The Chemistry of 2,1-Benzisothiazoles. Part V.[1] Diels–Alder Reactions of 2,1-Benzisothiazoles

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Simple 2,1-benzisothiazoles, unlike 2,1-benzisoxazoles, do not react with maleic anhydride. 3-Amino-2,1-benzisothiazole reacts to form the maleamic acid; 3-methylamino- and 3-ethylamino-2,1-benzisothiazoles give substituted thioamides, possibly *via* a Diels–Alder addition product.

2,1-Benzisoxazole (anthranil) (I; X = O, R = H) has been reported to react with maleic anhydride [2] or *N*-phenylmaleimide [3,4] with the formation of 1 : 1 adducts; these appeared to be derived from Diels–Alder addition of the dienophile to the isoxazole ring. We have attempted to bring about similar reactions between a number of 2,1-benzisothiazoles (I; X = S) and maleic anhydride under the usual Diels–Alder reaction conditions.

2,1-Benzisothiazole itself did not react; neither did 5-methoxy-2,1-benzisothiazole (I; X = S, R = OMe), in which the methoxy-group might be expected to make the heterocyclic ring (and the benzenoid ring) more susceptible to dienophilic attack.

3-Amino-2,1-benzisothiazole (II; R = H) on treatment with maleic anhydride in boiling benzene solution gave the maleamic acid (III; R = H), presumably by simple nucleophilic attack of the amino-group on the anhydride. This product (III; R = H) readily formed a sodium salt; the n.m.r. spectrum of the salt in deuterium oxide showed two doublets, at δ 6·01 and 6·44 p.p.m. (*J* 13 Hz), indicative of a *cis*-disubstituted ethylene.

The reaction between 3-methylamino-2,1-benzisothiazole (II; R = Me) and maleic anhydride followed a different course. The product was a yellow solid, the n.m.r. spectrum of which (in [$^2H_6$]dimethyl sulphoxide) displayed a singlet at δ 3·63 (methyl), a singlet at δ 6·00 (vinyl proton), a complex multiplet between δ 7·3 and 7·7 (4 aromatic protons) and two broad singlets at δ 10·37 and 10·63 p.p.m. (two NH groups). The compound gave a black precipitate with lead acetate solution, indicating the presence of a thioamide group and it did not dissolve in the cold in sodium carbonate solution. Its i.r. spectrum showed bands characteristic of NH and of an anhydride function. This product is, therefore, the thioamide (V; R = Me).

3-Ethylamino-2,1-benzisothiazole (II; R = Et) reacted with maleic anhydride to give an analogous product (V; R = Et), showing a similar n.m.r. spectrum.

It seems possible that these ring-opened products (V) arise by initial Diels–Alder reaction of the anhydride with the heterocyclic ring, giving the bridged compounds (IV), which then undergo ring fission at the weak sulphur–nitrogen bond. The reaction between 2,1-benzisoxazole and *N*-phenylmaleimide is reported [4] to take a similar course, although in this case a reasonably stable bridged adduct (VI) was isolated. We have been unable to isolate a similar intermediate, suggesting that the sulphur–nitrogen bond in our presumed intermediates (IV) is weaker than the oxygen–nitrogen bond in the benzisoxazole adduct (VI).

3-Acetylamino-2,1-benzisothiazole (II; R = Ac) did did not react with maleic anhydride. It appears a strongly electron-donating substituent on the isothiazole ring is essential for reaction to occur. Although the *o*-quinonoid structure (I) suggests that Diels–Alder addition should occur across the benzenoid ring, such a reaction has not been observed, presumably because of extensive electron delocalisation in both series of compounds.

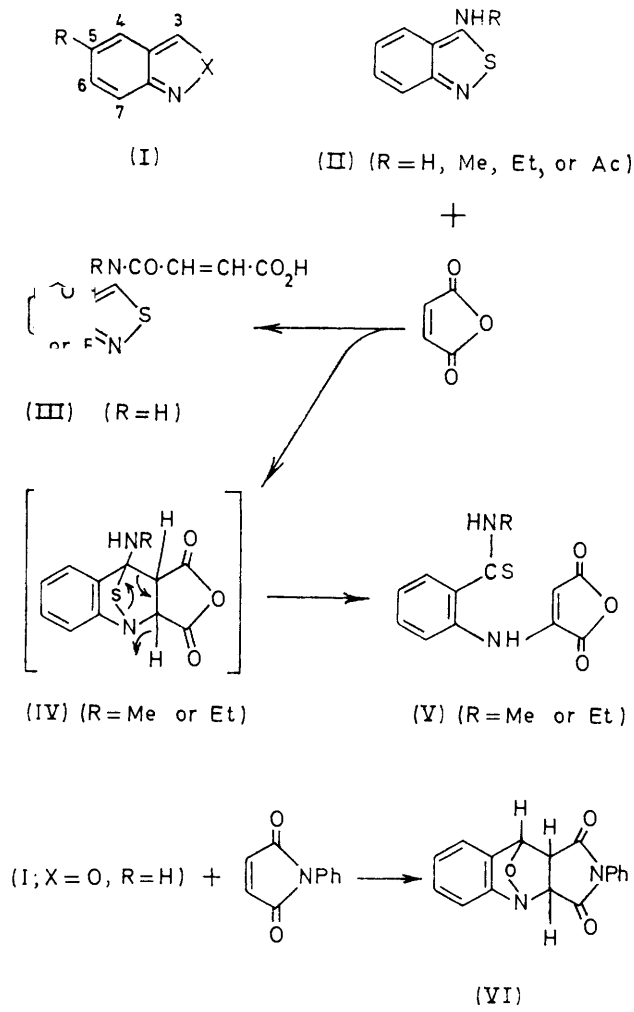
EXPERIMENTAL

Microanalyses were performed by the Australian Microanalytical Service, Melbourne. N.m.r. spectra were obtained with a Varian T-60 instrument; i.r. spectra are of

[1] Part IV, R. K. Buckley, M. Davis, and K. S. L. Srivastava, *Austral. J. Chem.*, 1971, **24**, 2405.
[2] A. Schönberg and A. Mostafa, *J. Chem. Soc.*, 1943, 654.
[3] C. D. Nenitzescu, E. Ciorănescu, and L. Bîrlădeanu, *Comm. Acad. Rep. populare Romune*, 1958, **8**, 775 (*Chem. Abs.*, 1959, **53**, 18,003).
[4] E. C. Taylor, D. R. Eckroth, and J. Bartulin, *J. Org. Chem.*, 1967, **32**, 1899.

potassium bromide discs, recorded with a Perkin-Elmer 257 spectrophotometer.

5-Methoxy-2,1-benzisothiazole.—This compound was prepared by the general procedure of Davis and White.[5] 2-Amino-5-methoxytoluene [6] (7·5 g), xylene (25 ml), and thionyl chloride (16 g) were mixed cautiously and then the mixture was heated under reflux for 28 h. The solution



was cooled and extracted with hydrochloric acid. Dilution of the extracts afforded an oil which partially crystallised. The residual oil (1 g) was separated from the crystals (4·0 g) and diluted with saturated methanolic picric acid (50 ml), thus affording yellow needles (2·5 g), m.p. 155—156° (from methanol) of the *picrate* of 5-methoxy-2,1-benzisothiazole (Found: C, 42·5; H, 2·7; N, 14·2. $C_{14}H_{10}N_4O_8S$ requires C, 42·6; H, 2·6; N, 14·2%). Decomposition of this picrate with dilute sodium hydroxide solution yielded the free *base* as leaflets, m.p. 55° (from light petroleum) (Found: C, 58·1; H, 4·2; N, 8·4. C_8H_7NOS requires C, 58·2; H, 4·3; N, 8·5%), δ (CCl_4) 3·80 (s, Me), 7·0—7·6 (m, aromatic), and 8·75 p.p.m. (d, heterocyclic ring H).

The residual crystals afforded needles of *4-chloro-5-methoxy-2,1-benzisothiazole*, m.p. 122—123° (from ethanol) (Found: C, 48·4; H, 3·0; N, 6·8. C_8H_6ClNOS requires C, 48·1; H, 3·0; N, 7·0%), δ ($CDCl_3$) 7·20 (d) and 7·60 (d) (*J* 9 Hz, indicative of vicinal aromatic protons), 3·92 (s, Me) and 8·90 p.p.m. (s, heterocyclic ring H). This chlorinated by-product is probably formed by the prolonged action of excess of thionyl chloride on the 5-methoxy-2,1-benzisothiazole.

Reaction of Maleic Anhydride with 2,1-Benzisothiazoles.—Reactions were carried out in boiling benzene or xylene, and an excess of maleic anhydride was used. No reaction, even after 24 h heating, was detected between maleic anhydride and 2,1-benzisothiazole,[7] 5-methoxy-2,1-benzisothiazole, or 3-acetylamino-2,1-benzisothiazole,[1] and in each case the starting compound was recovered unchanged.

With 3-amino-2,1-benzisothiazole [8] an immediate reaction occurred, with the quantitative formation of *N-(2,1-benzisothiazol-3-yl)maleamic acid* (III; R = H) as a yellow precipitate which afforded shining yellow needles, m.p. 218—219° (from ethanol) (Found: C, 53·0; H, 3·4; N, 11·4; S, 12·9. $C_{11}H_8N_2O_3S$ requires C, 53·2; H, 3·2; N, 11·3; S, 12·9%); for n.m.r. data (sodium salt) see Discussion section.

3-Methylamino-2,1-benzisothiazole,[8] heated with an excess of maleic anhydride in benzene for 5 h, afforded yellow crystals (40%) of *o-[methyl(thiocarbamoyl)]anilinomaleic anhydride* (V; R = Me), m.p. 185—187° (decomp.) (from benzene) (Found: C, 55·1; H, 3·8; N, 10·4. $C_{12}H_{10}N_2O_3S$ requires C, 54·9; H, 3·8; N, 10·7%); for n.m.r. data see Discussion section; $\nu_{max.}$ 3375, 3140, 3100, 3030, 2970, 1840, 1773, 1650, 1590, 1535, 1475, 1455, 1355, 1290, 1275, 1223, 1050, 950, 900, 825, 795, 750, 650, and 620 cm^{-1}.

A similar reaction with 3-ethylamino-2,1-benzisothiazole [8] gave the analogous *o-[ethyl(thiocarbamoyl)]anilinomaleic anhydride* (V; R = Et) as yellow needles (85%), m.p. 159° (from benzene) (Found: C, 56·5; H, 4·3; N, 10·3. $C_{13}H_{12}N_2O_3S$ requires C, 56·5; H, 4·4; N, 10·1%), $\nu_{max.}$ 3310, 3245, 3100, 3025, 2985, 1835, 1750, 1643, 1600, 1585, 1525, 1473, 1450, 1390, 1325, 1275, 1220, 1208, 1035, 983, 900, , 805, 768, 750, 730, 708, 690, and 665 cm^{-1}.

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[5] M. Davis and A. W. White, *J. Org. Chem.*, 1969, **34**, 2985.
[6] M. Heidelberger and W. A. Jacobs, *J. Amer. Chem. Soc.*, 1919, **41**, 1454.
[7] M. Davis and A. W. White, *Chem. Comm.*, 1968, 1547.
[8] R. F. Meyer, B. L. Cummings, P. Bass, and H. O. J. Collier, *J. Medicin. Chem.*, 1965, **8**, 515.