CHLORAMPHENICOL SERIES

Part I. Nitrophenyl Alkyl Sulphides, Sulphoxides and Sulphones

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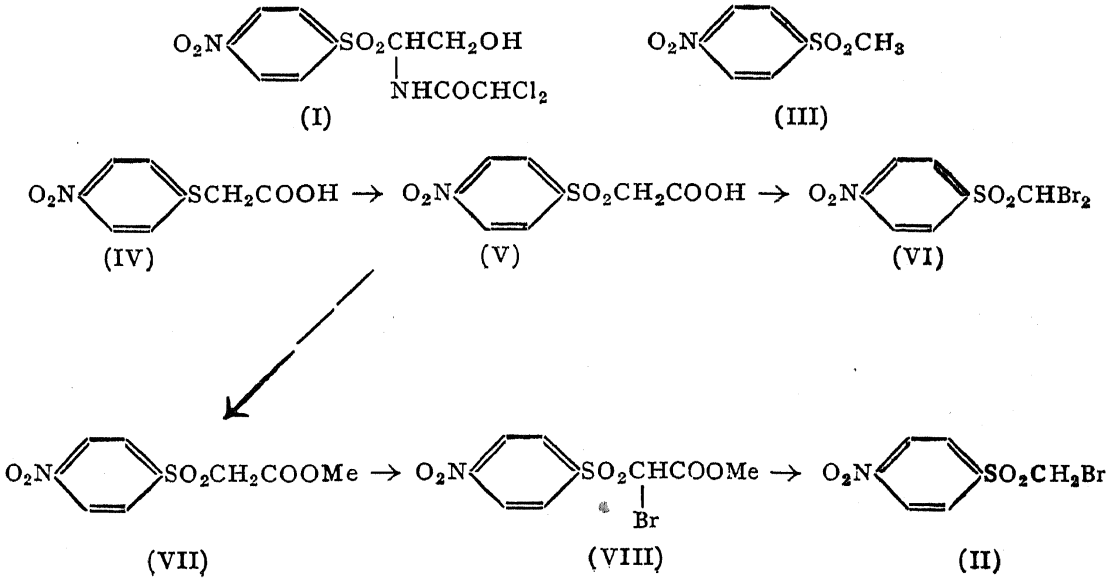
IN view of the high antibacterial activity of compounds containing the sulphone group, such as sulphanilamides and 4 : 4′-diaminodiphenyl sulphone, the synthesis of *p*-nitrophenyl α-dichloroacetamido-β-hydroxyethyl sulphone (I) was undertaken. Compound (I) contains all the structural features of chloramphenicol (Chloromycetin, Parke Davis & Co.) with the exception of the —CHOH— group, which has been replaced by the sulphone group in (I). While this work was in progress, highly active sulphide and sulphone analogues of chloramphenicol, in which the nitro group is replaced by thioalkyl and alkyl sulphonyl groups have been reported.[1]

The synthesis of (I) from *p*-nitrophenyl bromomethyl sulphone (II), by analogy with the synthesis of chloramphenicol from *p*-nitrophenacyl bromide, was first planned; but in contrast to the facile bromination of *p*-nitroacetophenone, the bromination of *p*-nitrophenyl methyl sulphone (III) could not be effected by any of the usual methods. An alternative synthesis of (II) from *p*-nitrophenyl carboxymethyl sulphone (V) was then

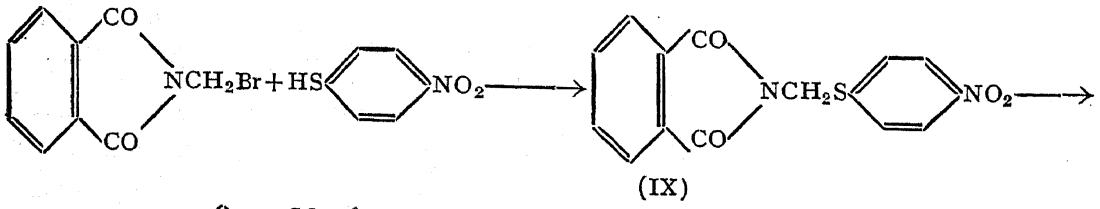


attempted, (V) being obtained by oxidation of *p*-nitrophenyl carboxymethyl sulphide (IV). However, bromination of (V) in acetic acid gave *p*-nitrophenyl dibromomethyl sulphone (VI) and not the desired monobromo acid or (II). The bromo compound (II) was finally synthesized by bromination of *p*-nitrophenyl carbomethoxymethyl sulphone (VII) to *p*-nitrophenyl bromocarbomethoxymethyl sulphone (VIII) and treatment of the latter with aqueous sodium hydroxide.

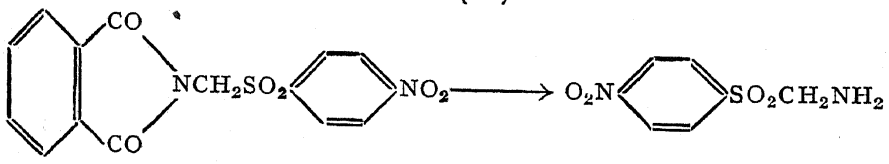
The bromo derivative (VIII) was unaffected by treatment with hexamine and gave phenyl methyl sulphone on heating at 160° with liquor ammonia under pressure.

Attempts to react (II) with reagents which should lead to the synthesis of *p*-nitrophenyl aminomethyl sulphone (XI) (or its hydrochloride) were unsuccessful. Among the reagents which were employed in these attempts were hexamine, sodamide, liquor ammonia and potassium phthalimide.

On the basis of the known synthesis of chloramphenicol from *p*-nitrophenyl acetamidomethyl ketone, the following alternative route to (I) was then investigated:



(IX)



(X) (XI)

Hydrolysis of *p*-nitrophenyl phthalimidomethyl sulphide (IX) and *p*-nitrophenyl phthalimidomethyl sulphone (X), however, proved unsuccessful. Attempts to hydroxymethylate (X) were also unsuccessful.

These results indicate that the methyl group attached to the sulphone group in *p*-nitrophenyl methyl sulphone (III) is not active, unlike the methyl group in *p*-nitroacetophenone. Similarly the bromine atom in (II) is not reactive, unlike the bromine atom in *p*-nitrophenacyl bromide. The deactivating influence of the sulphone group in contrast with the activating influence of the carbonyl has also been reported in the literature.[2] Alternative routes to (I) starting from benzene sulphenyl chloride and nitroalkanes, are under investigation.

In view of the reported[3] activity of *p*-nitrophenyl ω-hydroxyethyl sulphide, sulphoxide and sulphone, the following compounds have been prepared: *p*-Nitrophenyl ω-hydroxyethyl sulphide, *p*-nitrophenyl ω-hydroxyethyl sulphoxide, *p*-nitrophenyl ω-hydroxyethyl sulphone, 2: 6-diiodo-4-nitrophenyl carboxymethyl sulphide, *p*-nitrophenyl carboxymethyl sulphoxide, *p*-nitrophenyl carboxyamidomethyl sulphide, *p*-aminophenyl ω-hydroxyethyl sulphide and *p*-nitrophenyl 2: 3-dihydroxypropyl sulphide. The synthesis of these compounds was briefly reported earlier[4] and the present paper gives experimental details. Prof. B. V. Bhide and Mr. P. Y. Dighe have informed us that some of the compounds are highly active bacteriostatic agents, especially against the dysentery organisms of the Shigella group.[3]

Experimental

p-*Nitrophenyl carboxymethyl sulphone* (*V*)

p-Nitrophenyl carboxymethyl sulphide[5] (2 g.), hydrogen peroxide (5 c.c., 36%) and glacial acetic acid (10 c.c.) were heated on a water-bath at 80° for 10 hrs. After removal of acetic acid under reduced pressure, a dark brown solid (1·8 g.) was obtained. After three crystallizations from aqueous alcohol, it gave small white needles, m.p. 167° (Found: C, 39·2; H, 2·7; N, 5·8. $C_8H_7NO_6S$ requires C, 39·2; H, 2·8; N, 5·7%).

p-*Nitrophenyl dibromomethyl sulphone* (*VI*)

The foregoing sulphone (V) (1·3 g.) was dissolved in glacial acetic acid (10 c.c.) and bromine (0·5 c.c.) in glacial acetic acid (10 c.c.) was gradually added. The solution was then refluxed on an oil-bath at 140° for 4 hrs. At the end of the reaction, the colour of the solution was changed to greenish yellow. Acetic acid was then removed under reduced pressure and water (10 c.c.) was added to the reaction mixture when a white precipitate immediately separated (0·8 g.). It was filtered and washed with water. It gave pale yellow curved needles from benzene-*n*-hexane mixture, m.p. 170° (Found: C, 23·7; H, 1·4; Br, 43·8. $C_7H_5Br_2NO_4S$ requires C, 23·7; H, 1·4; Br, 44·5%).

p-*Nitrophenyl carbomethoxymethyl sulphone* (*VII*)

The sulphone (V) (1·2 g.), dimethyl sulphate (0·6 g.), sodium bicarbonate (0·75 g.) and acetone (50 c.c.) were refluxed for 10 hrs. After removal of acetone, the mixture was diluted with water. The product (1·5 g.), m.p. 110–15°, after three crystallizations from benzene-*n*-hexane mixture, gave small white needles, m.p. 125–26° (Found: C, 41·5; H, 3·4. $C_9H_9NO_6S$ requires C, 41·7; H, 3·5%).

p-*Nitrophenyl bromocarbomethoxymethyl sulphone (VIII)*

The ester (VII) (2·5 g.) was dissolved in glacial acetic acid (20 c.c.) and bromine (3 g.) in glacial acetic acid (20 c.c.) was gradually added. The solution was then refluxed for 4 hrs. at 140°. The colour of the solution gradually turned to greenish yellow. Acetic acid was removed under reduced pressure and the dark brown liquid was diluted with cold water. The product which separated was crystallized from aqueous alcohol, when it gave small white needles (2 g.), m.p. 118–20°; raised to 130–31° by further recrystallization from benzene-*n*-hexane (Found: C, 31·5; H, 2·4. $C_9H_8BrNO_6S$ requires C, 31·9; H, 2·4%).

p-*Nitrophenyl bromomethyl sulphone (II)*

A mixture of the sulphone (VIII) (0·4 g.) and aqueous sodium hydroxide (10%) (5 c.c.) was shaken vigorously. The colour of the mixture first became orange and slowly changed to pale yellow and finally white. The crystalline structure of the sulphone (VIII) rapidly changed and small needles were obtained. The mixture was kept at room temperature for 2 hours and filtered. The residue was washed free from alkali and the crystalline product (0·26 g.), m.p. 134–42°, was recrystallized thrice from alcohol when it gave long white needles, m.p. 163–64° (Found: C, 30·1; H, 2·4; N, 5·2. $C_7H_6BrNO_4S$ requires C, 30·0; H, 2·1; N, 5·0%).

p-*Nitrophenyl phthalimidomethyl sulphide (IX)*

Sodium (1 g.) was dissolved in absolute alcohol (30 c.c.), *p*-nitrothiophenol (6·9 g.) was added and the mixture was refluxed for 10–15 mins. Bromomethyl phthalimide[6] (10·7 g.) was added and the mixture was refluxed further for 4 hours. At the end of the reaction the colour of the solution changed from dark red to yellow and a yellow precipitate was obtained. The mixture was concentrated, cooled and the yellow crystalline compound (12 g.), m.p. 175°, which separated was collected. It was purified by three crystallizations from acetic acid when (IX) gave m.p. 180–81° (Found: C, 57·7; H, 3·3; N, 8·9. $C_{15}H_{10}N_2O_4S$ requires C, 57·3; H, 3·1; N, 8·8%).

p-*Nitrophenyl phthalimidomethyl sulphone (X)*

The foregoing sulphide (X) (1 g.), hydrogen peroxide (112 vols.) (10 c.c.) and glacial acetic acid (20 c.c.) were heated on a water-bath at 70–80° for 12 hrs. The yellow solid gradually changed to white. Acetic acid was then removed under reduced pressure and the white product (1 g.) crystallized thrice from dioxane when it gave white plates, m.p. 265° (dec.) (Found: C, 52·2; H, 3·1; N, 8·2. $C_{15}H_{10}N_2O_6S$ requires C, 52·0; H, 2·9; N, 8·2%).

p-*Nitrophenyl ω-hydroxyethyl sulphide*

An alcoholic solution of *p*-nitrothiophenol (9·0 g. in 20 c.c.) was added to sodium ethoxide prepared by dissolving sodium (1·36 g.) in absolute alcohol (25 c.c.). The mixture was refluxed for 15 mins. and then ethylene monochlorhydrin (7 g.) was added, when the red colour of the thiophenolate solution immediately changed to yellow. The mixture was refluxed for 4 hrs. and alcohol was then removed by distillation. The mixture was diluted with water and extracted with ether. The ether extract was washed and dried (Na_2SO_4) and ether removed. The dark yellow liquid (10 g.), which was obtained as residue, soon solidified on cooling. Crystallization of the product from alcohol gave yellow plates, m.p. 60°, of the sulphide. Bennett and Berry,[7] who have prepared the sulphide from *p*-nitrochlorobenzene without isolation of the intermediate thiol give m.p. 62° (Found: C, 48·5; H, 4·8. Calc. for $C_8H_9NO_3S$: C, 48·2; H, 4·5%).

The hydroxyethyl sulphide (200 mg.) and phenyl isocyanate (110 mg.) were heated on a water-bath under anhydrous conditions for 3 hrs. The reaction product, after three crystallizations from benzene *n*-hexane, gave lemon yellow needles, m.p. 122° of the urethane (Found: N, 8·8. $C_{15}H_{14}N_2O_4S$ requires N, 9·0%).

p-*Nitrophenyl ω-acetoxyethyl sulphide*

A mixture of the foregoing sulphide (3 g.), acetic anhydride (10 c.c.) and a drop of pyridine was refluxed for 6 hrs. The excess of acetic anhydride was then removed under reduced pressure and the dark oil obtained was poured into crushed ice. The dark-coloured precipitate (3·1 g.) was filtered, washed and crystallized from aqueous alcohol, when it gave colourless needles, m.p. 44° (Found: N, 6·1. $C_{10}H_{11}NO_4S$ requires N, 5·8%).

p-*Nitrophenyl ω-hydroxyethyl sulphoxide*

A mixture of the above acetoxy sulphide (1·1 g.), hydrogen peroxide (112 vols.) (0·8 c.c.) and glacial acetic acid (5 c.c.) was heated in a boiling water-bath for 1 hour. It was poured into a saturated solution of sodium chloride. The white precipitate (1 g.) of the sulphoxide which separated was collected, dried and crystallized from alcohol when it gave lustrous colourless flakes, m.p. 125–26° (Found: C, 44·2; H, 4·2. $C_8H_9NO_4S$ requires C, 44·6; H, 4·2%). The oxidation could also be effected by means of 50 vols. hydrogen peroxide. The elementary analysis of the product indicated that the acetyl group in *p*-nitrophenyl ω-acetoxyethyl sulphide was cleaved during the oxidation.

The above sulphoxide was also obtained directly from *p*-nitrophenyl ω-hydroxyethyl sulphide by oxidation with hydrogen peroxide (100 vols.) in one experiment, but attempts to repeat the preparation were unsuccessful. The sulphoxide is, however, consistently obtained through the acetoxy sulphide as described above.

p-*Nitrophenyl ω-hydroxyethyl sulphone*

p-Nitrophenyl ω-hydroxyethyl sulphide (2 g.), hydrogen peroxide (120 vols.) (20 c.c.) and acetic acid (10 c.c.) were heated on a water-bath at 70–80° for 10 hrs. Removal of acetic acid under reduced pressure, gave a white product which on crystallization from aqueous alcohol, gave small colourless needles (1·56 g.), m.p. 124–25° of the sulphone (Found: C, 42·0; H, 4·0. $C_8H_9NO_6S$ requires C, 41·6; H, 4·0%). The sulphone was also obtained when 50 vol. hydrogen peroxide was used. The mixed m.p. of the above sulphoxide and the sulphone was 100–05°. *p*-Nitrobenzoyl chloride (0·7 g.) (freshly prepared from *p*-nitrobenzoic acid), the above sulphone (0·5 g.) and dry pyridine (0·5 c.c.) were heated on an oil-bath at 130–40° for 2 hrs. The liquid was then poured into ice. The white precipitate obtained was separated by filtration, washed with sodium bicarbonate and then with water. The *p*-nitrobenzoate of the sulphone gave colourless needles from benzene-*n*-hexane mixture, m.p. 164–65° (Found: C, 47·7; H, 3·4. $C_{15}H_{12}N_2O_8S$ requires C, 47·4; H, 3·1%).

p-*Aminophenyl ω-hydroxyethyl sulphide*

A mixture of *p*-nitrophenyl ω-hydroxyethyl sulphide (3 g.) and absolute alcohol (20 c.c.) and Raney nickel (0·5 g.) was shaken in a Parr hydrogenator with hydrogen at 42 lb./sq. inch for 6 hrs. The mixture was filtered and alcohol removed by distillation when a dark brown liquid (2·5 g.) was obtained. It gave a pale coloured liquid after four distillations and was finally collected at 190° (bath temp.)/15 mm. Morgan and Hamilton[8] quote m.p. 43–44° and b.p. 232–35°/38 mm. (Found: C, 56·1; H, 6·5. Calc. for $C_8H_{11}NOS$: C, 56·8; H, 6·5%).

p-*Nitrophenyl carboxyamidomethyl sulphide*

p-Nitrophenyl carboxymethyl sulphide (IV) (2 g.) and thionyl chloride (10 c.c.) were heated on a water-bath for 2 hrs. After removal of thionyl chloride, the dark liquid obtained was slowly added to liquor ammonia kept in an ice-bath. Yellow precipitate, m.p. 146–48°, immediately separated. It gave long lemon yellow needles, m.p. 159–60°, of the amide from aqueous alcohol (literature,[9] m.p. 159–60°) (Found: N, 13·1. Calc. for $C_8H_8N_2O_3S$: N, 13·2%).

2: 6-*Diiodo*-4-*nitrophenyl carboxymethyl sulphide*

p-Nitrophenyl carboxymethyl sulphide (IV) (1·24 g.) was heated on a water-bath at 70–80° with glacial acetic acid (10 c.c.). A solution of iodine monochloride (0·6 c.c.) in glacial acetic acid (4 c.c.) was slowly added under stirring, and the mixture was heated at 70–80° for 20 minutes under stirring. The brown yellow precipitate which separated was collected, washed with water and then with acetone. It crystallized in brownish yellow plates (0·55 g.), m.p. 112° (decomp.) from acetic acid (Found: N, 3·0. $C_8H_5I_2NO_4S$ requires N, 3·0%). The iodo derivative decomposes on keeping.

p-*Nitrophenyl carboxymethyl sulphoxide*

p-Nitrophenyl carboxymethyl sulphide (IV) (2 g.), glacial acetic acid (10 c.c.) and hydrogen peroxide (4 c.c.) were heated on a water-bath at 70–80° for 4 hrs. After removal of acetic acid under reduced pressure a dark brown liquid was obtained (1·8 g.) which solidified at room temperature. The product crystallized from aqueous alcohol in pale yellow needles, m.p. 140–41° (Found: C, 41·9; H, 3·4. $C_8H_7NO_5S$ requires C, 41·9; H, 3·1%).

p-*Nitrophenyl* 2: 3-*dihydroxypropyl sulphide*

p-Nitrothiophenol (5 g.) was added to a solution of sodium (0·75 g.) in absolute alcohol (30 c.c.). The solution was refluxed for 15 mins. and a solution of glycerine α-monochlorhydrin (4 g.) in absolute alcohol (10 c.c.) was slowly added. The mixture was refluxed on a water-bath for 4 hrs., the solvent removed by distillation and the mixture, after dilution with water, was extracted with ether. Removal of ether gave a dark yellow liquid (8·2 g.) which solidified after cooling. The sulphide crystallized from aqueous alcohol in yellow needles, m.p. 93° (Found: C, 47·2; H, 4·6; N, 6·2. $C_9H_{11}NO_4S$ requires C, 47·2; H, 4·8; N, 6·1%).

Summary

p-Nitrophenyl bromomethyl sulphone (II) and *p*-nitrophenyl phthalimidomethyl sulphone (X) were prepared with the view to synthesize the sulphone analogue (I) of chloramphenicol. In contrast with the synthesis of chloramphenicol from analogous phenacyl derivatives, (II) and (X) could not be converted to (I) on account of the deactivating influence of the sulphone group in aryl methyl sulphones.

In view of the activity of *p*-nitrophenyl ω-hydroxyethyl sulphide, sulphoxide and sulphone, several *p*-nitrophenyl alkyl sulphides, sulphoxides and sulphones and other related compounds were prepared.

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