A REINVESTIGATION OF A POSSIBLE ROUTE TO 1,2-BENZISOTHIAZOLES: THE REACTION BETWEEN *N*-BENZYL-SUBSTITUTED SULPHONAMIDES AND TRICHLOROMETHANESULPHENYL CHLORIDE IN THE PRESENCE OF BASE

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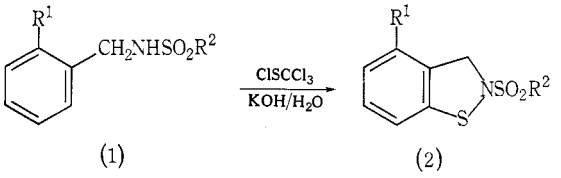
Abstract

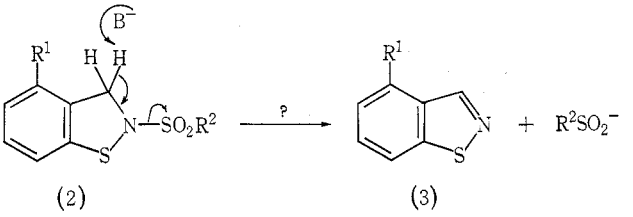
The reaction between *N*-benzyl-substituted sulphonamides (1) and trichloromethanesulphenyl chloride in the presence of base afforded the expected *N*-trichloromethanesulphenyl derivatives (4); the previously reported 1,2-benzisothiazolines (2) were not obtained. Treatment of the derivatives (4) with base under various conditions gave no indication of cyclization to 1,2-benzisothiazolines (2).

There is a report in the patent literature[1] that reaction of *N*-benzyl-substituted sulphonamides (1) with trichloromethanesulphenyl chloride in the presence of base affords *N*-sulphonyl-1,2-benzisothiazolines (2).



	R^1	R^2
(a)	H	Me
(b)	H	*p*-MeC_6H_4
(c)	Cl	Me

We thought it likely that the reported products (2) of this reaction would eliminate a sulphinate anion $R^2SO_2^-$ on treatment with strong base, thus affording a synthesis of the 1,2-benzisothiazole system (3). As there are few simple synthetic



routes to 1,2-benzisothiazoles, the fundamental ring system of a number of biologically active substances,[2] further investigation of this method seemed warranted.

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[1] Epstein, P. F., and Lukes, G. E., U.S. Pat. 3,166,563 (*Chem. Abstr.*, 1965, **62**, 7764g).

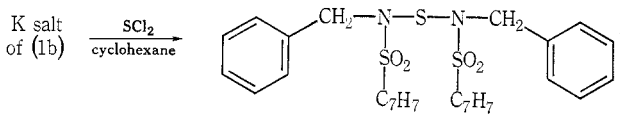
[2] Davis, M., *Adv. heterocyc. Chem.*, 1972, **14**, 43.

Three sulphonamides (1a), (1b), and (1c) have been prepared, including the specific compound (1c) cited in the patent referred to above. Each of these was treated with trichloromethanesulphenyl chloride in the presence of potassium hydroxide solution, using in each case a variety of temperatures, times of reaction, and concentrations of alkali. In each case, the only compounds isolated were the *N*-trichloromethanesulphenyl derivatives (4) of the sulphonamides and starting material in combined yields of over 90%; 1,2-benzisothiazolines (2) were not obtained.

(1) (4)

We considered it possible that benzisothiazolines (2) might be formed by an intramolecular displacement of trichloromethyl anion from the *N*-trichloromethanesulphenyl derivatives (4). The heating of these derivatives (4) in various solvents, in the absence or presence of added base, failed to bring about cyclization; the only product obtained in such attempts was the starting sulphonamide (1).

A further attempt to obtain the desired 1,2-benzisothiazolines was made by treatment of the dry potassium salt of the sulphonamide (1b) with sulphur dichloride. In this case, however, the reaction product was the sulphide (5).



(5)

We conclude that if 1,2-benzisothiazolines (2) are formed in any of the reactions we have investigated, then the yields are too small for such reactions to be of any practical value in the synthesis of the desired heterocyclic compounds.

Experimental

Analyses were performed by the Australian Microanalytical Service, Melbourne. P.m.r. data are of solutions in deuterochloroform, the spectra being recorded on a Varian A60-D instrument.

Preparation of Sulphonamides (1)

These were prepared by the addition of the appropriate sulphonyl chloride (75 mmol) to the benzylamine (50 mmol) dissolved in dry pyridine (50 ml). The mixture was heated on the steam bath for 30 min, cooled, and added to excess cold dilute hydrochloric acid; the precipitated product was collected and recrystallized. Yields were essentially quantitative. In this way was prepared *N*-benzylmethanesulphonamide (1a), m.p. 63° (lit.[3] 64–65°), from benzene and light petroleum; *N*-benzyl-*p*-toluenesulphonamide (1b), m.p. 112° (lit.[4] 113–114°), from aqueous ethanol; and *N*-*o*-chlorobenzylmethanesulphonamide (1c), m.p. 51–52°, needles from carbon tetrachloride (Found: C, 44·0; H 4·5; N, 6·4. Calc. for $C_8H_{10}ClNO_2S$: C, 43·7; H, 4·6; N, 6·4%).

[3] Nickon, A., and Hill, A. S., *J. Am. chem. Soc.*, 1964, **86**, 1152.

[4] Kretov, A. E., and Rovinski, M. S., *Zh. obshch. Khim.*, 1957, **27**, 2174 (*Chem. Abstr.*, 1958, **52**, 6243e).

Reaction of Sulphonamides (1) with Trichloromethanesulphenyl Chloride

The general procedure is exemplified by the reaction of the sulphonamide (1c), following the cited patent.[1] *N-o*-Chlorobenzylmethanesulphonamide (1c) (2 g, 9·1 mmol) was dissolved in potassium hydroxide solution (1·5M, 9·1 ml) at room temperature, and trichloromethanesulphenyl chloride (1·69 g, 9·1 mmol) added dropwise with stirring. The temperature rose from 14° to 19° during the addition. The mixture was stirred at room temperature for 6 hr, and the liquid was decanted from a sticky solid which had separated. Trituration of this solid with ice-cold ethanol (15 ml) afforded a colourless solid which after recrystallization from aqueous ethanol gave needles, m.p. 64–65° (1·14 g, 34%), of the *N*-trichloromethanesulphenyl derivative (4c) (Found: C, 29·6; H, 2·4; N, 3·6. Calc. for $C_9H_9Cl_4NO_2S_2$: C, 29·3; H, 2·5; N, 3·8%). Dilution of the ethanol mother liquor with water afforded a second crop of product (0·82 g, 24%); acidification of the supernatant potassium hydroxide solution yielded starting amide (1c) (0·69 g, 35%).

The other sulphonamides (1a) and (1b) by a similar procedure afforded the *N*-trichloromethanesulphenyl derivatives (4a), colourless needles from aqueous ethanol, m.p. 94–95° (Found; C, 32·6; H, 3·1; N, 3·9; S, 19·2. Calc. for $C_9H_{10}Cl_3NO_2S_2$: C, 32·3; H, 3·0; N, 4·2; S, 19·2%), and (4b), colourless needles from light petroleum, m.p. 74–76° (Found: C, 44·2; H, 3·5; N, 3·4, Calc. for $C_{15}H_{14}Cl_3NO_2S_2$: C, 43·9; H, 3·4; N, 3·4%).

Attempts to Cyclize the N-*Trichloromethanesulphonamides (4)*

(i) The heating of the compound (4c) in ethanol or toluene, under reflux, led only to the recovery of unchanged (4c).

(ii) Compound (4c) (0·2 g), ethanol (3 ml), and potassium hydroxide solution (1·5M, 2·5 ml) were heated under reflux for 75 min. Addition of dilute hydrochloric acid to the cooled solution afforded a quantitative yield of the starting sulphonamide (1c).

(iii) Treatment of (4a) with bases, including potassium t-butoxide, sodium hydride, and pyridine gave no evidence (t.l.c.) of reaction other than removal of the $SCCl_3$ group and production of the starting sulphonamide (1a).

Reaction of the Potassium Salt of the Sulphonamide (1b) with Sulphur Dichloride

The salt[5] (5·68 g, 19 mmol) was suspended in cyclohexane (120 ml) and sulphur dichloride (2·22 g, 21·6 mmol) added dropwise with vigorous stirring. The mixture was heated under reflux for 4·5 hr. Solvent and excess sulphur dichloride were removed under vacuum and the resulting mixture was heated with ethanol (50 ml) and water (20 ml). The solution was filtered hot (to remove sulphur) and the solid which separated on cooling was dried and recrystallized from toluene, affording colourless prisms of the *sulphide* (5) (1·90 g, 36%), m.p. 157–158° (Found: C, 61·3; H, 5·2; N, 5·0; S, 17·5. Calc. for $C_{28}H_{28}N_2O_4S_3$: C, 60·9; H, 5·1; N, 5·1; S, 17·4%).

P.M.R. Data

(1c): δ 2·93 s (CH_3), 4·41 d (*J* 6 Hz) (CH_2), 5·18 broad (NH), and 7·2–7·5 m (arom.). (4a): 2·92 s (CH_3), 5·11 d (*J* 3 Hz) (CH_2), and 7·2–7·5 m (arom.). (4b): 2·40 s (CH_3), 5·01 s (CH_2), 7·0–7·8 m (arom.). (4c): 3·06 s (CH_3), 5·24 s (CH_2), and 7·2–7·5 (arom.).

[5] Fraser, E., Paterson, W., and Proctor, G. R., *J. chem. Soc.*, 1963, 5107.