SULPHAMOYLBENZO-1,2,3,4-THIATRIAZINE 1,1-DIOXIDES: A NEW CLASS WITH ORAL DIURETIC ACTIVITY

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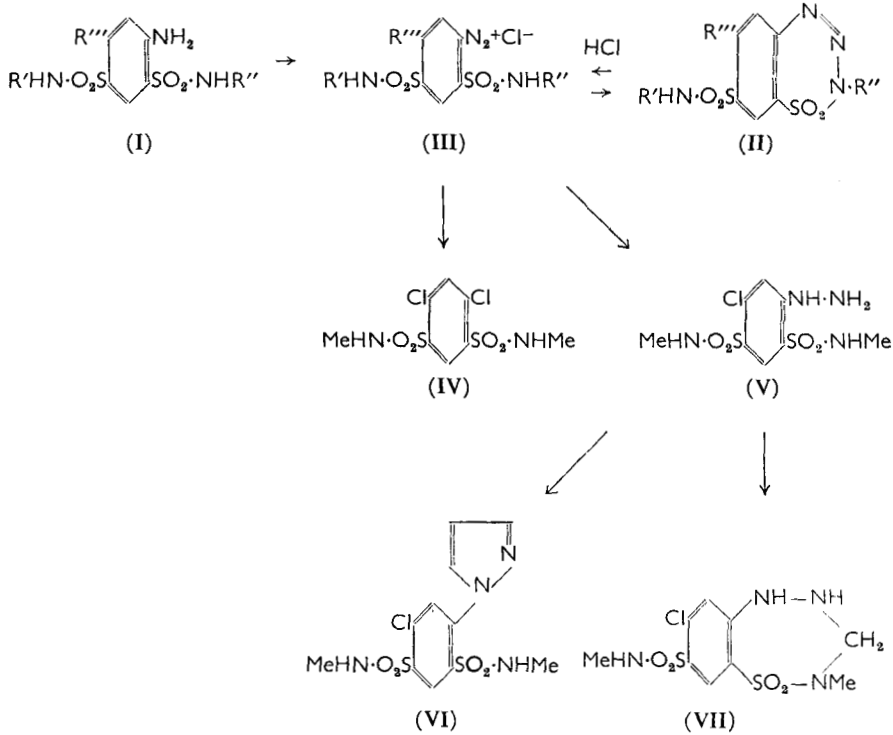
A series of sulphamoylbenzo-1,2,3,4-thiatriazine 1,1-dioxides has been prepared. While some of them were found to cause diuresis in rats on oral administration, none was more active than chlorothiazide.

During the past three years a search has been made in these laboratories for new orally active diuretic agents. One line of approach has been to synthesise analogues of known diuretics, introducing structural features which were sufficiently novel for there to be a reasonable chance that the products might possess, in addition to diurectic activity, the advantage of producing a low relative potassium ion excretion.

During one phase of this work, some compounds related to chlorothiazide were prepared in which the amino-group of the active diuretic 4-amino-6-chlorobenzene-1,3-disulphonamide (Sprague, 1958) (I; R′ = R″ = H, R‴ = Cl) was modified in various ways.



This compound was readily diazotised with nitrosyl sulphuric acid, but the product was unstable, nitrogen being evolved at 0–5°; on diluting the reaction mixture no precipitate was formed. By sharp contrast, diazotisation of the *N*-substituted sulphonamides (I; R′ = R″ = Me, R‴ = Cl), (I; R′ = H, R″ = Me, R‴ = Cl) and (I; R′ = H, R″ = $-CH_2$·Ph, R‴ = Cl) under similar conditions yielded stable diazonium salts which, on diluting the reaction mixture with water, were precipitated as pale-cream crystalline plates having properties conforming with the benzothiatriazine structure (II).

As expected, a solution of the benzo-1,2,3,4,-thiatriazine 1,1-dioxide (II; R′ = R″ = Me, R‴ = Cl) in concentrated hydrochloric acid behaved as if it were a solution of the corresponding diazonium salt (III). For example, on heating the solution at 95°, the dichloro-compound (IV) was formed. Also, treatment of the solution with stannous chloride gave the hydrazino-compound (V), characterised as its *N*-acetyl derivative. The hydrazino-compound (V) also gave the expected cyclic derivatives (VI) and (VII) when treated with tetraethoxypropane in ethanolic hydrochloric acid, and with formaldehyde in alcoholic sodium hydroxide, respectively.

By contrast with the parent amine (I; R′ = R″ = Me, R‴ = Cl), the hydrazine (V) had little or no diuretic activity in the rat. This could have been due to the fact that the hydrazine was more strongly basic than the parent amine. Modification of the basicity of the hydrazino- group in two different ways—by *N*-acetylation and by conversion to the cyclic derivative (VII)—also gave inactive compounds; the pyrazol-1-yl derivative (VI), however, had approximately one-quarter the activity of chlorothiazide.

The benzo-1,2,3,4-thiatriazine 1,1-dioxide (II; R′ = R″ = Me, R‴ = Cl, Brit. Pat., 1959) was approximately as active a diuretic in rats as chlorothiazide; the compound also resembled chlorothiazide in the ion-excretion pattern (K^+, Na^+ and Cl^-) it produced. Similar biological results were obtained with the corresponding unmethylated sulphonamide (II; R′ = H, R″ = Me, R‴ = Cl) and with the trifluoromethyl compound (II; R′ = R″ = Me, R‴ = CF_3). Replacement of the methyl group R″ in position-2 in the benzo-1,2,3,4-thiatriazine 1,1-dioxide (II; R′ = H, R″ = Me, R‴ = Cl) by a benzyl group reduced the activity to one-tenth of that of the 2-methyl compound.

The fact that these position–3 nitrogen isosteres of the corresponding derivatives of chlorothiazide should also be active diuretics is of considerable theoretical interest; similar nitrogen isosteres of certain quinazolone diuretics analogous to chlorothiazide have likewise been shown by Gadekar and Frederick (1962) to have diuretic activity.

One of the foregoing compounds (II; R′ = R″ = Me, R‴ = Cl) has recently been prepared by Childress (1962) and found to have a statistically significant diuretic activity in rats.

Experimental

6-Chloro-2-methyl-7-methylsulphamoylbenzo-1,2,3,4-thiatriazine 1,1-dioxide (II; R′ = R″ = Me, R‴ = Cl). 5-Chloro-2,4-di-(methylsulpha-

moyl)aniline (S. African Pat., 1958) (3·13 g.) was dissolved in concentrated sulphuric acid (40 ml.). To this solution was added with stirring at 0–5° a solution of sodium nitrite (0.7 g.) in concentrated sulphuric acid (20 ml.). The solution was stirred for 2 hr. at 0–5°, poured on to ice (100 g.), diluted at 0–5° to 325 ml., and rapidly filtered through a sintered-glass funnel. The filtrate was now diluted to 900 ml., whereupon a pale orange crystalline precipitate was formed. This solid (2·53 g., m.p. 165–167°) was filtered off, washed with water, and dried at room temperature *in vacuo* over silica gel. Found: Cl, 11·3; N, 17·35; S, 19·8. Calc. for $C_8H_9ClN_4O_4S_2$: Cl, 11·0; N, 17·3; S, 19·7 per cent.

6-*Chloro*-2-*methyl*-7-*sulphamoylbenzo*-1,2,3,4-*thiatriazine* 1,1-*dioxide* (*II;* $R' = H$, $R'' = Me$, $R''' = Cl$). 5-Chloro-2-methylsulphamoyl-4-sulphamoylaniline (S. African Pat., 1958) (31·6 g.) was dissolved in concentrated sulphuric acid (416 ml.). To this solution was added with stirring at 0–5° a solution of sodium nitrite (7·3 g.) in concentrated sulphuric acid (206 ml.). The solution was stirred for 30 min., poured into water (625 ml.) at 0–5°, and filtered. The clear filtrate was poured into water (9 litres), and the buff precipitate (17 g., m.p. 166–170°) was filtered off, washed with water, and dried at room temperature *in vacuo* over silica gel. Found: C, 26·5; H, 2·3; Cl, 11·0; N, 18·3; S, 20·1. $C_7H_7ClN_4O_4S_2$ requires C, 27·0; H, 2·26; Cl, 11·4; N, 18·0; S, 20·6 per cent.

2-*Benzyl*-6-*chloro*-7-*sulphamoylbenzo*-1,2,3,4-*thiatriazine* 1,1-*dioxide* (*II;* $R' = H$, $R'' = CH_2Ph$, $R''' = Cl$). 6-Chloro-3,4-dihydro-3-oxo-7-sulphamoyl-1,2,4-benzothiadiazine 1,1-dioxide (Close, Swett, Brady, Short and Vernsten, 1960) (10 g.) was dissolved in dry dimethylformamide (30 ml.), and sodium hydride (1·5 g., 50 per cent oil dispersion) added in portions. The solution was heated to 70°, and benzyl bromide (5·5 g.) added. The solution was heated at 70° for 1 hr., cooled, and poured on to ice. The crude material was recrystallised from ethanol/water to give a product with a m.p. of 250–252°. This material was hydrolysed with 20 per cent sodium hydroxide solution to give 2-benzylsulphamoyl-5-chloro-4-sulphamoylaniline, m.p. 155–160°. Found: C, 41·7; H, 4·1; N, 11·2. $C_{13}H_{14}ClN_3O_4S_2$ requires C, 41·6; H, 3·74; N, 11·1 per cent.

2-Benzylsulphamoyl-5-chloro-4-sulphamoylaniline (18·3 g.) was dissolved in a mixture of glacial acetic acid (490 ml.) and water (245 ml.). To this solution was added 2N sulphuric acid (61 ml.), followed at 0–5° by a solution of sodium nitrite (3·42 g.) in water (49 ml.). The reaction mixture was diluted with water (600 ml.), and the precipitated solid washed with water, dried, and recrystallised from methanol to give pale yellow prisms (10·4 g.), m.p. 158° (decomp.). Found: C, 40·4; H, 3·9; Cl, 8·9. $C_{13}H_{11}ClN_4O_4S_2$ requires C, 40·4; H, 2·9; Cl, 9·2 per cent.

2-*Methyl*-7-*methylsulphamoyl*-6-*trifluoromethylbenzo*-1,2,3,4-*thiatriazine* 1,1-*dioxide* (*II;* $R' = R'' = Me$, $R''' = CF_3$). 2,4-Di(methylsulphamoyl)-5-trifluoromethylaniline (Yale, Losee and Bernstein, 1960) (20 g.) was dissolved in a solution of concentrated sulphuric acid (246 ml.) in water (56 ml.). To this solution was added with stirring at 0–5° a solution of sodium nitrite (3·9 g.) in concentrated sulphuric acid (56 ml.), and the

clear solution was further diluted with water (3 litres). The precipitated buff solid (18 g., m.p. 148–149°) was filtered off, washed with water, and dried at room temperature *in vacuo* over silica gel. Found: N, 15·4; S, 17·8. $C_9H_9F_3N_4O_4S_2$ requires N, 15·7; S, 17·9 per cent.

1,5-*Dichloro*-2,4-*di*(*methylsulphamoyl*)*benzene* (*IV*). 6-Chloro-2-methyl-7-methylsulphamoylbenzo-1,2,3,4-thiatriazine 1,1-dioxide (20 g.) was dissolved in concentrated hydrochloric acid (150 ml.), and the solution heated on a steam-bath until no further solid was precipitated. The solid was filtered off, washed with water, dried, and recrystallised from ethanol/water to give pale pink prisms, m.p. 184–186°. Bourdais and Meyer (1961) have prepared this compound by a different method and quote m.p. 186°. Found: Cl, 20·9; N, 8·45; S, 19·5. $C_8H_{10}Cl_2N_2O_4S_2$ requires Cl, 21·4; N, 8·4; S, 19·3 per cent.

5-*Chloro*-2,4-*di*(*methylsulphamoyl*)*phenylhydrazine* (*V*). 6-Chloro-2-methyl-7-methylsulphamoylbenzo-1,2,3,4-thiatriazine 1,1-dioxide (24·8 g.) was dissolved in cold concentrated hydrochloric acid (220 ml.). To this solution was added stannous chloride (100 g.) in concentrated hydrochloric acid (100 ml.). This solution was kept at room temperature for 48 hr. The crystalline substituted phenylhydrazine which formed was filtered off, suspended in water, again filtered off, washed with water, dried, and recrystallised from water to give a cream solid (15·5 g., m.p. 234–236°). Found: Cl, 11·0; N, 17·25; S, 19·8. $C_8H_{13}ClN_4O_4S_2$ requires Cl, 10·8; N, 17·0; S, 19·5 per cent.

5-Chloro-2,4-di(methylsulphamoyl)phenylhydrazine (14·7 g.) was dissolved in hot 2N hydrochloric acid (100 ml.), the solution cooled to 20°, and acetic anhydride (15 ml.) added, followed by sodium acetate (100 g.) in water (100 ml.). The precipitated white *N*-acetyl derivative was filtered off, washed with water, and recrystallised from water to give colourless prisms (10 g., m.p. 197–198°). Found: C, 32·4; H, 4·25; Cl, 9·8; N, 14·9; S, 17·3. $C_{10}H_{15}ClN_4O_5S_2$ requires C, 32·5; H, 4·05; Cl, 9·6; N, 15·1; S, 17·4 per cent.

5-*Chloro*-2,4-*di*(*methylsulphamoyl*)-1-*pyrazol*-1′-*ylbenzene* (*VI*). 5-Chloro-2,4-di(methylsulphamoyl)phenylhydrazine (0.92 g.) was suspended in 2N hydrochloric acid (2 ml.) and ethanol (20 ml.). Tetraethoxypropane (1 ml.) was added, and the solution heated at reflux for 2½ hr. The white solid formed on cooling was recrystallised from ethanol, m.p. 203–205°. Found: Cl, 10·0; N, 15·15; S, 17·6. $C_{11}H_{13}ClN_4O_4S_2$ requires Cl, 10·1; N, 15·4; S, 17·6 per cent.

7-*Chloro*-2,3,4,5-*tetrahydro*-2-*methyl*-8-*methylsulphamoylbenzo*-1,2,4,5-*thiatriazepine* 1,1-*dioxide* (*VII*). 5-Chloro-2,4-di(methylsulphamoyl)-phenylhydrazine (3.28 g.) was suspended in industrial methylated spirit (200 ml.). Sodium hydroxide (1 ml. of a 4 per cent solution) and aqueous formaldehyde (0·75 ml. of 40 per cent solution) were added, and the now green solution was heated at reflux for 30 min. The solution was evaporated to dryness *in vacuo*, and the residue recrystallised from water to give a golden solid, m.p. 210–212°. Found: Cl, 10·5; N, 16·7; S, 18·7. $C_9H_{13}ClN_4O_4S_2$ requires Cl, 10·4; N, 16·4; S, 18·8 per cent.

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