Ring-expansion of 3-Bromoalkyl-1,2-Benzisothiazole 1,1-Dioxides to (2*H*)-1,2-Benzothiazin-4(3*H*)-one 1,1-Dioxides

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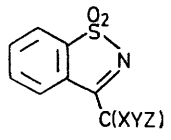
Summary A simple three-step synthesis of (2*H*)-1,2-benzothiazin-4(3*H*)-one 1,1-dioxides from saccharin has been achieved by the base-mediated ring-expansion of 3-(α-bromoalkyl)-1,2-benzisothiazole 1,1-dioxides.

THERE has been much interest recently in the synthesis of (2*H*)-1,2-benzothiazin-4(3*H*)-one 1,1-dioxides,[1] some of which are reported[2] to be potent anti-inflammatory agents in animal models. We now report a simple three-step synthesis of such compounds starting from saccharin, which involves a novel ring-expansion.

Bromination of the dioxide (**1a**)[3] with an excess of bromine in boiling benzene gave the tribromomethyl compound (**1b**), m.p. 178—180 °C, quantitatively.† With **1**

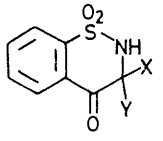
† All new compounds were fully characterised by their spectral data and microanalysis.

equiv. of bromine in benzene at room temperature, (**1a**) gave the bromomethyl compound (**1c**) (100%), m.p. 149—151 °C. Heating (**1c**) with NaOEt in EtOH gave the benzothiazine dioxide (**2c**) (66%), m.p. 156—158 °C, identical with an authentic sample.[1d] Similarly, the bromoethyl compound (**1d**) (100%), m.p. 110 °C, gave (**2d**) (90%), m.p. 155 °C.

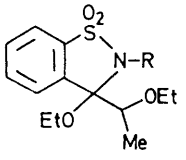


(1)

a; X=Y=Z=H
b; X=Y=Z=Br
c; X=Y=H; Z=Br
d; X=H, Y=Me; Z=Br
e; X=Me, Y=Et; Z=Br

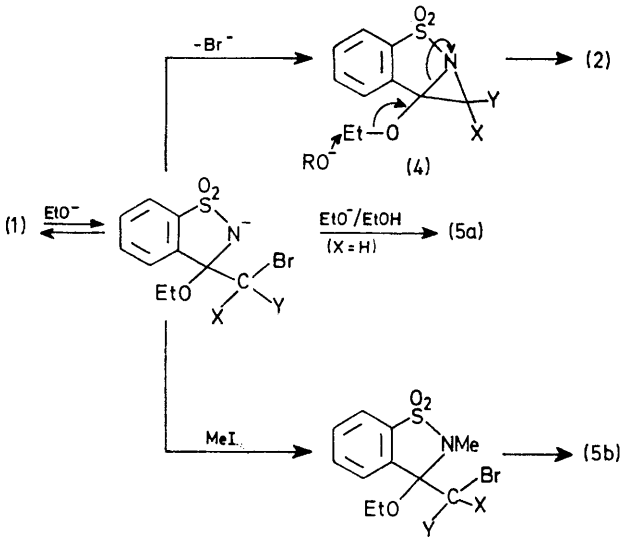


(2c–e)



(5) a; R=H
b; R=Me

A possible mechanism for the ring-expansion could be hydrolysis of (**1b**) to an *o*-(α-bromoacyl)benzenesulphonamide anion followed by recyclisation with loss of Br^-. This could be eliminated, however, since both (**1a**) and 3-phenyl-1,2-benzisothiazole 1,1-dioxide were stable to boiling alkali, to hot NaOEt in EtOH, and to hot dilute HCl. Of two other possible mechanisms considered, that involving nucleophilic addition of EtO^- to the azomethine linkage followed by cyclisation to (**4**) is favoured. When (**1d**) was treated with EtO^- in EtOH below 50 °C both (**2d**) (30%), and (**5a**) (50%),[4] m.p. 100 °C, were obtained, whereas if MeI was added to the reaction mixture only the *N*-methyl derivative (**5b**) (75%), m.p. 80 °C was isolated. When the bromo-s-butyl compound (**1e**) (100%), which does not have an α-hydrogen atom in the side-chain, was heated with 20% aqueous KOH at 100 °C the ring-expanded product (**2e**) (70%), b.p. 170 °C at 0·001 mmHg, was obtained. Formation of the products can be rationalized as in the Scheme.



SCHEME

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[1] (a) J. G. Lombardino and H. A. Watson, Jr., *J. Heterocyclic Chem.*, 1976, **13**, 333; (b) H. Zinnes, N. A. Lindo, J. C. Sircar, M. L. Schwartz, and J. Shavel, Jr., *J. Medicin. Chem.*, 1973, **16**, 44; (c) H. Zinnes, R. A. Comes, F. R. Zuleski, A. N. Caro, and J. Shavel, Jr., *J. Org. Chem.*, 1965, **30**, 2241; (d) H. Zinnes, R. A. Comes, and J. Shavel, Jr., *ibid.*, 1966, **31**, 162; (e) *J. Medicin. Chem.*, 1967, **10**, 223.

[2] J. G. Lombardino and E. H. Wiseman, *J. Medicin. Chem.*, 1973, **16**, 493, and refs. cited therein; U.S. patents 3,591,584 (1971), 3,892,740 (1975), and 3,853,862 (1974).

[3] 3-Alkyl- and -aryl-1,2-benzisothiazole 1,1-dioxides are readily prepared from saccharin (R. A. Abramovitch, E. M. Smith, M. Humber, B. Purtschert, P. C. Srinivasan, and G. M. Singer, *J.C.S. Perkin I*, 1974, 2589).