Ring Opening and Closing in Heterocyclic Compounds. ^{1}H Nuclear Magnetic Resonance Studies on the Reaction between 6-Nitrobenzothiazole and Methoxide Ion in Dimethyl Sulphoxide–Methanol

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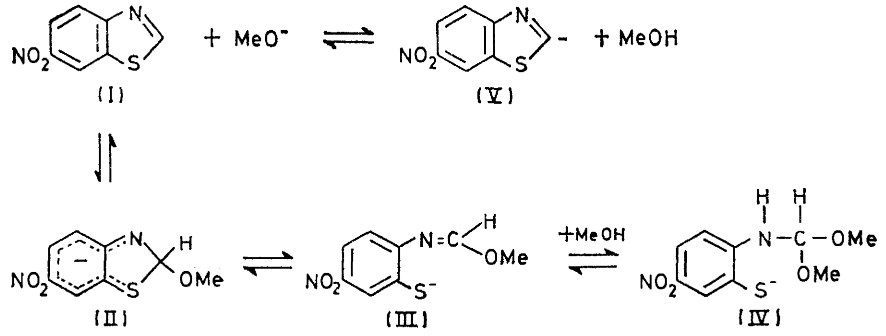
The reversible interaction between 6-nitrobenzothiazole and methoxide ion in DMSO or DMSO–MeOH mixtures leads to the open anion 2-methoxymethyleneamino-5-nitrobenzenethiolate (III), *via* a Meisenheimer-like adduct. Addition of CH_3I or Br_2–pyridine in CCl_4 to the reaction mixtures yields 2-methoxymethyleneamino-5-nitrophenyl methyl sulphide or bis-(2-methoxymethyleneamino-5-nitrophenyl) disulphide respectively. ^{1}H N.m.r. studies show that in DMSO–MeOH rapid addition of MeOH to the N=C double bond of (III) occurs.

STABLE σ anionic complexes can be obtained easily from electron-deficient azoles and strong bases.[1] A cyclic structure, in which the carbon atom involved in the nucleophilic attack has tetrahedral geometry, is generally assigned to these compounds on the basis of ^{1}H n.m.r. or *X*-ray studies.[2]

We reported recently [3] that the reaction between 6-nitrobenzothiazole (I) and methoxide ion in DMSO probably follows a more complex course. Indeed, the addition of electrophilic agents to the reaction mixture leads to ring opening. We report here a complete investigation of these processes.

Only a few examples of irreversible ring cleavage by the action of secondary aliphatic amines on mono-[4] and polynitro-thiophens [5] or 2-halogeno-5-nitrothiazoles [6] are known. Furthermore, special interest attaches to our system whose behaviour is closely related to that of thiamine [7] under basic conditions.



SCHEME

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[5] C. Dell'Erba, D. Spinelli, and G. Leandri, *Chem. Comm.*, 1969, 549.

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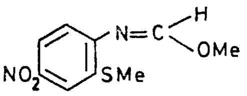
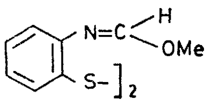
RESULTS AND DISCUSSION

When 6-nitrobenzothiazole was mixed with methoxide ion in DMSO under nitrogen a dark red colour soon developed which rapidly faded by addition of CH_3I or bromine–pyridine in CCl_4 giving the ring-opened derivatives (VI) or (VII). The structures were assigned on the basis of elemental analyses and ^1H n.m.r. spectra (see Experimental section). Moreover, if aqueous acetic acid is added to the red mixture the starting material (I) is quantitatively regenerated, whereas the addition of a strong mineral acid gives a mixture of (I) and bis-(2-amino-5-nitrophenyl) disulphide. These results strongly suggest the presence of an anionic open form (III), which could originate from S–C(2) bond cleavage of (II) (see Scheme).



(VI)



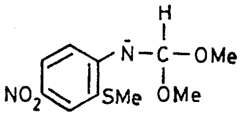
(VII)

Moreover ^1H n.m.r. spectroscopic studies show that, when the reaction is performed in DMSO–MeOH, rapid addition of methanol to (III) occurs to give the anion (IV) (see Scheme).

The spectrum (60 MHz) of (I) in DMSO–MeOH (95 : 5 v/v) consists of three bands, τ 0.42 (s, 2-H), 0.93 (m, 7-H), and 1.80 (m, 4- and 5-H), of relative intensity 1 : 1 : 2. The addition of <1 mol. equiv. of solid potassium methoxide gives new resonances of equal intensity at higher fields as expected for an anionic adduct, τ 2.05 (d), 2.30br (d), 2.55 (q), 3.60 (d), and 4.55 (d). The doublets at τ 2.05 and 3.60 and the quartet at 2.55 on the basis of their coupling constants can be attributed to the aromatic 7-, 4-, and 5-H)* respectively, of any one of species (II)—(IV). The resonance at τ 4.55 was found to be consistent only with $CH(OMe)_2$ of (IV) by observing the n.m.r. spectrum of the 2-deuterio-compound and on the basis of behaviour under different basic conditions. $CH(OMe)_2$ Is coupled with the broad resonance at τ 2.30 assigned to NH, which is partially hidden by the 5-H quartet. An increase of the potassium methoxide: substrate ratio to 1 : 1 causes coalescence of the doublet at τ 2.05 and a shift of the broad signal under that for 5-H. The positions of the 7-, 4-, and 5-H signals remain unchanged. Finally, further addition of base sharpens the $CH(OMe)_2$ signal and causes the disappearance of the resonance hidden by 5-H.

If the reasonable assumption is made that there is only a small amount of free methoxide in the reaction mixture when the base: substrate ratio is <1 : 1, the resulting basicity of the medium will be too low to allow rapid hydrogen abstraction and reprotonation of the NH function of the charged species (IV). Consequently, coupling can exist between NH and the proton bonded to the α-carbon. As the base concentration increases relative to that of the substrate exchange of NH becomes faster and causes coalescence and sharpening of the doublet at τ 4.55. Further information on this coupling state cannot be obtained by using deuteriated solvents, owing to the rapid exchange of 2-H with deuterium in the starting material (I) under basic conditions (see Scheme).

On the other hand our conclusion was also strongly supported by parallel studies [8] on the addition of base to the N=C double bond. We have found that the interaction between methoxide ion and 2-methoxymethyleneamino-5-nitrophenyl methyl sulphide (VI) in DMSO at room temperature leads to the anionic adduct (VIa). The ^1H n.m.r. spectra of (VIa) in $(CD_3)_2SO$ showed a chemical shift for $CH(OMe)_2$ (τ 4.6) close to that observed for the same proton in (IV). The aromatic protons were also shifted to comparably higher fields and it was possible to detect two resonances at τ 7.80 (3H) and 6.75 (6H), which were assigned respectively to the methylthio- and to the two equivalent methoxy-groups.



(VIa)

Recently Osata and Kawasaki [9] have also found that in MeCN–MeOH addition of alcohols to substituted benzylideneanilines occurs easily in basic media and that these reactions are not followed by subsequent cleavage of the C–N bond. These observations are at variance with the usual opinion that the addition reaction is often obscured by subsequent C–N cleavage. According to these findings we have observed that under nitrogen compound (IV) is stable for several hours. No products arising from complete cleavage of N=C bond or oxidation of S^- were detected by ^1H n.m.r. spectroscopy or by means of CH_3I addition.

When attempts were made to isolate compound (IV) as a thiol or a sulphide by addition of dilute acetic acid or CH_3I, only the starting material (I) or the sulphide (VI) were recovered. This is not surprising in view of the fact that in the absence of strong bases an unfavourable equilibrium exists for the addition of hydroxylic nucleophiles to an N–C linkage.[10] In contrast the addition of thiols is favoured reaction.[10-12] Thus the Schiff's bases of *o*-aminobenzenethiols exist almost exclusively as cyclic tautomers.[13] Therefore neutralization of the reaction mixture produced a complete reversion to 6-nitrobenzothiazole (see Scheme). On the other hand, as mentioned above, strong mineral acids cause the cleavage of the N–C bond of (IV), giving 2-amino-5-nitrobenzenethiol, which is rapidly oxidized by air.

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* For the sake of simplicity the numbering of benzothiazole is preserved throughout the Scheme.

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[10] W. P. Jenks, *J. Amer. Chem. Soc.*, 1959, **81**, 475.

[11] T. M. Oakes and G. W. Stacy, *J. Amer. Chem. Soc.*, 1972, **94**, 1594.

[12] G. W. Stacy, R. I. Day, and R. J. Morath, *J. Amer. Chem. Soc.*, 1955, **77**, 3869.

[13] A. H. Land, *Chem. Heterocyclic Compounds*, 1957, **5**, 508.

Having settled the structure of the final compound (IV), we turned our attention to the spectroscopic identification of the intermediate (III). When the reaction is performed in absolute DMSO with solid potassium methoxide, freed as much as possible from methanol, the ^1H n.m.r. spectrum gives a different picture, τ 1.95 (s), 2.10 (d), 2.45 (q), and 3.60 (d). The chemical shift value of the singlet at τ 1.95 is consistent with that of N=CH of the ion (III) as is suggested by comparison of the resonances of the neutral derivatives (VI) and (VII).* The doublets at τ 2.10 and 2.45 and the quartet at 3.60 were assigned respectively to 7-, 5-, and 4-H of (III). These shifts are close to those observed for (IV) as expected from the fact that the addition of methanol does not change the charge state of (III). Small signals partially hidden by the larger resonances of (III) were attributed to compounds arising from addition of traces of water or methanol to (III).

Furthermore it was possible to single out compound (III) as a transient species in DMSO–MeOH. In fact a fast scan of the reaction (substrate:MeOK mole ratio 1 : 0.5) in DMSO–MeOH (95 : 5 v/v) results at first in a spectrum with overlapping signals from both species (III) and (IV) in addition to the broadened bands of the starting material. In a subsequent scan the bands of (IV) increase at expense of those of (III). Finally, the broadness of the bands of (I) suggests a fast equilibrium with a charged species, most probably of the Meisenheimer-type.

However, the situation may be due to anion (V), which could originate from (I) after base-promoted hydrogen abstraction. This hypothesis is supported by the observation of fast exchange of the $CH(OMe)_2$ under basic conditions in deuteriated solvents.

In order to distinguish between these two possibilities we have allowed the reaction to take place over times ranging from milliseconds to minutes in a continuous-flow apparatus and then quenching with a large excess of CH_3CO_2D in D_2O. Incorporation of the label was not observed in any case, thus ruling out the presence of (V) in sufficient quantity to justify the broadening of the bands in the reaction mixture. Furthermore, the hypothesis that this broadening could be due to the presence of a radical anion species[14] can be rejected on the basis of e.s.r. experiments.

Conclusions.—Our results show that the interaction between MeO^- and 6-nitrobenzothiazoles in DMSO and DMSO–MeOH leads to open anions (III) and (IV) whose relative amount depends upon the presence of methanol in the reaction. These benzenethiolate ions are formed by cleavage of the S–C(2) bond of a cyclic anionic adduct. This is in turn formed as intermediate from nucleophilic attack of the base on C(2). The cleavage of the C–S bond in a thiazole Meisenheimer-like adduct is not surprising if we take into account that the transformation (I)$\rightarrow$(III) would formally correspond to a nucleophilic substitution on an sp^2 carbon and that in similar reactions the SPh system is a good leaving group.

EXPERIMENTAL

^1H N.m.r. spectra were recorded with a JEOL 60 MHz instrument, using tetramethylsilane as internal standard.

Materials.—Methanol (reagent grade) was purified by distillation over magnesium; DMSO was distilled twice and dried over 4A molecular sieves. Solid potassium methoxide was obtained by dissolving clean potassium metal in methanol under nitrogen and distilling off the solvent under reduced pressure. 6-Nitrobenzothiazole was prepared by nitration of benzothiazole as described by Ward.[15]

Preparation and Characterization of Products.—*2-Methoxymethyleneamino-5-nitrophenyl methyl sulphide* (VI). 6-Nitrobenzothiazole (0.01 mol) was dissolved in DMSO (5 ml) and mixed with potassium methoxide (0.01 mol) in methanol (1 ml). After 10 min the red-violet mixture was added to a stoicheiometric amount of CH_3I and then poured into cold water. The *product* (VI) was recovered from the aqueous mixture in quantitative yield by extraction with CH_2Cl_2, m.p. 103—104° (from CH_2Cl_2–hexane) (Found: C, 47.8; H, 4.2; N, 12.3. $C_9H_{10}N_2O_3S$ requires C, 47.8; H, 4.4; N, 12.4%), τ ($CDCl_3$) 2.13—2.33 (2 H, m, 4- and 6-H)), 2.45 (1 H, s, N=CH), 3.32 (1 H, d, 3-H), 6.10 (3 H, s, Me), and 7.55 (3 H, s, SMe).

Bis-(2-methoxymethyleneamino-5-nitrophenyl) disulphide (VII). A CCl_4 (5 ml) solution of Br_2 (0.01 mol) and pyridine (0.05 mol) was added to the red reaction mixture obtained as above. Completion of the reaction was monitored by the disappearance of the colour. Dilution with water and extraction with CH_2Cl_2 yielded *compound* (VII) which decomposed above 170° (Found: C, 45.7; H, 3.2; N, 13.5. $C_{16}H_{14}N_4O_6S_2$ requires C, 45.5; H, 3.3; N, 13.3%), τ ($CDCl_3$) 1.72 (1 H, d, 6-H), 2.10 (1 H, dd, 4.H), 2.25 (1 H, s, N=CH), 3.17 (1 H, d, 3-H), and 5.99 (3 H, s, OCH_3). As expected[16] for these compounds, no *syn–anti*-isomerism was detected at room temperature.

Bis-(2-amino-5-nitrophenyl) disulphide (VIII). Br_2 (0.01 mol) in CCl_4 (5 ml) was added to the red mixture prepared as above. The usual work-up yielded *compound* (VIII) quantitatively m.p. *ca.* 180° (decomp.) (Found: C, 43.0; H, 3.0; N, 16.2. $C_{12}H_{10}N_4O_4S_2$ requires C, 42.6; H, 3.0; N, 16.6%), τ [$(CD_3)_2SO$] 2.11 (1 H, dd, 4-H), 2.53 (1 H, d, 6-H), 2.97br (2 H, NH_2), and 3.25 (1 H, d, 3-H).

[5/325 *Received*, 17*th February*, 1975]

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* This assignment was confirmed by deuterium labelling.

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