Electrophilic Subsitution in 2,1-Benzisothiazoles

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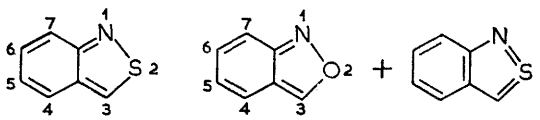
Bromination of 2,1-benzisothiazole (I) under conditions in which Br^+ is the electrophilic species gives a mixture of 5- and 7-bromo-2,1-benzisothiazole, together with a smaller quantity of 4,7-dibromo-2,1-benzisothiazole. Nitration of 2,1-benzisothiazole affords mainly 5-nitro-2,1-benzisothiazole with smaller quantities of the 7-nitro- and 4-nitro-isomers. Nitration of monosubstituted 2,1-benzisothiazoles gives products which indicate that the substituent group already present in the benzenoid ring is the decisive directing influence.

THE recent development of a simple synthesis of 2,1-benzisothiazole (I)[1] and of substituted 2,1-benzisothiazoles[2] allows the properties of this hitherto neglected heterocyclic system to be investigated in more detail. We now report the results of our work on electrophilic substitution in these compounds.



(I) (II) (III)

The early observations of Bamberger and Lublin[3] on the halogenation of 2,1-benzisoxazole ('anthranil') (II) have been interpreted and extended by A. J. Boulton and his co-workers.[4,5] This latter group found that 2,1-benzisoxazole, on halogenation, yields the 5-substituted isomer; on nitration, a small amount of the 7-nitro-compound was detected, the main product being 5-nitro-2,1-benzisoxazole.

Orientation of the substituted 2,1-benzisoxazoles was established primarily by alkaline hydrolysis to known substituted anthranilic acids. 2,1-Benzisothiazoles, on the other hand, are quite stable to such treatment and, for the present work, other means of orientation of isomers were sought. N.m.r. studies in this laboratory have shown[6] that in 2,1-benzisothiazoles the proton at C-3, which resonates downfield of the usual aromatic region, is coupled with the proton at C-7 (J *ca.* 0·9 Hz). The coupling constant between the protons at C-4 and C-5 is *ca.* 9 Hz, and between those at C-5 and C-6 it is *ca.* 7·5 Hz. These coupling constants are very similar to those determined earlier for 2,1-benzisoxazole.[5,7] The n.m.r. spectrum of a substituted 2,1-benzisothiazole, together with evidence of identity or otherwise with compounds prepared earlier[2] are sufficient to establish the substitution pattern without the need for degradative studies.

We find that 2,1-benzisothiazole, on bromination with

[1] M. Davis and A. W. White, *Chem. Comm.*, 1968, 1547.
[2] M. Davis and A. W. White, *J. Org. Chem.*, in the press.
[3] E. Bamberger and J. Lublin, *Ber.*, 1909 **42**, 1676.
[4] K.-H. Wünsch, H. Linke, A. J. Boulton, and Altaf-ur-Rahman, *Chem. Comm.*, 1965, 408.
[5] Altaf-ur-Rahman and A. J. Boulton, *Tetrahedron*, 1966, Suppl. 7, 49.
[6] M. Davis, B. Ternai, and A. W. White, unpublished work.
[7] B. Ternai, unpublished work (1965), quoted by K.-H. Wünsch and A. J. Boulton in 'Advances in Heterocyclic Chemistry,' A. R. Katritzky and A. J. Boulton, ed., Academic Press, New York, 1967, vol. 8, p. 320.

molecular bromine in sulphuric acid in the presence of silver sulphate,[8] yields a mixture. 5-Bromo-2,1-benzisothiazole (31%) and 7-bromo-2,1-benzisothiazole (31%) are the major products; 4,7-dibromo-2,1-benzisothiazole (16%) is also formed, together with a trace (<1%) of a compound believed to be 4-bromo-2,1-benzisothiazole. Unchanged 2,1-benzisothiazole (22%) is recovered.

The products of bromination differ in basicity, and these differences were exploited in separating the compounds formed. Attempts to brominate 2,1-benzisothiazole by other methods (*e.g.*, bromine in acetic acid, or in carbon tetrachloride) failed to give satisfactory results; vigorous conditions were required for reaction to occur, and a highly complex mixture of products was then produced.

Nitration of 2,1-benzisothiazole, with nitric acid in sulphuric acid solution, also produces a mixture; 5-nitro-2,1-benzisothiazole (57%) is the major product. 7-Nitro-2,1-benzisothiazole (26%) and 4-nitro-2,1-benzisothiazole (17%) are also formed. These isomeric nitro-2,1-benzisothiazoles are readily separated by fractional crystallisation. No resinification or oxidation of 2,1-benzisothiazole has been observed in this reaction.

We have also investigated the nitration, under various conditions, of monosubstituted 2,1-benzisothiazoles. This generally produced one major product only (Table 1).

Attempts to acylate 2,1-benzisothiazole, under Friedel–Crafts or Vilsmeier–Haack conditions, have been unsuccessful.

TABLE 1

Nitration of substituted 2,1-benzisothiazoles

2,1-Benzisothiazole nitrated	2,1-Benzisothiazole product	Yield of product obtained (%)
4-Me	4-Me, 7-NO_2	65
5-Cl	5-Cl, 4-NO_2	67
5-NO_2	5,7-$(NO_2)_2$	36
6-Br	6-Br, 7-NO_2	66
6-NO_2	4,6-$(NO_2)_2$	24
7-Me	7-Me, 4-NO_2	52
7-NO_2	5,7-$(NO_2)_2$	72

Several conclusions may be drawn from these results. Firstly, it is clear that 2,1-benzisothiazole is a stable, aromatic heterocyclic system. It appears to react with bromine only by substitution, not, as can occur with 2,1-benzisoxazoles, by addition across the C(4)–C(5) bond.[5] In nitration experiments we have as yet detected no evidence of scission of the heterocyclic ring.

Secondly, electrophilic substitution reactions give products analogous to those obtained with 2,1-benzisoxazole; however, on nitration some of the 4-substituted product is formed. This behaviour is similar to that of quinoline, which yields a mixture of 5- and 8-nitroquinolines;[9] these positions correspond to the 4- and 7-positions in 2,1-benzisothiazole. 2,1-Benzisothiazole thus shows properties intermediate between those of 2,1-benzisoxazole and of quinoline.

Finally, the formation of three isomeric nitro-compounds on nitration of the parent heterocycle, and the ease with which groups already present in the benzenoid ring, in substituted 2,1-benzisothiazoles, control the orientation of further electrophilic substitution, suggest that the perturbing effect of the heterocyclic ring on the benzenoid ring is relatively slight.

An *ortho*-quinonoid formulation of the benzenoid ring, as in the classical structure (I), suggests that such a ring should be capable of an addition reaction with bromine, as in the comparable case of anthranil [5] already mentioned. We have no such reaction in the present case; and 2,1-benzisothiazole does not exhibit the instability or reactivity usually associated with *ortho*-quinonoid compounds such as, for example, isoindoles [10] or isobenzothiophens.[11] Salmond, in a recent review,[12] has discussed the valence-shell expansion of sulphur in heterocyclic systems; in the present context the tetracovalent sulphur structure (III) would seem to give a rather more accurate representation of the properties of 2,1-benzisothiazoles.

EXPERIMENTAL

M.p.s are uncorrected and were obtained with a Büchi apparatus. N.m.r. spectra were recorded in deuteriochloroform solution (*ca.* 5%) with tetramethylsilane as internal standard, on a Varian A60-D spectrometer. Analyses were by the Australian Microanalytical Service, Melbourne. Microanalytical and n.m.r. data for novel compounds are listed in Table 2.

2,1-Benzisothiazole and monosubstituted 2,1-benzisothiazoles used were prepared by the reaction between *o*-toluidine, or a substituted *o*-toluidine, and thionyl chloride, as described earlier.[1,2]

Bromination of 2,1-Benzisothiazole.—To a mixture of 2,1-benzisothiazole (1·35 g., 10 mmole), silver sulphate (1·57 g., 5 mmole) and sulphuric acid (15 ml.) was added bromine (1·60 g., 10 mmole) and the resulting mixture was shaken at room temperature. Reaction was complete after 30 min. Dilution of the mixture with water, neutralisation, and extraction with chloroform afforded a mixture which was analysed by n.m.r. Integration of the signal in the region of the C-3 proton resonances (between τ 0 and 1·25) gave the product ratios directly. These were confirmed by gas chromatographic examination of the mixture on a silicone rubber column at 225°.

Separation of the Products of Bromination.—The crude reaction mixture (1·9 g.) from evaporation of the chloroform solution (above) was dissolved in hydrochloric acid (10M; 15 ml.) and extracted with carbon tetrachloride (2 × 10 ml.); evaporation of the latter afforded 4,7-dibromo-2,1-benzisothiazole (0·25 g.). The n.m.r. spectrum of this compound consisted of a singlet of τ 0·57 (3-H), and an AB pattern, centred at τ 2·58 (J 7·5 Hz). This coupling constant is indicative of coupling between protons at C-5 and C-6

[8] P. B. D. de la Mare, M. Kiamud-din, and J. H. Ridd, *J. Chem. Soc.*, 1960, 561.
[9] M. H. Palmer, 'Heterocyclic Compounds,' Edward Arnold, London, 1967, p. 118.
[10] N. V. Sidgwick, 'Organic Chemistry of Nitrogen,' Oxford University Press, London, 3rd edn., 1966, pp. 642—643.
[11] R. Mayer, H. Kleinert, S. Richter, and K. Gewald, *Angew. Chem.*, 1962, **74**, 118.
[12] W. G. Salmond, *Quart. Rev.*, 1968, **22**, 253.

rather than between those at C-4 and C-5 (J 9 Hz) as in a possible alternative structure, 6,7-dibromo-2,1-benzisothiazole.

Repeated extraction of the residual hydrochloric acid solution with chloroform (5 × 10 ml.) afforded mainly 7-bromo-2,1-benzisothiazole (0·5 g.), the 5-bromo-isomer remaining almost wholly in the acid layer. Dilution of the acid to 8M and further extraction with chloroform (5 × 10 ml.) yielded 5-bromo-2,1-benzisothiazole (0·5 g.), identified by direct comparison with an authentic sample;[2] from the acid after further dilution and extraction unchanged 2,1-benzisothiazole (0·35 g.) was obtained.

A further compound with a retention time similar to that of the other monobromo-2,1-benzisothiazoles was also detected (<1%) by g.l.c. examination of the crude reaction product. It was not identical with 6-bromo-2,1-benzisothiazole[2] and is therefore believed to be 4-bromo-2,1-benzisothiazole.

(0·3 g.) of 7-nitro-2,1-benzisothiazole. Dilution of the residual ethanol solution with an excess of water yielded 4-nitro-2,1-benzisothiazole (0·15 g.) as pale yellow needles. Recrystallisation of the 5-nitro- and 7-nitro-2,1-benzisothiazoles from ethanol, and of 4-nitro-2,1-benzisothiazole from aqueous ethanol, afforded isomerically pure products.

The 7-nitro-isomer was identified as such by the singlet nature of the C-3 proton signal in its n.m.r. spectrum. This isomer, and 5-nitro-2,1-benzisothiazole, gave on nitration the same product. This product possessed an n.m.r. spectrum with three lines—a singlet at τ −0·55 and narrow doublets at τ 0·57 and 1·05. The coupling constant between these doublets, 2·0 Hz., identified them as resulting from *meta*-protons. The nitration product is therefore 5,7-dinitro-2,1-benzisothiazole and the orientation of the 5-nitro-isomer is confirmed. The structure of the remaining nitration product, 4-nitro-2,1-benzisothiazole, followed from its non-identity with 6-nitro-2,1-benzisothiazole.[2]

TABLE 2

M.p.s, n.m.r. data, and microanalyses of novel 2,1-benzisothiazoles

Substituents	M.p.	τ(3-H)	Found (%) C	Found (%) H	Found (%) N	Formula	Required (%) C	Required (%) H	Required (%) N
7-Br	70—71·5°	0·65 s	39·4	1·8	6·4	C_7H_4BrNS	39·3	1·9	6·5
4,7-Br_2	144—145	0·57 s	29·2	1·1	4·6	$C_7H_3Br_2NS$	28·7	1·0	4·8
4,5,7-Br_3	216—217	0·50 s	22·9	0·5	3·8	$C_7H_2Br_3NS$	22·6	0·6	3·8
4-NO_2	92	−0·07 d	46·7	2·2	15·3	$C_7H_4N_2O_2S$	46·7	2·3	15·5
5-NO_2	180	0·37 d	46·8	2·3	15·2	$C_7H_4N_2O_2S$	46·7	2·3	15·5
7-NO_2	127	0·45 s	46·7	2·4	15·2	$C_7H_4N_2O_2S$	46·7	2·3	15·5
4-Me, 7-NO_2	115	0·43 s	49·6	3·1	14·5	$C_8H_6N_2O_2S$	49·5	3·1	14·4
5-Cl, 4-NO_2	140—140·5	0·55 d	39·3	1·4	12·9	$C_7H_3ClN_2O_2S$	39·2	1·4	13·1
5,7-$(NO_2)_2$	220—221	−0·55 * s	37·3	1·7	18·6	$C_7H_3N_3O_4S$	37·3	1·4	18·6
6-Br, 7-NO_2	151—152	0·58 s	32·4	1·2	10·7	$C_7H_3BrN_2O_2S$	32·4	1·2	10·8
4,6-$(NO_2)_2$	198—198·5	1·03 * d	37·2	1·4	18·3	$C_7H_3N_3O_4S$	37·3	1·4	18·6
7-Me, 4-NO_2	134—135	−0·04 s	49·6	3·2	14·1	$C_8H_6N_2O_2S$	49·5	3·1	14·4

* In Me_2SO; s = singlet; d = doublet.

Bromination of 2,1-benzisothiazole with an excess of bromine and silver sulphate yielded a tribromo-compound which we suggest is 4,5,7-tribromo-2,1-benzisothiazole; the 6-position seems to be the one least likely to be substituted.

All the products of bromination could be readily recrystallised from light petroleum (b.p. 60—80°) and formed, in each case, long needles.

Nitration of 2,1-Benzisothiazole.—Nitric acid (67%; 5 ml.) was added slowly to a cooled solution of 2,1-benzisothiazole (1·35 g., 10 mmole) in sulphuric acid (10 ml.). The mixture was heated (1 min.) on a steam-bath, cooled, and poured onto ice (100 g.); the resulting mixture was extracted with chloroform (3 × 25 ml.). Evaporation of the dried chloroform extracts gave a brown solid (1·5 g.). The isomer ratios in this mixture were determined, as above, by integration of the 3-H resonance signals in the n.m.r. spectrum of a sample, a CAT being used to improve the signal-to-noise ratio and thus the accuracy of measurement.

Separation of Products of Nitration.—The crude product (1·5 g.) dissolved in hot chloroform (10 ml.) and gave 5-nitro-2,1-benzisothiazole as yellow needles (0·6 g.) when cooled. The mother liquor was evaporated and the residue was crystallised from ethanol (8 ml.), to give yellow needles

Nitration of Substituted 2,1-Benzisothiazoles.—Nitration of methyl-substituted 2,1-benzisothiazoles was carried out in the same way as nitration of the parent compound. Nitration of 5-chloro- and 6-bromo-2,1-benzisothiazoles was also effected in similar fashion, except that the time of heating was increased to 10 min. With nitro-2,1-benzisothiazoles, further nitration was achieved only by replacing sulphuric acid by oleum (20% SO_3) and by heating the mixture for 30 min. on the steam bath. The products of nitration were, in general, highly crystalline pale yellow compounds, readily recrystallised from ethanol. Orientation of these nitration products was achieved by methods similar to those indicated earlier. Nitration at C-7 was immediately obvious; in other cases measurement of the coupling constant, in the n.m.r. spectrum, between the remaining two protons on the benzenoid ring was sufficient to establish the structure.

6-Bromo-7-nitro-2,1-benzisothiazole causes severe erythema of areas of skin exposed to its vapour.

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