton in 3,5-diarylisoxazoles on the Hammett σ_{para} constant at $C_{(5)}$ in the benzene ring[97,98]. Rather earlier a more general relation

$$\delta_4 = \delta_4(s) + \alpha_1 + \alpha_3 + \alpha_5$$

had been discovered in the pyrazole series, in which $\delta_4(s)$ is the chemical shift of the 4-proton of 1,3,5-trimethylpyrazole in a given solvent and δ_4 is the chemical shift of the 4-proton in the substituted pyrazole in the same solvent, while α_1, α_3, and α_5 are the constants of substituents at positions 1, 3, and 5 (they correlate with the Hammett constants)[94].

Spin–spin interaction constants can usually be measured for neighbouring protons in 1,2-azoles[59,85-87]. Their values (1.6–2.3 Hz) are characteristic of all carbon–carbon bonds in azoles other than the $C_{(4)}=C_{(5)}$ bond in isothiazoles ($J_{4,5}$ = 4.5–5.0 Hz). The low values of the constants are probably due to strong polarisation of the bonds of the heteroatoms. The constants $J_{3,5}$ and J_{H,CH_3} are still smaller[99].

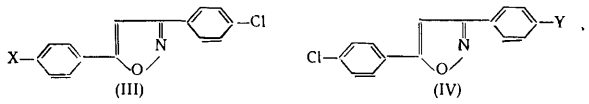
Preferred tautomeric forms and conformations of several substituted pyrazoles in solution have been established from the ^{1}H n.m.r. spectra. Analysing the chemical shifts of ring protons and of methyl groups in *N*-hydro- and *N*-methyl-pyrazoles, Habraken and Moore[93] found that the equilibrium



(I) (II)

is displaced to the right. On the basis of the ^{1}H n.m.r. spectra it is proposed to describe the structure of pyrazolium salts in terms of analogous resonance structures[100].

In contrast to n.m.r. spectroscopy the second type of microwave spectroscopy—nuclear quadrupole resonance—has hitherto been little used for studying derivatives of 1,2-azoles. Only n.q.r. spectra on nitrogen-14 nuclei in pyrazole and *N*-acetylpyrazole have been described; an asymmetry parameter has been found for the "pyrrole" nitrogen atom, which is proportional to the degree of double-bondedness of this atom (~45%).[101] Quadrupole nitrogen-14 nuclear interaction constants have been calculated for pyrazole and isoxazole[102]. Interesting possibilities of the n.q.r. method have been demonstrated by Soviet authors, who find correlations between the chlorine-35 signal frequency and electronic effects of substituents in 3,5-diarylisoxazoles of types



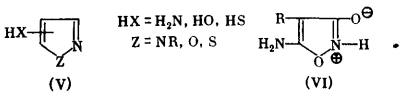
(III) (IV)

which are conjugated systems[103].

6. Tautomerism

This subsection contains a brief account of the tautomerism of hydroxy-, mercapto-, and amino-derivatives of 1,2-azoles, which has been studied by ultraviolet, infrared, and n.m.r. spectroscopy and also by determination of basic or acidic properties. During the past decade Katritzky's reviews and monographs have repeatedly summarised the factual information that has accumulated[11,104,105]. The most recent of these publications[105] gives a clear and concise report on the preferred tautomeric forms of these functional derivatives, but it is based on results that appeared only up to 1968 inclusive, with no references to the work of Soviet scientistis. Below is given a short discussion of the most general data on tautomerism based on work published during 1969–1974.

Azoles containing an amino-group at position 3, 4, or 5, a hydroxy-group at position 3 or 4, or a mercapto-group at position 5 exist as heteroaromatic structures (V)[38,105-110]

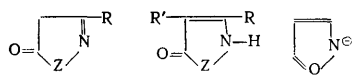


(V) (VI)

Equilibrium formation constants of the zwitterions have been calculated for 4-hydroxyazoles[111]; these are the preferred structures for 5-amino-3-hydroxyisoxazoles (VI).[112]

Complicated tautomerism has been observed in azol-5-ones, especially in *N*-unsubstituted pyrazolones[113].

Quantum-chemical calculations for unsubstituted isoxazol-5-one have shown[114] that the Δ^2(C–H) structure (VII)



(VII) (VIII) (IX)

is advantageous, in agreement with experimental results[115]. 3-Substituted dihydro-5-oxoazoles exist in the same form; in the presence of a 4-substituent these compounds exist in the solid state and in aqueous solution as the Δ^3(N–H) form (VIII), and in non-polar solvents the equilibrium is displaced in favour of the C–H structure[106,116-119]. If the 4-substituent is electron-accepting, the oxo-compounds are strong N–H acids: $pK_a < 2$.[120]

The above results show that 1,2-azoles are heteroaromatic compounds, which are characterised by substitution reactions. However, the presence in every azole of a bond between the heteroatoms that differs from the other bonds leads to variation in the stability of the rings in redox reactions. The nitrogen–oxygen bond in isoxazoles should break the most readily. The peculiarities of the heteroaromatic isoxazole system are probably best explained by Kamiya[19]: stabilisation of the π electrons is caused by electrostatic interaction of two oppositely polarised atoms—nitrogen and oxygen (limiting structure IX)—despite the diminished conjugation in the ring.

III. REACTIONS WITH RETENTION OF HETEROCYCLIC RING

Reactions of this type are in considerable measure characteristic of 1,2-azoles as heteroaromatic compounds. They include substitution in the heterocyclic ring and in a side-chain, and also addition to the ring.

1. Substitution in the Ring

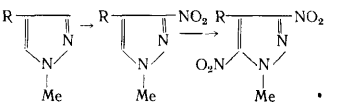
The reactivity indices (localisation energy[14,60], π or total electron density[23,60]) suggest that electrophilic substitution in bases and conjugate acids of pyrazoles and isothiazoles should take place preferentially at carbon atom 4. On the other hand, attack by radicals is directed at positions 5 and 3.[14] For isoxazole the localisation energies indicate preferential substitution at carbon atom 5, independently of the nature of the reactant species; correct conclusions on the direction of attack can be reached on the basis of the calculated π-electron density[15].

(*a*) Electrophilic substitution

Electrophilic substitution is most characteristic of aromatic and heteroaromatic compounds. In the case of nitrogen heterocycles, including 1,2-azoles, the ease of occurrence of such reactions is determined not only by the activity of the reactant species but also by the basicity of the compound and the acidity of the medium. Only in the past decade has study of the reactions of nitrogen-containing heterocycles on the basis of criteria elaborated by Katritzky and Johnson[121] permitted precise establishment of the form (base or conjugate acid) in which the compound reacts. Because of this specific effect it is helpful to discuss separately the electrophilic substitution of 1,2-azoles occurring in strong acids (isotopic exchange of hydrogen, nitration, sulphonation).

Reactions in acid medium (isotopic hydrogen exchange, nitration, sulphonation). In conformity with quantum-chemical calculations and the chemical shifts of nuclei in the n.m.r. spectra, which indicate maximum electron density on the "pyridine" nitrogen atom and carbon atom 4, these are the positions in 1,2-azoles that are attacked by electrophilic species. Attack by a proton on a nitrogen atom gives a protoned base (conjugate acid), whose stability depends on the basicity of the initial azole and the acidity of the medium. Electrophilic substitution at carbon atom 4 then takes place either in the base or in the conjugate acid. Its ease falls in the sequence pyrazole $\gg$ isothiazole $\geqslant$ isoxazole. Thus 4-deuteropyrazole can be obtained by the action of CH_3COOD,[122] but 3,5-dimethylisoxazole undergoes deuterium exchange only under more severe conditions—in a mixture of deuterotrifluoroacetic and dideuterosulphuric acids[123]: both compounds react as the base. On the other hand, the nitration of pyrazole involves the conjugate acid[124]. The first comparative study of the reactivities of 3,5-dimethyl derivatives of *N*-methylpyrazole, isoxazole, and isothiazole towards nitration and isotopic hydrogen exchange in a strongly acid medium was published in 1971.[35] Pyrazole and isothiazole are nitrated as the conjugate acids; deuterium exchange occurs either in the bases or (with an acidity function D_0 exceeding -4.5 to -6.0) in the conjugate acids of these azoles. 3,5-Dimethylisoxazole, the weakest base of the three isosteres, undergoes both reactions as the base. Similar results have been obtained for deuterium exchange in six *N*-methylpyrazoles[125]. French workers[60] have given quantitative data on the reactivities of isothiazole and of its 3- and 5-methyl and 3,5-dimethyl derivatives; their relative rates of nitration are 1 : 2.3 : 4 : 67, i.e. the effect of a substituent is transmitted more strongly from position 5; in 3,5-dimethylisothiazole the effects are non-additive.

Habraken et al.[128–130] and Coburn[131,132] have shown that 1,4-disubstituted pyrazoles (X) can be nitrated at both 3 and 5 positions—compounds (XI) and (XII):

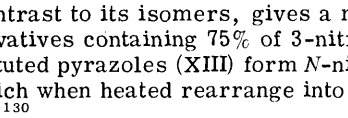


(X) (XI) (XII)

R=Alk, Ar, Br

This unusual orientation on nitration is attributed to the strongly nucleophilic character of the pyrazole ring. A study has been made[132] also of the complicated kinetics of the nitration of 4-(2,4-dinitrophenyl)-1-methylpyrazole, which is converted into 3- and 5-mono- and 3,5-di-nitro-derivatives.

When nitrated in acetic anhydride 5-methyl-1-phenylpyrazole, in contrast to its isomers, gives a mixture of mononitro-derivatives containing 75% of 3-nitropyrazole.[127]. 3(5)-Substituted pyrazoles (XIII) form *N*-nitro-derivatives (XIV), which when heated rearrange into 5-nitropyrazoles (XV):[130]



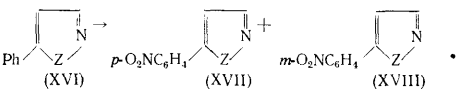
(XIII) (XIV) (XV)

Nitration of 2-hydroxy-1-methylpyrazole yields, as in the case of *N*-hydroxypyridine, a γ-nitro-derivative, i.e. 5-nitropyrazole[133]. The form undergoing the reaction is the base, for which first-order kinetics is observed in the H_0 range from -5 to -6.5; a dinitro-derivative is also formed in a more acid medium.

Unusual orientation—at the 5 position—has been observed also in the sulphonation of 4-methylisothiazole[87]. In the isoxazole series no single example has yet been found of electrophilic substitution at carbon atom 3 or 5 in the ring.

Various physical methods have shown the presence of conjugation in *N*-phenylpyrazole, which favours electrophilic attack at position 4 in the pyrazole base, as follows from nitration in acetic anhydride[1] and the action of chlorosulphuric acid in chloroform[134]. In sulphuric acid the conjugate acid—the *N*-phenylpyrazolium cation—reacts,[127] and the substituent enters the *para*-position of the benzene ring[134], which has only 1% of the activity of unsubstituted benzene[127]. Comparative activities towards nitration have been given[135] for substituted *N*-phenylpyrazoles. In sulphuric acid the nitration of *N*-arylpyrazoles is a first-order reaction; disturbance of the coplanarity of the two rings by $N_{(2)}$- or $C_{(5)}$-substituents in the pyrazole ring diminishes the activity of the benzene ring[127].

Numerous papers have appeared on the nitration and the sulphonation of other mono- and poly-phenylated 1,2-azoles; several later publications have reviewed results obtained earlier[24,92,130,136–141]. Substitution in isomeric 3- and 5-phenyl-azoles occurs in the *para*- and *meta*-positions of the benzene ring, usually with predominant formation of *para*-derivatives:



(XVI) (XVII) (XVIII)

An exception is the preferential appearance of *meta*-isomers in the nitration of 3-phenylisothiazole[24] and the chlorosulphonation of 5-phenylisoxazole[135]; both compounds evidently react as the conjugate acids. In 4-phenylazoles the *para*- and *ortho*-positions of the benzene ring are the most active, and dinitro-derivatives are also readily formed[92,130,139].

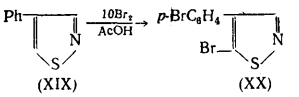
The presence of acceptor substituents in the heterocyclic ring of phenyl-azoles often changes the orientation of an incoming nitro-group[126,142]. Several papers have appeared[129,143,144] on substitution in arylazoles; among such reactions the nitration of 3- and 5-arylisoxazoles has been studied in the greatest detail[144]. With respect to ease of nitration aryl and heterocyclic substituents in arylazoles can be arranged in the sequence—fur-2-yl[145] > pyrazol-4-yl > phenyl $\simeq$ pyrazol-3(5)-yl > pyrazol-4-yl in the pyrazolium cation > isoxazol-4-yl > isothiazol-4-yl > *p*-nitrophenyl.

Halogenation. The nucleophilic character of the pyrazole ring is clearly developed during halogenation. Kinetic investigation of the iodination[146,147] and the bromination[148] of pyrazole and its methyl homologues has established that these compounds react as neutral molecules or conjugate bases. Isoxazole derivatives are halogenated in non-protonated form not only in acetic[2] but also in sulphuric[149] acid.

Treatment with molecular chlorine or bromine in water or an organic solvent yields 4-halogeno-derivatives of all 1,2-azoles[1,2,118]. With the less active isoxazoles and isothiazoles, however, the reaction is slow and incomplete. The iodination of 1,2-azoles, including pyrazole, goes similarly. The use of buffered solutions is sufficient to obtain 4-iodopyrazole[146,147], but the iodination of isoxazoles goes smoothly only in the presence of nitric acid[2]. Whereas in pyrazoles a halogen atom can be introduced at any position in the ring (to obtain trihalogeno-derivatives

it is convenient to use silver salts of pyrazoles[150]), with isothiazoles halogenation at positions 3 and 5 is exceptional[10,92]. Alkyl- and aryl-pyrazoles undergo thiocyanation at position 4 in the ring[151].

The greater selectivity of halogen molecules and ions than of the nitryl ion results in diverse products of the halogenation of phenylazoles. The aggregate effect of several factors—the activity of the halogen species, the electron density on the carbon atom involved, the energetic advantage of the transition state (intermediate compound)—probably determines the direction of attack. Complexes formed by azoles with halogens undoubtedly have an important role in halogenation. The process is most unambiguous with phenylisoxazoles: in all cases only 4-halogenoisoxazoles have been obtained, uncontaminated by isomers[2]. Among pyrazoles and isothiazoles examples are known in which halogenation occurs even in the benzene ring of the phenylazoles[92,152]:

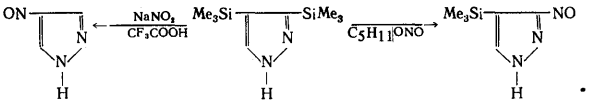


(XIX) (XX)

The bromination of phenylisoxazoles in aqueous acetic acid is a second-order reaction[153]. The activity of the isoxazole ring is significantly greater than that of benzene, and is determined by the nature and the position of substituents in the ring.

Other electrophilic substitutions. Pyrazoles and isoxazoles undergo hydroxy- and chloromethylation at the 4 position in the ring[1,2]. Carbonium ions, in contrast, attack the heterocycle at the nitrogen atom to form isoxazolium cations[154,155]. The highly nucleophilic character of the pyrazole ring is confirmed by the possibility of thermal and Friedel–Crafts acylation[1], and also Vilsmeier formylation[156]. Derivatives of isoxazoles do not undergo Friedel–Crafts acylation[157].

The presence of a labile carbon–silicon bond in a pyrazole derivative (XXI) enables a nitroso-group to be introduced at position 3 or 4 of the non-activated ring (XXII and XXIII):[158]



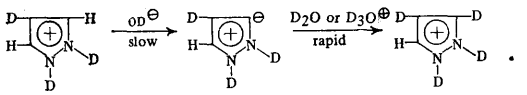
(XXIII) (XXI) (XXII)

Among isothiazoles only the 3,5-bismethylthio-derivative undergoes nitrosation[159].

(*b*) Protophilic substitution

At the present time protophilic substitution of hydrogen includes isotopic exchange in the presence of bases and metallisation by alkali-metal compounds[160]. The reactions involve intermediate formation of carbanions after detachment of a proton.

Only during recent years have studies been made on basic hydrogen exchange in pyrazole[122,161] and isothiazoles[10,162] catalysed by CH_3C^- and OD^- ions. The reaction involves the hydrogen atoms at positions 5 and 3. Isotopic exchange of the 5-proton in isothiazoles is a second-order reactions[162]. In the isothiazolium cation both protons are exchanged at high rates ($k \simeq 10$–6000 $M^{-1}\ s^{-1}$), but the 5-proton always the more rapidly[163]. Kinetic investigation of the deuteration of pyrazole has shown[161] that the reaction velocity is independent of the pD value; a mechanism with intermediate formation of an ylid was suggested:

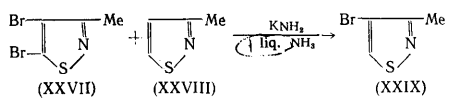


(XXIV) (XXV) (XXVI)

In pyrazole and isothiazole derivatives the 5-proton is always the most easily detached by n-butyl-lithium[10,164,165]. In monosubstituted isoxazoles strong bases attack the 3-proton first, and the resulting carbanion immediately rearranges into an open-chain enolate anion (see below). 3,5-Disubstituted isoxazoles containing functional groups (alkoxy, alkylthio, chloro) can be metallated at the 4 position[166,167].

The great reactivity of lithium derivatives of azoles has enabled many syntheses to be made. Organometallic synthesis is especially valuable for introducing various substituents at position 5 in the isothiazole ring[10,165,168], since the most widely used methods for obtaining isothiazoles yield 3- and 4-derivatives[10]. During this reaction such reactive groups as cyano and carboxy at position 4, as also halogen atoms, remain unaffected[10], which indicates the high kinetic acidity of the 5-proton in the isothiazole ring, and is fully consistent with kinetic data for isotopic hydrogen exchange.

The interesting migration of halogens from the 5 to the 4 carbon atom in 5-halogenoisothiazoles on treatment with potassamide in liquid ammonia is due to the greater stability of the isothiazol-5-yl than of the isothiazol-4-yl anion[169]. This was explained by a five-stage mechanism, supported by the quantitative debromination of the 4,5-dibromoisothiazole (XXVII) by the unsubstituted compound (XXVIII) to the 4-bromoisothiazole (XXIX):



(XXVII) (XXVIII) (XXIX)

A similar mechanism to the above reactions underlies that reported by Begtrup between pyrazolium salts and sodium hydride in the presence of oxygen or sulphur, with intermediate formation of an ylide of type (XXV) to yield pyrazolones or pyrazolethiones respectively[170,171].

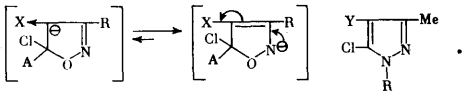
(*c*) Nucleophilic substitution

Reactions involving nucleophilic substitution by an S_N2 mechanism have been reported mainly for halogeno-derivatives of 1,2-azoles. In contrast to the inert 3- and 5-halogenopyrazoles and 5-halogenoisothiazoles, the isoxazole analogues undergo such reactions when heated to 100°C.[2,172] A 3-nitro-group in isoxazoles is also readily substituted by hydroxy- and alkoxy-groups[173,174]. Reaction with copper(I) cyanide has great value for the preparation of isothiazole derivatives; 5-bromoisothiazoles react more readily than do the 4-isomers[10].

Introduction of an electron-accepting 4-substituent increases appreciably the mobility of a 5-halogen, especially in the isoxazole ring[1,2,10,118,175,176]. Even the two nitro-groups in 4-bromo-1-methyl-3,5-dinitropyrazole activate the halogen atom[131] far more weakly than the benzoyl substituent in 4-benzoyl-5-chloroisoxazoles[2].

The ^1H n.m.r. spectra of 4-nitro-azoles indicate that unreactive molecules have approximately equal electron densities on the 5-carbon atom. Therefore the decisive

factor for easy occurrence of S_N2 reactions in the isoxazole series should be a lower activation energy, whose magnitude is undoubtedly governed by formation of the transition state (XXX). Isomerisation of the carbanion (XXX) into the energetically favourable anion (XXXI) is promoted by strong polarisation of the nitrogen–oxygen bond in the heterocycle:



(XXX) (XXXI) (XXXII)

Nucleophilic substitution takes place readily also in 3-halogenoisoxazolium [177] and 3- and 5-halogenopyrazolium [178] cations.

Kost and Grandberg [1] studied the kinetics of the action of excess of hexamethyleneimine on 5-chloropyrazoles of type (XXXII). Under the given conditions the reaction was pseudounimolecular. The influence of substituents Y diminishes in the sequence

$$NO_2 \gg C_6H_5N : N > C_6H_5CO \gg Br > H .$$

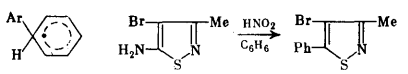
(*d*) Homolytic substitution

Arylation. It was established during the 1960s that arylation takes place by the same mechanism involving a σ complex (XXXIII) independently of the source of the radicals. Results obtained on the phenylation of 1-methyl- and 1-phenyl-pyrazoles and of isothiazole and its methyl homologues have been summarised in a French review on the homolytic arylation of heterocycles [179]. Decreasing rates of phenylation in a neutral medium give the sequence

4-MeIth (1.85) > C_6H_6 (1) ≃ Ith (0.95) > 3-MeIth (0.65) ≃ 1-MePyr (~0.6) > 5-MeIth (~0.3)

where Ith and Pyr represent isothiazolyl and pyrazolyl respectively. Individual positions in the heterocyclic ring differ greatly in activity: in isothiazole the carbon atoms 3 and 5 are attacked by the phenyl radical five times as frequently as carbon atom 4; in 1-methylpyrazole attack occurs almost exclusively at position 5. In *N*-phenylpyrazole reaction occurs to ~55% at the *ortho* position of the benzene ring and 30% at the 3-carbon atom of the pyrazole.

The reverse reaction to arylation—attack on aromatic compounds by azolyl radicals—has been reported in several papers [180–182]. Such a reaction has been used [10] to obtain 4- and 5-phenylisothiazoles from the corresponding amines, e.g. (XXXV) from (XXXIV):



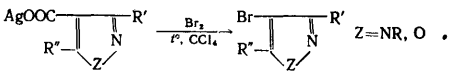
(XXXIII) (XXXIV) (XXXV)

Organometallic compounds from halogeno-azoles. During the past decade a radical mechanism has been firmly established by various methods for the reaction of halogeno-derivatives with magnesium, and also for the exchange of organo-magnesium and -lithium compounds with halides, which occurs "in a cage".

Halogeno-derivatives of pyrazole and isoxazole do not react with magnesium except in the form of another Grignard reagent [1,2]. The activities of halogenopyrazoles fall in the sequences 5-Hal > 4-Hal > 3-Hal and I > Br > Cl. [1] The same rules apply to isoxazole derivatives [2,183], with the exception of 5-halogenoisoxazoles, whose reactivities have not been finally elucidated. As noted above, pyrazol-5-yl- and isothiazol-5-yl-lithium can be obtained by direct metallisation. Exchange therefore finds application in the preparation of 4-derivatives of pyrazole [1] and isoxazole [184] that cannot be obtained in other ways, e.g. 4-deuteroisoxazoles.

Other homolytic reactions. Diazo-reactions, which probably occur by a radical mechanism, have proved especially important for obtaining 5- and 4-halogenoisothiazoles by the Sandmeyer reaction [10]. During recent years 3(5)-halogeno-derivatives of pyrazole and isoxazole have been obtained by the diazo-reaction; for the reaction to proceed normally the ring must contain electron-accepting substituents, which enhance the stability of the diazo-compounds [185–187].

The Borodin–Hunsdecker reaction also takes place by a free-radical mechanism. It has been used to convert *N*-substituted pyrazole-4(5)-carboxylic [1,152] and isoxazole-4-carboxylic [188] acids into bromo-derivatives:



(XXXVI) (XXXVII)

The isomeric pyrazole-3-carboxylic acids do not react, and isoxazole-3(5)-carboxylic acids decompose [188]. Isoxazol-3(5)-yl radicals are probably unstable, and isomerise with cleavage of the ring [189].

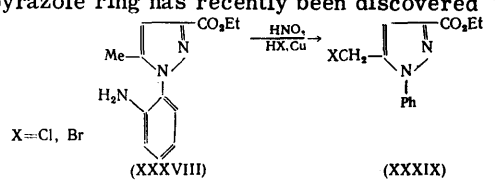
2. Substitution in a Side-chain

(*a*) Preparation and reactions of halogeno-derivatives

Two different methods—halogenomethylation and the halogenation of methyl groups—can be used to obtain halogenomethyl-azoles, which find widespread application for the preparation of various derivatives. The latter method can be regarded as effective only for the selective introduction of one or two halogen atoms. Therefore chlorination in acetic acid is not employed for this purpose, for it yields mixtures of chloro-derivatives of pyrazole [1] and isoxazole [190]. In polymethyl-azoles methyl groups are completely chlorinated at positions 5 and 3, but not at 4. This reaction must therefore be regarded as electrophilic substitution at a saturated carbon atom.

N-Bromosuccinimide, which reacts by a radical mechanism, is most convenient for obtaining monohalogenomethyl-azoles. Great differences in the activity of methyl groups are observed depending on the nature of the heterocycle, the position of the groups in the ring, and other substituents. The reactivity of methyl groups in different positions in isoxazole derivatives falls in the sequence $C_{(4)} > C_{(5)} \gg C_{(3)}$; [2,191] the reaction is completely inhibited by strong acceptors of electrons (nitro, benzoyl). In the isothiazole series, on the other hand, a 3-methyl group is highly active: mono-, di-, and tri-bromo-derivatives can be obtained by the action of *N*-bromosuccinimide, with no bromination of the heterocyclic ring [10,192].

An unusual homolytic halogenation of a 5-methyl group in the pyrazole ring has recently been discovered [193]:

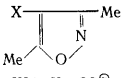


(XXXVIII) (XXXIX)

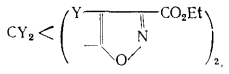
Nucleophilic substitution of the halogen atom in halogenomethylated azoles has been used to obtain physiologically active compounds, especially amines, in the isoxazole [2,194] and isothiazole [10,195] series. Dihalogenoazoles are converted smoothly into aldehydes either by direct hydrolysis or with preliminary formation of intermediate products [2,10,196].

(*b*) Protophilic substitution

Isotopic hydrogen exchange. Such exchange in the presence of bases has been studied mainly in azoles containing methyl groups and acceptor substituents in adjacent positions. Deuterium exchange catalysed by the OD^- ion has been accomplished [10] only in methylisothiazoles. The activity of methyl groups falls in the sequence of positions 5 ≫ 3 > 4, with relative rate constants $10^2 : 1 : 10^{-4}$. In the isoxazole series deuterium exchange in methyl groups has been investigated in the 4-substituted 3,5-dimethylisoxazoles (XL)–(XLII) [197,198] and in diethyl methanebis-5-isoxazole-3-carboxylate (XLIIIa) [199]



(XL), X = $CO_2^{\ominus}$;
(XLI), X = C_6H_5N : N
(XLII), X = NO_2;

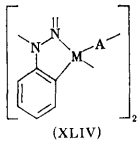


(XLIII) a) Y = H,
b) Y = D

Under the most severe conditions (catalysis by the OD^- ion) reaction occurs in the carboxylate anion (XL). Isotopic hydrogen exchange is greatly facilitated in compounds (XLI) and (XLII), and the rate could not be measured for the reaction of the nitroisoxazole (XLII) with *N*-deuterodiethylamine. Entry of deuterium into the 5-methyl groups was demonstrated by ^1H n.m.r. spectroscopy for all three compounds. Only the ^1H n.m.r. spectrum will reveal instantaneous deuterium exchange in compound (XLIIIa), which yields (XLIIIb) via methineisoxazoles.

Metallation. The metallation of methyl groups by butyl-lithium and organometallic synthesis from the resulting lithium derivatives have been reported in the isoxazole [165,166,200–203] and pyrazole [164,165] series. In methylisoxazoles a 5-methyl group always reacts, being more active than the 4-proton, but in methylpyrazoles an *N*-methyl group reacts. The influence of the 1-heteroatom is clearly evident here: it carries a definite positive charge, and governs the kinetic acidity of adjacent protons. In pyrazole derivatives the activity of individual positions and substituents diminishes in the sequence 5-H > *N*-C_6H_5 > *N*-CH_3, 5-CH_3 ≈ 5-Cl.

In contrast to methylpyridines, in which selective metallation can be achieved by the use of various reagents, 3,5-dimethylisoxazole reacts with any strong base only at the 5-methyl group. Treatment with metal amides followed by alkyl halides gives good yields of 5-n- and 5-iso-alkylisoxazoles [204], as well as di- and tri-isoxazolylalkanes [205].



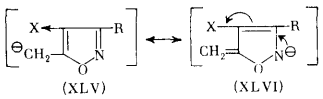
(XLIV)
M = Pd, Mn, Rh, Ir

During recent years selective metallation of *N*-phenylpyrazole in the *ortho*-position of the benzene ring has been accomplished not only with ethylmagnesium bromide [206] but also with compounds of heavy metals [207–209], which gives rise to intramolecular complexes of type (XLIV).

Condensation. Most of the condensation reported for methyl derivatives of 1,2-azoles are catalysed by bases and can also be included among protophilic substitutions (for the condensation of 5-methylisothiazole in acetic anhydride see review [10]). Selective activation of a 5-methyl group is achieved in the presence of an electron-accepting substituent at position 4 in the heterocycle. The most marked effect is observed among the isoxazole derivatives (XL) and (XLII); the catalysts and conditions of condensation are similar to those discussed above for deuterium exchange [2,210]. 5-Methyl-4-nitroisothiazoles react with aldehydes under more severe conditions [10], but 3,5-dimethyl-4-nitropyrazole does not condense at all with aldehydes in the presence of amines [1].

Michael addition of activated methylene and methyl groups in isoxazole derivatives has also been described [2,199]. In 1,2-azolium cations 3-methyl groups are also active [1,2].

Results for protophilic substitution in methyl groups indicate that 5-methylisoxazoles tend to form isoxazol-5-ylmethyl anions (XLV). This occurs especially readily in the compounds (XL)–(XLII), in which X is an electron-accepting substituent. They obviously contain a localised $C_{(4)}=C_{(5)}$ bond, which transmits the effects of substituents. However, the low activation energy, associated with resonance stabilisation of the resulting carbanion



(XLV) (XLVI)

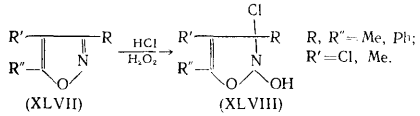
is probably the decisive factor in the ready occurrence of protophilic substitution.

3. Addition to the Heterocyclic Ring

Reactions involving addition have been studied far less thoroughly than those involving substitution. Here we shall consider only reactions which enable di- and tetrahydro-derivatives to be obtained, as well as those in which isomerisation into 3*H*- or 4*H*-pyrazoles takes place.

(*a*) Electrophilic addition

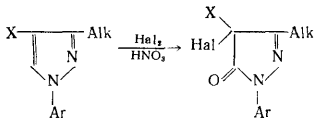
In 1964 Sokolov and Kochetkov described the first reaction involving addition to the isoxazole ring [211,212], in which hypochlorous acid adds at the $C_{(3)}-N$ bond of the heterocycle (XLVII) to form 3-chloro-2-hydroxy-Δ^4-isoxazolines (XLVIII):



(XLVII) (XLVIII)

R, R″ = Me, Ph;
R′ = Cl, Me.

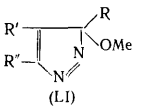
Under corresponding conditions 3-alkyl-*N*-(2,4-dinitrophenyl) pyrazoles react with hypohalous acids at the $C_{(4)}=C_{(5)}$ bond with intermediate formation of 4-halogeno-5-hydroxy-Δ^2-pyrazolines, which undergo further oxidation to the pyrazol-5-ones (L):[213,214]



(XLIX) (L)

Ar=2,4-$(O_2N)_2C_6H_3$; X=Br, Cl, Me; Hal=Br, Cl.

The unstable structure of 4-alkyl-4-bromopyrazoles is confirmed by ^{1}H n.m.r. spectroscopy for products of the reaction of 3,4,5-trialkylpyrazoles with bromine or *N*-bromosuccinimide[215,216]. In the presence of methanol 3*H*-pyrazole derivatives



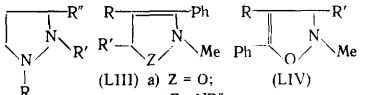
(LI)

are formed.

In all the above reactions the attacking halogen-containing species are evidently electrophilic. Dichlorocarbene, which is also an electrophile, reacts with the ring of 3,4,5-trimethylpyrazole to give a whole range of products, including a quite stable 4*H*-pyrazole derivative[217].

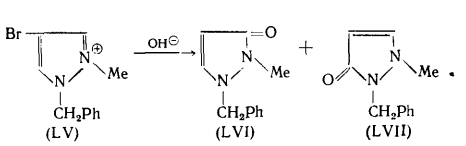
(*b*) Nucleophilic addition

Like quaternary salts of various nitrogen heterocycles 1,2,3-substituted pyrazolium and isoxazolium cations readily add hydride ions. Sodium tetrahydroborate reduces pyrazolium ions to pyrazolidines (LII),[218-220] whereas reduction of isoxazolium ions usually halts at the stage of formation of Δ^3- and Δ^4-isoxazolines (LIIIa) and (LIV).[221] Δ^3-Pyrazolines (LIIIb) can be obtained by means of lithium tetrahydroaluminate[218]. Adachi et al.[222,223] have been able to add carbanions from organomagnesium compounds to 3*H*- and 5*H*-isoxazolium ions at 0°C to form (LIIIa) and (LIV). Under the same conditions secondary amines also add to the 5-carbon atom in the 5*H*-isoxazolium ion[222].



(LII) (LIII) a) Z = O; b) Z=NR". (LIV)

An interesting reaction involving addition and elimination begins with attack by the hydroxide ion at positions 3 and 5 in the cation (LV) followed by detachment of hydrogen bromide to give the pyrazol-3- and -5-ones (LVI) and (LVII):[224]

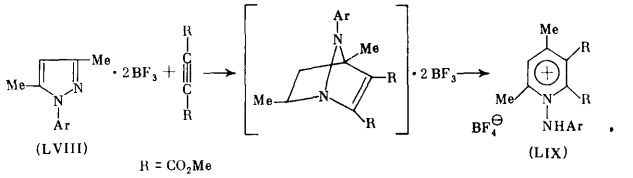


(LV) (LVI) (LVII)

(*c*) Molecular addition

Catalytic hydrogenation, which can be regarded as a homolytic process, yields di- and tetra-hydro-derivatives only in the case of pyrazoles[1]: the isoxazole and isothiazole rings undergo hydrogenolysis under these conditions (see below). Electrochemical reduction of the $C_{(4)}=C_{(5)}$ bond in the pyrazole ring has also been described[225].

In 1974 the possibility was discovered of effecting diene synthesis in the pyrazole series, catalysed by boron trifluoride[226]:



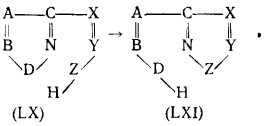
(LVIII) R = CO_2Me (LIX)

IV. REACTIONS WITH CLEAVAGE OF HETEROCYCLIC RING

Reactions of isoxazole derivatives accompanied by cleavage of the heterocyclic ring have found widespread application in organic synthesis. The numerous publications on this topic have been systematically surveyed in the reviews of Nishiwaki[3] and Subrahmanyam[4], which are complementary: the former covers syntheses of various heterocycles based on isoxazoles, and the latter the preparation of peptides and carbocyclic systems, including steroids and terpenes. The following account will make considerable use of these reviews, with references only to the main publications covered, as well as to papers that have appeared since.

1. Rearrangement

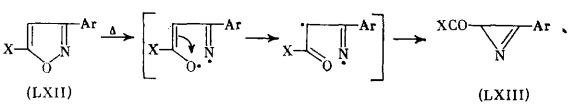
Rearrangements of isoxazole derivatives, the greatest contribution to whose study has been made by Adachi and Kano[3], had already become known by the end of the 1930s. More recently data have been summarised[227] on one of the rearrangements, termed[227] "monocyclic" and occurring under the influence of bases:



(LX) (LXI)

The conversion of isoxazoles into furazans, 1,2,3- and 1,2,4-triazoles, and tetrazoles takes place by the same mechanism.

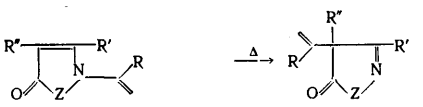
Nishiwaki made a detailed study of the thermal isomerisation of isoxazoles (LXII) containing alkoxy, alkylthio, or amino at the 5 position[3]. In contrast to 3,5-dialkyl(or aryl)isoxazoles these compounds are converted at 150–230°C into azirine derivatives (LXIII):



(LXII) (LXIII)

Komendantov and Bekmukhametov have discovered a catalytic isomerisation of 5-methoxy-3-phenylisoxazole[228], for which they suggest homolytic fission of the nitrogen–oxygen bond with intermediate formation of biradicals[3], which is supported by kinetic results[228]. Reactions of (LXII) with arylamines and trialkyl phosphites also involve formation of azirine derivatives[3].

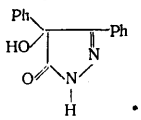
N-Allyl-azol-5-ones (LXIV) when heated undergo an amino-Claisen rearrangement through a cyclic transition state into 4-allyl-azolones (LXV),[229,230] with inversion of the allyl group:



(LXIV) (LXV)

Z=NPh, O

Among alkali-catalysed rearrangements note must be taken of the acyl–lactone rearrangement of 4-acylisoxazol-5-ones [2,231] and the oxidation of 4-hydroxy-3,5-diphenylpyrazole to the acylion [232]



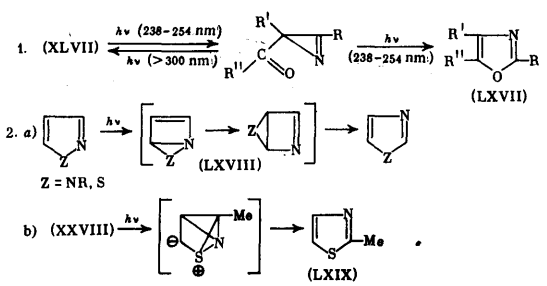
(LXVI)

The mechanism of the latter complicated process has not yet been established.

The lability of the isoxazole ring is evident also in the rearrangement accompanied by fragmentation occurring when di(or tri)alkylisoxazoles are treated with diphenylcyclopropenone [3].

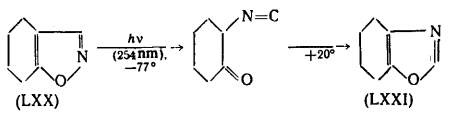
2. Photolytic Isomerisation

Whereas heating and chemical reagents cause rearrangement mainly of isoxazole derivatives, exposure to ultraviolet radiation causes the isomerisation of all 1,2-azoles, on which the first publications appeared during the mid-1960s. From the vast quantity of information that has now accumulated we must single out results on the isomerisation of pyrazoles [233,234], isoxazoles [3,235], and isothiazoles [236-238]. Photorearrangements of 1,2-azoles can occur in two ways—(1) ring contraction–expansion (XLVII) ⇌ (LXVII) [3] or (2) ring isomerisation through (*a*) bicyclic transition states (LXVIII) or (*b*) intermediate zwitterions (XXVIII) → (LXIX):



Isomerisation of pyrazoles into imidazoles sometimes also follows the first route [234], but such rearrangement usually takes place according to Scheme 2*a*. [233,234] Modes of transition of isothiazoles into thiazoles are the most diverse, owing to the tendency of the sulphur atom to form a sulphonium ion, but path (1) is not followed at all by isothiazoles.

The course of the photoisomerisation of 1,2-azoles may vary depending on the nature and the position of substituents in the heterocycles. Thus, whereas 5-amino-3-phenylisoxazoles are converted into the corresponding oxazole derivative, aminoisoxazoles unsubstituted at the 3 position rearrange into acyclic compounds [3]. Photoinduced attack by the solvent on intermediate products of the isomerisation of isoxazoles also yields polyfunctional acyclic compounds [3,239]. In 1973 a novel photoisomerisation was discovered, of the isoxazole (LXX) into the oxazole (LXXI) via a β-keto-isocyanide [3]:

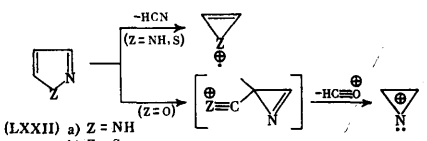


(LXX) (LXXI)

As a result of photoinduced redox reactions *N*-*o*-nitrophenylpyrazoles are converted into *N*-oxides of benzotriazoles [240].

3. Mass Spectra of 1,2-Azoles

The first bonds to break under mass-spectroscopic conditions are the most unstable, which in 1,2-azoles are those between the heteroatoms. Indeed, the most intense peaks in the mass spectra of the unsubstituted azoles



(LXXII) a) Z = NH
b) Z = S
c) Z = O

are due to the molecular ions and the $[M-HCN]^+$ ions for pyrazole [241,242] and isothiazole [243] or $[M-HCO]^+$ ions for isoxazole [244]. Removal of the ring carbon atom 3 (or 5) has been proved [242] for such fragmentation of pyrazole. The molecular ion of isoxazole (LXXIIc) is the least stable [244]. As with other isomerisations, an intermediate azirine derivative (LXIII) is formed here. Conversion of 5-substituted isoxazoles into azirine derivatives under the influence of electron bombardment has been studied by Nishiwaki [245] in comparison with corresponding thermal and photoinduced isomerisations.

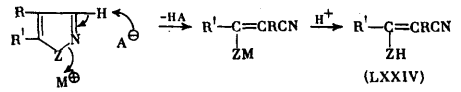
Differences in behaviour are observed between *C*-methyl homologues of pyrazole and isothiazole and of isoxazole: whereas in the first two series a hydrogen atom is removed from the methyl groups of the molecular ions with the formation of six-membered rearranged ions [61,241,243], the molecular ions of methylisoxazoles first undergo rupture of the cyclic nitrogen–oxygen bond [246]. The position in the ring of the substituent in the isomeric monomethylisothiazoles can be determined from the mass spectra [243]. In contrast, the peaks due ionic fragments in the mass spectra of three dimethylpyrazoles differ only in intensity [241]. The stability of the pyrazole ring on electron impact (the quantity W_M) falls in the sequence pyrazole > 1-methylpyrazole > 3(5)-methylpyrazole.

The fragmentation of phenyl derivatives has been discussed in several papers [184,243,247,248]. Isomeric arylphenylisoxazoles can easily be distinguished by their mass spectra [249].

4. Nucleophilic Cleavage

The numerous studies of various aspects of the nucleophilic cleavage of 3*H*-isoxazoles (LXXIIIa) and of the 5*H* isomers, which was discovered as early as 1891, have been summarised in reviews [2,7,8]. Nucleophilic fission of the pyrazole ring unsubstituted at the 3 position (LXXIIIb)

is possible under severe conditions [250,251]. The scission products of isoxazoles and pyrazoles are respectively β-keto-nitriles (LXXIVa) and β-aminoacrylonitriles (LXXIVb):



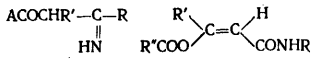
(LXXIII) a) Z = O, b) Z = NR
M = Na, K; A = OH, OR'' .

The products (LXXIVa) are used in organic synthesis [2,4,154].

Electron-acceptor substituents diminish the electron density on the 3-carbon atoms and facilitate nucleophilic cleavage. Thus potassium t-butoxide affects ring opening only in 1-phenylpyrazoles containing benzoyl, cyano, or toluene-*p*-sulphonyl at position 4.

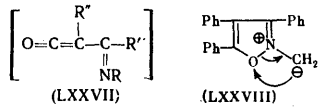
Pino et al. established the mechanism of the cleavage of isoxazoles [2,252]. Overall the reaction has kinetic second order; for the isomerisation of 5-arylisoxazoles a good correlation has been found between $\lg K$ and σ ($\rho = 0.51$, $r \simeq 1$). The nucleophilic cleavage of pyrazoles probably has the same mechanism.

3,4-Disubstituted isoxazoles open with greater difficulty in the presence of bases; 5-methylisoxazole cleaves more rapidly than the 3-isomer [252] by a factor of 14. A review [2] has given different decomposition paths for such compounds, which depend on the stability of the intermediate product (LXXV).



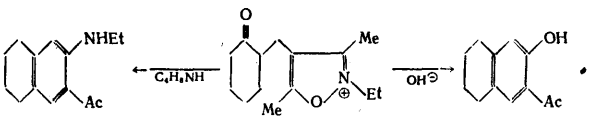
(LXXV) (LXXVI)

In isoxazolium and isothiazolium cations the acidity of the 3-protons has so increased that ring cleavage takes place under mild conditions. 2-Alkylisothiazolium salts on treatment with hydroxide ions at 20°C break down with the formation of resins [253]. The action of weaker nucleophiles is often accompanied by recyclisation into 1,2-azoles [10]. Ring opening takes place in 3*H*-isoxazolium ions even under the influence of carboxylate anions. The true mechanism of this multistage reaction was established by Woodward and Olofson by spectroscopic methods [254]. The enolic esters (LXXVI) formed during the reaction, which possess strong acylating power, have found application in the synthesis of peptides [4,255,256] and nucleotides [257] and in the modification of enzymes [258]. These esters are easily reduced by sodium tetrahydroborate, which forms the basis of a new method for preparing alcohols from acids [259].



(LXXVII) (LXXVIII)

Cleavage of 5*H*-isoxazolium can occur either in the presence of a strong base with detachment of the 5-proton and formation of the keten (LXXVII) or with addition of a weaker base (phenylhydrazine) to the 5-carbon atom followed by transcyclisation [3]. In the case of tetrasubstituted isoxazolium ions the direction of ring opening and subsequent reactions is determined by the nature of the substituents. Treatment of 2-methyl-3,4,5-triphenylisoxazolium with alkali forms 4,5,6-triphenyl-2*H*-1,3-oxazine, presumably via the ylid (LXXVIII). [2,3] Transformation of the heterocycle in the cation (LXXIX) has a completely different course: this compound can be selectively converted into functional derivatives of tetralin (LXXX) and (LXXXI): [4,260]

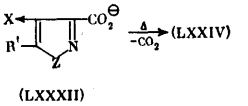


(LXXX) (LXXIX) (LXXXI)

This reaction has been used also for the synthesis of terpenes [260].

Ring opening is probably a consequence of attack by the base on the nitrogen atom. A similar cleavage mechanism—nucleophilic substitution at the sulphur atom—is assumed for the action of butyl-lithium on (XXVIII). [10,165]. The sulphur–nitrogen bond in 3-hydroxyisothiazoles has proved very labile: it is broken not only by carbanions but also by cyanide ions [10]. The ring in 3-chloro-4-nitroisothiazole is also opened by amines [261].

The decarboxylation of isoxazole-3-carboxylic acids is akin to nucleophilic ring cleavage in 3*H*-isoxazoles, since the same β-keto-nitrile products (LXXIVa) are formed. No special investigation has been made of the reaction mechanism, but intermediate formation of a zwitterion can be assumed [2]. The carboxylate anions formed in solution or in the presence of arylhydrazines are decarboxylated under milder conditions:



(LXXXII)

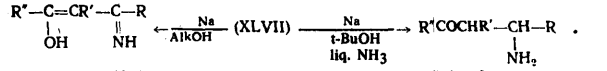
a) Z = O; b) Z = NPh; X = R .

The presence of an electron-accepting 4-substituent in the acid (LXXXIIa) so facilitates decarboxylation that it occurs even on alkaline hydrolysis of the esters; this reaction was used by Woodward et al. in synthesising polycondensed systems [4]. In boiling quinoline ring cleavage takes place even in the pyrazole analogues (LXXXIIb). [262]

5. Reductive and Oxidative Cleavage

The labile nitrogen–oxygen bond in the isoxazole ring is ruptured by very many reducing and oxidising agents. The behaviour of isoxazole derivatives is determined by the reaction conditions and the comparative activities of this bond and multiple bonds in a side-chain. In the absence of functional groups in a side-chain, for example, even lithium tetrahydroaluminate destroys the isoxazole ring [263]. An exocyclic double bond, on the other hand, can be subjected to ozonolysis without affecting the heterocycle [264].

Reductive cleavage of alkali-stable 3,4,5-trisubstituted isoxazoles (XLVII) by the action of sodium in alcohols yields β-imino-ketones (LXXXIII), [2] but reaction with t-butyl alcohol in liquid ammonia gives β-amino-ketones (LXXXIV): [265]

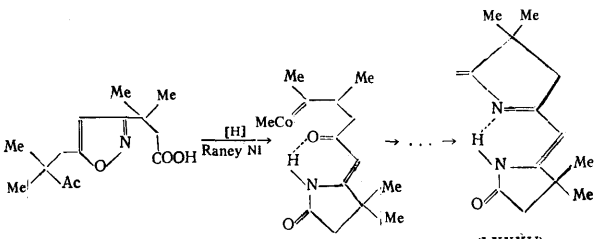


(LXXXIII) (LXXXIV)

Vinyl ketones [266] and β-diketones [204,205] can also be obtained.

It has been established during recent years that the acidity of the medium is a decisive factor in the selective hydrogenation of alkenylisoxazoles. Use of palladium as

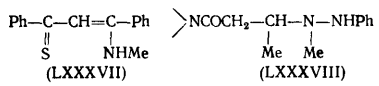
catalyst in an acid medium enables hydrogenation to be confined to the double bond in the side-chain[260,267]. In an alkaline medium, on the other hand, the cyclic nitrogen–oxygen bond is easily ruptured[4,268]. Applying this reaction to 4-chloromethylisoxazoles[269], Stork et al. developed a method for building up cyclohexanone rings in polycyclic systems[4] and used it to accomplish a complete synthesis of *dl*-*D*-homotestosterone[4,270]. The method of annellation has been further developed for the synthesis of steroids by Scott et al.[268,271,272] Numerous carbocyclic[4,273-275] and heterocyclic[3] systems have also been obtained from the hydrogenolysis products. An elegant method for obtaining semicorrins (LXXXV), devised by two groups of chemists[276,277] using the same polyfunctional isoxazole derivative (LXXXVI) as starting material,



(LXXXVI) (LXXXV)

can rightly be regarded as a great success for this trend in the synthetic use of isoxazoles. The electrochemical reduction of phenylisoxazoles, in contrast to that of pyrazoles, also leads to rupture of the heterocyclic nitrogen–oxygen bond[278].

Individual products cannot be obtained by the catalytic hydrogenation of isothiazole derivatives[10]. On the other hand, the 2-methyl-3,5-diphenylisothiazolium ion can be easily reduced by benzenethiol to the 2-aminovinyl thioketone (LXXXVII).[253] 5-Amino-2-methyl-1-phenylpyrazolium cations are reduced by lithium tetrahydroaluminate with rupture of the $N_{(1)}-C_{(5)}$ bond to β-hydrazino-amides (LXXXVIII).[219]



(LXXXVII) (LXXXVIII)

The course of the oxidation of 1,2-azole derivatives depends on the nature of the rings and the substituents. Pyrazoles and isothiazoles are quite stable when heated with alkaline potassium permanganate, so that this method can be widely used to obtain azolecarboxylic acids[1,10]. The cleavage of the isoxazole ring under these conditions has been used to establish orientation on electrophilic substitution in arylisoxazoles[2].

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During preparation of the manuscript for press several important publications have appeared—on the physical and physicochemical properties of 1,2-azoles[279-283], substitution in ring and side-chain[284-296] and addition to double bonds in azoles[297-299], and ring cleavage with syntheses based on the cleavage products[300-304] (the sequence of topics in this list corresponds to the treatment in the Review).

REFERENCES

1. A. N. Kost and I. I. Grandberg, Adv. Heterocyclic Chem., 6, 347 (1966).
2. N. K. Kochetkov and S. D. Sokolov, Adv. Heterocyclic Chem., 2, 365 (1963).
3. T. Nishiwaki, Synthesis, 20 (1975).
4. G. Subrahmanyam, J. Sci. Ind. Res. India, 33, 304 (1974).
5. T. L. Jacobs, in "Heterocyclic Compounds" edited by R. C. Elderfield (Translated into Russian), Inostr. Lit., Moscow, 1961, Vol. 5, p. 42.
6. R. H. Wiley and P. F. Wiley, "Pyrazolones, Pyrazolidones and Derivatives", Wiley–Interscience, New York, 1964.
7. R. A. Barnes, see Ref. 5, p. 368.
8. A. Quilico, in "The Chemistry of Heterocyclic Compounds", Wiley–Interscience, New York, 1962, p. 1.
9. R. Slack and K. R. H. Wooldridge, Adv. Heterocyclic Chem., 4, 107 (1965).
10. K. R. H. Wooldridge, Adv. Heterocyclic Chem., 14, 1 (1972).
11. A. R. Katritzky and J. M. Lagowski, "Principles of Heterocyclic Chemistry" (Translated into Russian), Inostr. Lit., Moscow, 1963, p. 212.
12. L. A. Paquette, "Principles of Modern Heterocyclic Chemistry" (Translated into Russian), Mir, Moscow, 1971, p. 165.
13. V. I. Minkin, A. F. Pozharskii, and Yu. A. Ostroumov, Khim. Geterotsikl. Soed., 551 (1966).
14. I. L. Finar, J. Chem. Soc. B, 725 (1968).
15. D. A. Bochvar, A. A. Bagatur'yants, and A. V. Tutkevich, Izv. Akad. Nauk SSSR, Ser. Khim., 353 (1966).
16. G. Del Re, J. Chem. Soc., 3324 (1962).
17. A. Adams and R. Slack, J. Chem. Soc., 3061 (1959).
18. M. Witanowski, L. Stefaniak, H. Januszewski, Z. Grabowski, and G. A. Webb, Tetrahedron, **28**, 637 (1972).
19. M. Kamiya, Bull. Chem. Soc. Japan, 43, 3344 (1970).
20. C. Aussems, S. Jaspers, G. Leroy, and F. von Remoortere, Bull. Soc. chim. belges, 78, 407 (1969).
21. W. Adam and A. Grimison, Theor. Chim. Acta, 7, 342 (1967).
22. G. Berthier, L. Praud, and J. Serre, "Quantum Aspects of Heterocyclic Compounds—Chemistry and Biochemistry", Proceedings of Second International Symposium, 1969, p. 40; Chem. Abs., 75, 122140 (1971).
23. R. E. Burton and I. L. Finar, J. Chem. Soc. B, 1692 (1970).
24. M. Baule, R. Vivaldi, J.-C. Poite, H. J. M. Dou, G. Vernin, and J. Metzger, Bull. Soc. chim. France, 4310 (1971).
25. G. L. Blackman, R. D. Brown, F. R. Burden, and A. Mishra, J. Mol. Structure, 9, 465 (1971).
26. R. E. Wasylishen, T. R. Clem, and E. D. Becker, Canad. J. Chem., 53, 596 (1975).
27. T. La Cour and S. E. Rasmussen, Acta Chem. Scand., 27, 1845 (2973).
28. S. Biagini, M. Cannas, and G. Marongiu, Acta Cryst., B25, 730 (1969).
29. F. K. Larsen, M. S. Lehmann, I. Søtofte, and S. E. Rasmussen, Acta Chem. Scand., 24, 3248 (1970).

30. L. Nygaard, D. Christen, J. T. Nielsen, E. J. Pedersen, O. Snerling, E. Vestergaard, and G. O. Sørensen, J. Mol. Structure, **22**, 401 (1974).
31. L. Brehm, P. Krogsgaard-Larsen, and H. Hjeds, Acta Chem. Scand., **B28**, 308 (1974).
32. J. L. Galigné and J. Falgueirettes, Acta Cryst., **B26**, 380 (1970).
33. M. Cannas and G. Marongiu, Z. Krist., **127**, 388 (1968).
34. J. Elguero, E. Gonzalez, and R. Jacquier, Bull. Soc. chim. France, 2744 (1964).
35. A. G. Burton, P. C. Forsythe, C. D. Johnson, and A. R. Katritzky, J. Chem. Soc. B, 2365 (1971).
36. J. Elguero, E. Gonzalez, and R. Jacquier, Bull. Soc. chim. France, 5009 (1968).
37. S. D. Sokolov, L. A. Kazitsyna, and L. K. Guseva, Zhur. Org. Khim., **2**, 731 (1966).
38. G. Bianchi, M. J. Cook, and A. R. Katritzky, Tetrahedron, **27**, 6133 (1971).
39. S. D. Sokolov and G. B. Tikhomirova, Khim. Geterotsikl. Soed., 1029 (1976).
40. A. Albert, in "Physical Methods in Heterocyclic Chemistry" edited by A. R. Katritzky (Translated into Russian), Khimiya, Moscow and Leningrad, 1966, p. 109.
41. C. L. Habraken, P. C. M. van Woerkom, H. W. de Wind, and C. G. M. Kallenberg, Rec. Trav. chim., **85**, 1191 (1966).
42. A. J. Boulton and A. R. Katritzky, Tetrahedron, **12**, 51 (1961).
43. I. I. Grandberg, S. V. Tabak, and A. N. Kost, Khim. Geterotsikl. Soed., 85 (1966).
44. A. D. Baker, D. Betteridge, N. R. Kemp, and R. E. Kirby, Analyt. Chem., **42**, 1064 (1970).
45. G. Salmona, Y. Ferré, and E.-J. Vincent, Compt. rend., **273C**, 863 (1971).
46. A. D. Garnovskii, Yu. V. Kolodyazhnyi, O. A. Osipov, V. I. Minkin, S. A. Giller, I. B. Mazheika, and I. I. Grandberg, Khim. Geterotsikl. Soed., 867 (1971).
47. S. A. Giller, I. B. Mazheika, and I. I. Grandberg, Khim. Geterotsikl. Soed., 103 (1965).
48. I. B. Mazheika, I. S. Yankovska, S. D. Sokolov, and I. M. Yudintseva, Khim. Geterotsikl. Soed., 460 (1972).
49. J. H. Griffiths, A. Wardley, V. E. Williams, N. L. Owen, and J. Sheridan, Nature, **216**, 1301 (1967).
50. W. H. Kirchhoff, J. Amer. Chem. Soc., **89**, 1312 (1967).
51. W. C. Mackrodt, A. Wardley, P. A. Curnuck, N. L. Owen, and J. Sheridan, Chem. Comm., 692 (1966).
52. S. A. Giller, I. B. Mazheika, and I. I. Grandberg, Khim. Geterotsikl. Soed., 107 (1965).
53. S. B. Bulgarevich, V. S. Bolotnikov, V. N. Sheinker, O. A. Osipov, and A. D. Garnovskii, Znur. Obshch. Khim., **45**, 1821 (1975).
54. S. A. Giller, I. B. Mazheika, I. I. Grandberg, and L. I. Gorbacheva, Khim. Geterotsikl. Soed., 130 (1967).
55. S. F. Mason, see Ref. 40, p. 370.
56. J. Elguero, R. Jacquier, and H. C. N. Tien Duc, Bull. Soc. chim. France, 3744 (1966).
57. I. I. Grandberg, Zhur. Obshch. Khim., **33**, 519 (1963).
58. V. Bertini, A. de Munno, D. Tafuri, and P. Pino, Gazzetta, **94**, 915 (1964).
59. R. A. Olofson, J. M. Landesberg, R. O. Berry, D. Leaver, W. A. H. Robertson, and D. M. McKinnon, Tetrahedron, **22**, 2119 (1966).
60. J.-C. Poite, J. Roggero, H. J. M. Dou, G. Vernin, and J. Metzger, Bull. Soc. chim. France, 162 (1972).
61. A. Perichaud, J.-C. Poite, G. Mille, and J.-P. Roggero, Bull. Soc. chim. France, 3830 (1972).
62. G. Speroni, "The Chemistry of Heterocyclic Compounds", Wiley–Interscience, New York, 1962, p. 11 p. 177.
63. J.-P. Rioux, C. Clément, R. Jacquier, G. Tarrago, and J. Elguero, Bull. Soc. chim. France, 2144 (1970).
64. I. I. Grandberg, S. V. Tabak, and A. N. Kost, Zhur. Obshch. Khim., **33**, 525 (1963).
65. S. V. Tabak, I. I. Grandberg, and A. N. Kost, Tetrahedron, **22**, 2703 (1966).
66. P. Cohen-Fernandes and C. L. Habraken, Rec. Trav. chim., **86**, 1249 (1967).
67. F. P. Doyle, J. C. Hanson, A. A. W. Long, J. H. C. Nayler, and E. R. Stove, J. Chem. Soc., 5838 (1963).
68. A. Zecchina, L. Cerruti, S. Coluccia, and E. Borello, J. Chem. Soc. B, 1363 (1967).
69. A. R. Katritzky and A. J. Boulton, Spectrochim. Acta, **17**, 238 (1961).
70. S. Califano, F. Piacenti, and G. Sbrana, Spectrochim. Acta, **20**, 339 (1964).
71. J.-L. Meyer, G. Davidovics, and J. Chouteau, Canad. J. Chem., **49**, 2254 (1971).
72. V. S. Troitskaya, Yu. D. Timoshenkova, Yu. A. Pentin, and V. I. Tyulin, Khim. Geterotsikl. Soed., 1388 (1974).
73. C. Pouchan, S. Senez, and J. Raymond, J. Chem. phys., **71**, 525 (1974).
74. J. Ackrell, M. Altat-ur-Rahman, A. J. Boulton, and R. C. Brown, J. Chem. Soc., Perkin Trans. I, 1594 (1972) (as a footnote).
75. R. G. Micetich, Canad. J. Chem., **48**, 467 (1970).
76. B. J. Wakefield and D. J. Wright, J. Chem. Soc. C, 1165 (1970).
77. A. R. Katritzky, Quart. Rev., **13**, 353 (1959).
78. A. R. Katritzky, S. Øksne, and A. J. Boulton, Tetrahedron, **18**, 777 (1962).
79. R. Jacquier, C. Petrus, F. Petrus, and T. Plagnes, Bull. Soc. chim. France, 2920 (1969).
80. G. Zerbi and C. Alberti, Spectrochim. Acta, **19**, 1261 (1969).
81. G. Mille, G. Davidovics, J.-C. Poite, and M. Guiliano, Compt. rend., **276B**, 31 (1973).
82. G. Mille, J. Chouteau, and J. Metzger, J. Chim. phys., **72**, 113 (1975).
83. J. Elguero, J. L. Imbach, and R. Jacquier, J. Chim. phys., **62**, 643 (1965).
84. J. Elguero and R. Jacquier, J. Chim. phys., **63**, 1242 (1966).
85. J. Elguero, R. Jacquier, and H. C. N. Tien Duc, Bull. Soc. chim. France, 3727 (1966).
86. S. D. Sokolov, I. M. Yudintseva, and P. V. Petrovskii, Zhur. Org. Khim., **6**, 2584 (1970).
87. H. A. Staab and A. Mannschreck, Chem. Ber., **98**, 1111 (1965).
88. R. J. Pugmire and D. M. Grant, J. Amer. Chem. Soc., **90**, 4232 (1968).
89. A. N. Nesmeyanov, E. B. Zavelovich, V. N. Babin, N. S. Kochetkova, and E. I. Fedin, Tetrahedron, **31**, 1461 (1975).
90. G. M. Buchan and A. B. Turner, J. Chem. Soc., Perkin Trans. I, 2115 (1975).

91. J. P. Kintzinger and J. M. Lehn, Mol. Phys., 14, 133 (1968).
92. J. H. Finley and G. P. Volpp, J. Heterocyclic Chem., 6, 841 (1969).
93. C. L. Habraken and J. A. Moore, J. Org. Chem., 30, 1892 (1965).
94. L. G. Tensmeyer and C. Ainsworth, J. Org. Chem., 31, 1878 (1966).
95. C. L. Habraken, H. J. Munter, and J. C. P. Westgeest, Rec. Trav. chim., 86, 56 (1967).
96. J. Elguero, R. Jacquier, and S. Mignonac-Mondon, Bull. Soc. chim. France, 4436 (1970).
97. P. Beltrame, C. Veglio, and M. Simonetta, J. Chem. Soc. B, 867 (1967).
98. A. Battaglia, A. Dondoni, and F. Taddei, J. Heterocyclic Chem., 7, 721 (1970).
99. R. E. Wasylishen, J. B. Rowbotham, and T. Schaefer, Canad. J. Chem., 52, 833 (1974).
100. H. Y. Aboul-Enein and R. L. Settine, J. Mol. Structure, 18, 498 (1973).
101. E. Schempp and P. J. Bray, Phys. Letters, A25, 414 (1967).
102. E. Kochanski, J. M. Lehn, and B. Levy, Chem. Phys. Letters, 4, 75 (1969).
103. T. A. Babushkina, G. K. Semin, S. D. Sokolov, and I. M. Yudintseva, Izv. Akad. Nauk SSSR, Ser. Khim., 2376 (1970).
104. A. R. Katritzky and J. M. Lagowski, Adv. Heterocyclic Chem., 2, 28 (1963).
105. A. R. Katritzky, Chimia, 24, 134 (1970).
106. V. G. Vinokurov, V. S. Troitskaya, I. I. Grandberg, and Yu. A. Pentin, Zhur. Obshch. Khim., 33, 2597 (1963).
107. V. G. Vinokurov, V. S. Troitskaya, and I. I. Grandberg, Zhur. Obshch. Khim., 34, 654 (1964).
108. M. J. Nye and W. P. Tang, Tetrahedron, 28, 455 (1972).
109. V. G. Vinokurov, V. S. Troitskaya, and I. I. Grandberg, Zhur. Obshch. Khim., 35, 1288 (1965).
110. J. J. Bergman and B. M. Lynch, J. Heterocyclic Chem., 11, 135 (1974).
111. M. J. Nye and W. P. Tang, Tetrahedron, 28, 463 (1972).
112. W. Barbieri, L. Bernardi, S. Coda, V. Coló, and G. Palamidessi, Tetrahedron, 23, 4395 (1967).
113. H. Dorn, J. prakt. Chem., 315, 382 (1973).
114. J. Teysseyre, H. Sauvaitre, J. Arriau, and J. Deschamps, J. Mol. Structure, 12, 191 (1972).
115. F. De Sarlo, G. Dini, and P. Lacrimini, J. Chem. Soc. C, 86 (1971).
116. A. Mequestiau, Y. van Haverbeke, and R. N. Müller, Bull. Soc. chim. belges, 79, 343 (1970).
117. R. Jacquier, C. Petrus, F. Petrus, and J. Verducci, Bull. Soc. chim. France, 2690 (1970).
118. I. D. H. Stocks, J. A. Waite, and K. R. H. Wooldridge, J. Chem. Soc. C, 1314 (1971).
119. A. Maquestiau, Y. van Haverbeke, and R. Jacquerye, Bull. Soc. chim. belges, 82, 233 (1973).
120. S. D. Sokolov, L. D. Ashkinadze, M. A. Chlenov, and N. K. Kochetkov, Izv. Akad. Nauk SSSR, Otd. Khim., Nauk, 964 (1963).
121. A. R. Katritzky and C. D. Johnson, Angew. Chem., 79, 629 (1967).
122. J. Elguero, R. Jacquier, V. Pellegrin, and V. Tabacik, Bull. Soc. chim. France, 1974 (1970).
123. V. N. Setkin and S. D. Sokolov, Izv. Akad. Nauk SSSR, Ser. Khim., 936 (1964).
124. M. W. Austin, J. R. Blackborow, J. H. Ridd, and B. V. Smith, J. Chem, Soc., 1051 (1965).
125. S. Clementi, P. P. Forsythe, C. D. Johnson, and A. R. Katritzky, J. Chem. Soc., Perkin Trans. II, 1675 (1973).
126. W. J. Barry, P. Birkett, and I. L. Finar, J. Chem. Soc. C, 1328 (1969).
127. M. R. Grimmett, S. R. Hartshorn, K. Schofield, and J. B. Weston, J. Chem. Soc., Perkin Trans. II, 1654 (1972).
128. C. L. Habraken, P. Cohen-Fernandes, S. Balian, and K. C. van Erk, Tetrahedron Letters, 479 (1970).
129. P. Cohen-Fernandes and C. L. Habraken, Rec. Trav. chim., 91, 1185 (1972).
130. J. W. Janssen and C. L. Habraken, J. Org. Chem., 38, 1777 (1973).
131. M. D. Coburn, J. Heterocyclic Chem., 8, 153 (1971).
132. M. D. Coburn, J. Heterocyclic Chem., 8, 293 (1971).
133. I. J. Ferguson, M. R. Grimmett, and K. Schofield, Tetrahedron Letters, 2771 (1972).
134. W. J. Barry, I. L. Finar, and G. V. Khatkhate, J. Chem. Soc. C, 1120 (1968).
135. A. G. Burton, A. R. Katritzky, M. Konya, and H. O. Tarhan, J. Chem. Soc., Perkin Trans. II, 389 (1974).
136. R. B. Woodward, R. A. Olofson, and H. Mayer, J. Amer. Chem. Soc., 83, 1010 (1961).
137. M. R. Langella and P. Vita Finzi, Chimica e Industria, 47, 996 (1965).
138. B. M. Lynch and L. Shiu, Canad. J. Chem., 43, 2117 (1965).
139. V. Bertini, A. De Munno, V. dell'Amico, and P. Pino, Gazzetta, 97, 1604 (1967).
140. S. D. Sokolov and I. M. Yudintseva, Zhur. Org. Khim., 4, 2057 (1968).
141. S. D. Sokolov, T. N. Egorova, and I. M. Yudintseva, Khim. Geterotsikl. Soed., 597 (1974).
142. F. P. Doyle, J. C. Hanson, A. A. W. Long, and J. H. C. Nayler, J. Chem. Soc., 5845 (1963).
143. B. D. Wilson and D. M. Burness, J. Org. Chem., 31, 1565 (1966).
144. S. D. Sokolov, I. M. Yudintseva, P. V. Petrovskii, and V. G. Kalyuzhnaya, Zhur. Org. Khim., 7, 1979 (1971).
145. A. A. Ponomarev and L. V. Cherkasova, Zhur. Obshch. Khim., 33, 3946 (1963).
146. J. D. Vaughan, D. G. Lambert, and V. L. Vaughan, J. Amer. Chem. Soc., 86, 2857 (1964).
147. J. D. Vaughan, G. L. Jewett, and V. L. Vaughan, J. Amer. Chem. Soc., 89, 6218 (1967).
148. B. E. Boulton and B. A. W. Coller, Austral. J. Chem., 24, 1413 (1971).
149. S. D. Sokolov and I. M. Yudintseva, Zhur. Org. Khim., 7, 1765 (1971).
150. H. Reimlinger, A. Noels, J. Jadot, and A. van Overstraeten, Chem. Ber., 103, 1942 (1970).
151. J. Kinugawa and M. Ochiai, Chem. and Pharm. Bull. (Japan), 12, 23 (1964).
152. I. L. Finar and D. B. Miller, J. Chem. Soc., 2769 (1961).
153. S. D. Sokolov and I. M. Yudintseva, Khim. Geterotsikl. Soed., 742 (1975).
154. C. H. Eugster, L. Leichner, and E. Jenny, Helv. Chim. Acta, 46, 543 (1963).
155. D. J. Woodman, J. Org. Chem., 33, 2397 (1968).
156. S. P. Mal'tseva, Z. A. Borodulina, and B. I. Stepanov, Zhur. Org. Khim., 9, 815 (1963).
157. S. D. Sokolov, L. P. Savochkina, and N. K. Kochetkov, Zhur. Obshch. Khim., 34, 2207 (1964).

158. L. Birkofer and M. Franz, Chem. Ber., **104**, 3062 (1971).
159. J.-C. Poite, J. Julien, E.-J. Vincent, and J. Roggero, Bull. Soc. chim. France, 2296 (1972).
160. A. I. Shatenshtein, Tetrahedron, **18**, 95 (1962).
161. E. Chung Wu and J. D. Vaughan, J. Org. Chem., **35**, 1146 (1970).
162. R. A. Clofson, J. M. Landesberg, K. N. Houk, and J. S. Michelman, J. Amer. Chem. Soc., **88**, 4265 (1966).
163. R. A. Clofson and J. M. Landesberg, J. Amer. Chem. Soc., **88**, 4263 (1966).
164. D. E. Butler and S. M. Alexander, J. Org. Chem., **37**, 215 (1972).
165. R. G. Micetich, Canad. J. Chem., **48**, 2006 (1970).
166. K. Bowden, G. Crank, and W. J. Ross, J. Chem. Soc. C, 172 (1968).
167. R. G. Micetich and C. G. Chin, Canad. J. Chem., **48**, 1371 (1970).
168. D. E. Horning and J. M. Muchowski, Canad. J. Chem., **52**, 2950 (1974).
169. D. A. de Bie and H. C. van der Plas, Tetrahedron Letters, 3905 (1968).
170. M. Begtrup, Chem. Comm., 334 (1975).
171. M. Begtrup, J. Chem. Soc., Perkin Trans. I, 507 (1975).
172. G. Adembri, F. Pontichelli, and P. Tedeschi, J. Heterocyclic Chem., **6**, 783 (1969).
173. P. Bravo and G. Gaudiano, Gazzetta, **96**, 454 (1966).
174. S. Rossi and E. Duranti, Tetrahedron Letters, 485 (1973).
175. I. Ya. Kvitko and B. A. Porai-Koshits, Zhur. Org. Khim., **2**, 169 (1966).
176. M. P. L. Caton, G. C. J. Martin, and D. L. Pain, J. Chem. Soc. C, 776 (1971).
177. J. Faust, D. Arndt, and R. Mayer, Z. Chem., **8**, 19 (1968).
178. M. Begtrup, N. Conradsen, and J. H. Olsen, Acta Chem. Scand., **27**, 2930 (1973).
179. G. Vernin, H. J.-M. Dou, and J. Metzger, Bull. Soc. chim. France, 1173 (1972).
180. G. Vernin, J.-C. Poite, H. J. M. Dou, and J. Metzger, Bull. Soc. chim. France, 3157 (1972).
181. G. Fukata, Y. Kawazoe, and T. Taguchi, Tetrahedron Letters, 1199 (1973).
182. J. W. Janssen, P. Cohen-Fernandes, and R. Louw, J. Org. Chem., **40**, 915 (1975).
183. S. Cabiddu and V. Solinas, Gazzetta, **99**, 1107 (1969).
184. B. K. Simons, R. K. Kallury, and J. H. Bowie, Org. Mass. Spectrometry, **2**, 739 (1969).
185. H. K. Reimlinger and A. van Overstraeten, Chem. Ber., **99**, 3350 (1969).
186. J. Goerdeler and M. Roegler, Chem. Ber., **103**, 112 (1970) [1966?].
187. N. Saito, T. Kurihara, S. Yasuda, and M. Akagi, Yakugaku Zasshi, **90**, 32 (1970).
188. S. D. Sokolov and T. N. Egorova, Khim. Geterotsikl. Soed., 1697 (1974).
189. G. S. King, P. D. Magnus, and H. S. Rzepa, J. Chem. Soc., Perkin Trans. I, 437 (1972).
190. S. African P. 6 808 152 (1969); Chem. Abs., **72**, 79 012 (1970).
191. S. D. Sokolov, T. N. Egorova, and P. V. Petrovskii, Khim. Geterotsikl. Soed., 602 (1974).
192. D. S. Noyce and B. B. Sandel, J. Org. Chem., **40**, 3381 (1975).
193. J. L. Huppatz, Tetrahedron Letters, 3637 (1972).
194. H. Kano, I. Adachi, R. Kido, and K. Hirose, Jap. P. 25 125 ('64) (1964); Chem. Abs., **62**, 13 152b (1965).
195. R. Raap and R. G. Micetich, J. Medicin. Chem., **11**, 70 (1968).
196. C. Caradonna and M. L. Stein, Ann. Chim. (Italy), **54**, 539 (1964).
197. V. N. Setkina and S. D. Sokolov, Khim. Geterotsikl. Soed., 377 (1968).
198. S. D. Sokolov and V. N. Setkina, Khim. Geterotsikl. Soed., 786 (1969).
199. T. Hiraoka, M. Yoshimoto, and Y. Kishida, Chem. and Pharm. Bull. (Japan), **20**, 122 (1972).
200. C. Kashima, N. Mukai, and Y. Tsuda, Chem. Letters, 539 (1973).
201. C. Kashima and Y. Tsuda, Bull. Chem. Soc. Japan, **46**, 3533 (1973).
202. Jap. P. 7 480 062 (1974); Chem. Abs., **82**, 156 261 (1975).
203. Jap. P. 74 134 672 (1974); Chem. Abs., **83**, 10 043 (1975).
204. C. Kashima, S. Tobe, N. Sugiyama, and M. Yamamoto, Bull. Chem. Soc. Japan, **46**, 310 (1973).
205. T. Tanaka, M. Miyazaki, and I. Iijima, Chem. Comm., 233 (1973).
206. A. Marxer and M. Siegrist, Helv. Chim. Acta, **57**, 1988 (1974).
207. S. Trofimenko, Inorg. Chem., **12**, 1275 (1973).
208. M. Nonoyama, J. Organometallic Chem., **86**, 263 (1975).
209. M. I. Bruce, B. L. Goodall, and I. Matsuda, Austral. J. Chem., **28**, 1259 (1975).
210. G. Renzi, V. Dal Piaz, and S. Pinzau, Gazzetta, **99**, 753 (1969).
211. S. D. Sokolov and N. K. Kochetkov, Dokl. Akad. Nauk SSSR, **156**, 1391 (1964).
212. S. D. Sokolov and I. M. Yudintseva, Khim. Geterotsikl. Soed., 1325 (1973).
213. J. Elguero, G. Guiraud, R. Jacquier, and H. C. N. Tien Duc, Bull. Soc. chim. France, 328 (1967).
214. J. Elguero, R. Jacquier, and H. C. N. Tien Duc, Bull. Soc. chim. France, 2617 (1967).
215. G. L. Closs and H. Heyn, Tetrahedron, **22**, 463 (1966).
216. P. Bouchet, J. Elguero, R. Jacquier, and F. Forissier, Compt. rend., **269C**, 570 (1969).
217. R. L. Jones and C. W. Rees, J. Chem. Soc. C, 2251 (1969).
218. A. V. El'tsov and N. M. Omar, Zhur. Org. Khim., **4**, 711 (1968).
219. J. Elguero, R. Jacquier, and S. Mignonac-Mondon, Bull. Soc. chim. France, 2807 (1972).
220. T. Isida, T. Akiyama, N. Mihara, S. Kozima, and K. Sisido, Bull. Chem. Soc. Japan, **46**, 1250 (1973).
221. I. Adachi, R. Miyazaki, and H. Kano, Chem. and Pharm. Bull. (Japan), **22**, 70 (1974).
222. I. Adachi and H. Kano, Chem. and Pharm. Bull. (Japan), **17**, 2201 (1969).
223. I. Adachi, K. Harada, R. Miyazaki, and H. Kano, Chem. and Pharm. Bull. (Japan), **22**, 61 (1974).
224. M. Begtrup, Acta Chem. Scand., **27**, 2051 (1973).
225. J. Grimshaw and J. Trocha-Grimshaw, J. Chem. Soc., Perkin Trans. I, 1275 (1973).
226. F. Abjean, Compt. rend., **278C**, 359 (1974).
227. A. J. Boulton, A. R. Katritzky, and A. Majid Hamid, J. Chem. Soc. C, 2005 (1967).

228. M. I. Komendantov and R. R. Bekhmukhametov, Khim. Geterotsikl. Soed., 1053 (1978).
229. Y. Makisumi, Tetrahedron Letters, 6413 (1966).
230. Y. Makisumi and T. Sasatani, Tetrahedron Letters, 543 (1969).
231. A. Padwa, E. Chen, and A. Ku, J. Amer. Chem. Soc., 97, 6484 (1975).
232. M. J. Nye and W. P. Tang, Chem. Comm., 1394 (1971).
233. P. Beak, J. L. Miesel, and W. R. Messer, Tetrahedron Letters, 5315 (1967).
234. P. Beak and W. R. Messer, Tetrahedron, **25**, 3287 (1969).
235. M. Nakagawa, T. Nakamura, and K. Tomita, Agric. and Biol. Chem. (Japan), **38**, 2205 (1974).
236. M. Ohashi, A. Iio, and T. Yonezawa, Chem. Comm., 1148 (1970).
237. A. Lablache-Combier and A. Pollet, Tetrahedron, **28**, 3141 (1972).
238. M. Maeda, A. Kawahara, M. Kai, and J. Kojima, Heterocycles, **3**, 389 (1975).
239. T. Sato and K. Saito, Chem. Comm., 781 (1974).
240. P. Bouchet, C. Coquelet, J. Elguero, and R. Jacquier, Tetrahedron Letters, 891 (1973).
241. R. A. Khmel'nitskii, A. P. Krasnoshchek, A. A. Polyakova, and I. I. Grandberg, Zhur. Org. Khim., **3**, 1540 (1967).
242. J. van Thuijl, K. J. Klebe, and J. J. van Houte, Org. Mass Spectrometry, **5**, 1101 (1971).
243. B. J. Millard, J. Chem. Soc. C, 1231 (1969).
244. K. K. Zhigulev, S. D. Sokolov, and R. A. Khmel'nitskii, Khim. Geterotsikl. Soed., 1336 (1972).
245. T. Nishiwaki, Org. Mass Spectrometry, **5**, 123 (1971).
246. M. Ohashi, H. Kamachi, H. Kakisawa, A. Tatematsu, H. Yoshizumi, H. Kano, and H. Nakata, Org. Mass. Spectrometry, **2**, 195 (1969).
247. A. P. Krasnoshchek, R. A. Khmel'nitskii, A. A. Polyakova, and I. I. Grandberg, Zhur. Org. Khim., **4**, 689 (1968).
248. J. H. Bowie, R. K. Kallury, and R. G. Cooks, Austral. J. Chem., **22**, 563 (1969).
249. D. C. Nonhebel, Org. Mass Spectrometry, **3**, 1519 (1970).
250. I. I. Grandberg and N. I. Bobrova, Khim. Geterotsikl. Soed., 566 (1965).
251. R. Fusco and M. Bianchi, Gazzetta, **97**, 410 (1967).
252. V. Bertini, A. De Munno, and P. Pino, Gazzetta, **97**, 185 (1967).
253. P. Sykes and K. Ullah, J. Chem. Soc., Perkin Trans. I, 2305 (1972).
254. R. B. Woodward and R. A. Olofson, J. Amer. Chem. Soc., **83**, 1007 (1961).
255. R. B. Woodward, R. A. Olofson, and H. Mayer, Tetrahedron, Suppl. No. 8, 321 (1966).
256. D. J. Woodman and A. I. Davidson, J. Org. Chem., **38**, 4288 (1973).
257. T. M. Jacob and H. G. Khorana, J. Amer. Chem. Soc., **86**, 1630 (1964).
258. P. Bodlaender, G. Feinstein, and E. Shaw, Biochemistry, **8**, 4941 (1969).
259. P. L. Hall and R. B. Perfetti, J. Org. Chem., **39**, 111 (1974).
260. M. Ohashi, T. Maruishi, and H. Kakisawa, Tetrahedron Letters, 719 (1968).
261. M. Winn, J. Org. Chem., **40**, 955 (1975).
262. R. Fusco, V. Rosnati, and G. Pagani, Tetrahedron Letters, 1739 (1966).
263. A. L. Khurana and A. M. Unrau, Canad. J. Chem., **53**, 3011 (1975).
264. I. Yavari, S. Esfandiari, A. J. Mostashari, and P. W. Hunter, J. Org. Chem., **40**, 2880 (1975).
265. G. Büchi and J. C. Vederas, J. Amer. Chem. Soc., **94**, 9128 (1972).
266. C. Kashima, J. Org. Chem., **40**, 526 (1975).
267. J. W. Scott, E. Widmer, W. Meier, L. Labler, P. Müller, and A. Fürst, J. Org. Chem., **37**, 3183 (1972).
268. J. W. Scott, B. L. Banner, and G. Saucy, J. Org. Chem., **37**, 1664 (1972).
269. N. K. Kochetkov, E. D. Khomutova, and M. V. Bazilevskii, Zhur. Obshch. Khim., **28**, 2736 (1958).
270. G. Stork and J. E. McMurry, J. Amer. Chem. Soc., **89**, 5464 (1967).
271. T. C. McKenzie, J. Org. Chem., **39**, 629 (1974).
272. J. W. Scott, P. Buchschacher, L. Labler, W. Meier, and A. Fürst, Helv. Chim. Acta, **57**, 1217 (1974).
273. S. Auricchio and A. Ricca, Gazzetta, **103**, 37 (1973).
274. S. Auricchio, S. Morrocchi, and A. Ricca, Tetrahedron Letters, 2793 (1974).
275. A. A. Akhrem, F. A. Lakhvich, V. A. Khripach, and I. B. Klebanovich, Khim. Geterotsikl. Soed., 329 (1975).
276. R. V. Stevens, L. E. Du Pree, Jr., W. L. Edmonson, L. L. Magid, and M. P. Wentland, J. Amer. Chem. Soc., **93**, 6637 (1971).
277. G. Traverso, G. P. Pollini, A. Barco, and G. de Giuli, Gazzetta, **102**, 243 (1972).
278. I. G. Markova, M. K. Polievktov, and S. D. Sokolov, Zhur. Obshch. Khim., **46**, 398 (1976).
279. A. V. Chapman, M. J. Cook, A. R. Katritzky, M. H. Abraham, A. F. Danil de Namor, L. Dumont, and J. Reisse, Tetrahedron, **34**, 1571 (1978).
280. J. L. McVicars, M. F. Mackay, and M. Davis, J. Chem. Soc., Perkin Trans. II, 1332 (1977).
281. I. D. Kalikhman, V. A. Lopyrev, E. F. Shibanova, V. A. Pestunovich, and M. G. Voronkov, Izv. Akad. Nauk SSSR, Ser. Khim., 2390 (1977).
282. N. N. Zatsepina, I. F. Tupitsyn, A. I. Belyashova, A. A. Kane, N. S. Kolodina, and G. N. Sudakova, Khim. Geterotsikl. Soed., 1110 (1977).
283. J. Elguero, C. Marzin, A. R. Katritzky, and P. Linda, "The Tautomerism of Heterocycles", Academic Press, 1976, Chapter 4.
284. M. R. Grimmett and K. H. R. Lim, Austral. J. Chem., **31**, 689 (1978).
285. A. R. Katritzky, H. O. Tarhan, and B. Terem, J. Chem. Soc., Perkin Trans. II, 1632 (1975).
286. S. Clementi, P. P. Forsythe, C. D. Johnson, A. R. Katritzky, and B. Terem, J. Chem. Soc., Perkin Trans. II, 399 (1974).
287. A. R. Katritzky, H. O. Tarhan, and B. Terem, J. Chem. Soc., Perkin Trans. II, 1620 (1975).
288. A. R. Katritzky, M. Konya, and H. O. Tarhan, J. Chem. Soc., Perkin Trans. II, 1627 (1975).
289. C. L. Habraken and E. K. Poels, J. Org. Chem., **42**, 2893 (1977).
290. J. P. Freeman and J. F. Lorenc, J. Org. Chem., **42**, 177 (1977).
291. C. L. Habraken and S. M. Bonser, Heterocycles, **7**, 259 (1977).
292. D. S. Noyce and B. B. Sandel, J. Org. Chem., **40**, 3381 (1975).

293. D. S. Noyce and B. B. Sandel, J. Org. Chem., **41**, 3640 (1976).
294. N. N. Zatsepina, I. F. Tupitsyn, A. I. Belyashova, A. V. Kirova, and E. Ya. Konyakhina, Khim. Geterotsikl. Soed., 1196 (1977).
295. C. Kashima, Y. Yamamoto, Y. Tsuda, and Y. Omote, Bull. Chem. Soc. Japan, **49**, 1047 (1976).
296. C. Kashima, Y. Yamamoto, Y. Tsuda, Heterocycles, **6**, 805 (1977).
297. C. Caristi and M. Gattuso, J. Chem. Soc., Perkin Trans. I, 679 (1974).
298. G. Stagno d'Alcontres, C. Caristi, A. Ferlazzo, and M. Gattuso, J. Chem. Soc., Perkin Trans. I, 1694 (1976).
299. D. N. Reinhoudt and C. G. Kouwenhoven, Rec. Trav. chim., **95**, 67 (1976).
300. K. Dietliker, P. Gilgen, H. Heimgartner, and H. Schmid, Helv. Chim. Acta, **59**, 2074 (1976).
301. C. Kashima, N. Mukai, Y. Yamamoto, Y. Tsuda, and Y. Omote, Heterocycles, **7**, 241 (1977).
302. A. De Munno, V. Bertini, and F. Lucchesini, J. Chem. Soc., Perkin Trans. II, 1121 (1977).
303. R. V. Stevens, C. G. Christensen, R. M. Cory, and E. Thorsett, J. Amer. Chem. Soc., **97**, 5940 (1975).
304. T. N. Mitchell and B. Kleine, Tetrahedron Letters, 2173 (1976).

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