Sulphides, Sulphoxides, and Sulphones derived from Salicylic Acids

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Methanesulphenyl chloride with 3-t-butyl-6-methylsalicylic acid (7) and pyridine affords the 5-chloro (9), 5-methylthio (10), and 5-pyridinium (11) derivatives. Arenesulphenyl chlorides similarly give chloro and arylthio derivatives. Sulphenylation is favoured by the use of sterically hindered bases. Less substituted salicylic acids give aryl sulphones by Friedel–Crafts reactions, and alkyl sulphides, sulphoxides, and sulphones by chlorosulphonation, reduction to the thiol, alkylation, and oxidation. Some electrophilic substitutions of these compounds are described.

SALICYLIC acids containing alkyl- or aryl-thio, sulphinyl, or sulphonyl substituents were required for studies on the effects of electron withdrawing and lipophilic substituents on the biological activity of salicylanilides. Few such acids have been described hitherto. Stewart [1] prepared 5-methylthiosalicylic acid (1) by chlorosulphonation of salicylic acid, reduction of the sulphonyl chloride, and alkylation of the thiol. Kaufmann and Rossbach [2] later prepared this thiol from 5-aminosalicylic acid through the diazonium and 5-thiocyanato compounds, and 4-methylsulphonylsalicylic acid has similarly been made from 4-aminosalicylic acid.[3] Some aminophenyl- and aminobenzyl-sulphonylsalicylic acids have been made from 5-chlorosulphonylsalicylic acid through the sulphinic acid,[4] and sulphones were obtained by the Fries rearrangement of the toluene-*p*-sulphonyl esters of methyl salicylate and salicylanilide.[5] Recently some arylsulphonylsalicylic acids have been made from hydroxydiarylsulphones by the Kolbe–Schmitt reaction.[6]

Salicylanilides are widely used as pesticides and antiparasitic agents, and like other acidic phenols they interfere with oxidative phosphorylation in mitochondria, possibly by facilitating the transport of hydrogen ions across the mitochondrial membrane.[7] Compounds in which the phenolic hydroxy-group is masked by a bulky lipophilic substituent such as a t-butyl group show particularly high biological activity,[8] and the preparation of salicylic acids having such substituents has presented some special problems.

We have extended Stewart's method to 5-bromo-3-chlorosulphonyl- and 5-chloro-3-chlorosulphonyl-salicylic acid and to 3,5-bis(chlorosulphonyl)salicylic acid, and have oxidised the alkylthio derivatives (2) to the sulphones (3). Nitration of (1) gave 5-methylsulphinyl-3-nitrosalicylic acid (4) and 5-methylsulphonyl-3-nitrosalicylic acid (5), and bromination gave the 3-bromo derivative (6) from which the sulphone was prepared. Chlorination of (1) occurred in the methyl group and not in the ring; this was shown by acidic methanolysis [9] to

[1] J. Stewart, *J. Chem. Soc.*, 1922, **121**, 2555.
[2] H. P. Kaufmann and E. Rossbach, *Ber.*, 1925, **58**, 1556.
[3] G. Purrello and G. Zerbo, *Boll. sedute accad. Gioenia sci. nat. Catania.*, 1957, **3**, 446 (*Chem. Abs.*, 1958, **52**, 20011).
[4] I.G. Farbenind., G.P. 436790, 634331; Brit. Dyestuffs Corp., U.S.P. 1766951.
[5] J. H. Amin and R. D. Desai, *J. Sci. Ind. Res.*, 1954, **13B**, 181.
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[7] A. Finkelstein, *Biochem. Biophys. Acta*, 1970, **205**, 1.
[8] R. L. Williamson and R. L. Metcalf, *Science*, 1967, **158**, 1694.
[9] J. M. Lavanish, *Tetrahedron Letters*, 1973, 3847.

5-mercaptosalicylic acid. 5-Methylsulphonylsalicylic acid was not attacked by bromine, but it could be nitrated. The chlorosulphonation route to thio derivatives was found to have limitations. Thymotic acid (3-isopropyl-6-methylsalicylic acid), for example, was not attacked by chlorosulphonic acid at 130°, and at higher temperatures decomposition occurred. Similarly, sulphonyl chlorides were not obtained from 5-nitrosalicylic acid, 3-phenylsalicylic acid, or 3-t-butyl-6-methylsalicylic acid (7). The latter compound loses its t-butyl group when it is treated with Lewis acids at temperatures above 5—10°. We therefore investigated the reaction of salicylic acids with sulphenyl chlorides under basic conditions.[10]

In our initial experiments we added the sulphenyl chloride dissolved in chloroform to a solution of the salicylic acid and two or three molar equivalents of pyridine in tetrachloroethane. Substitution did not occur when only one equivalent of base was used, and the addition of silica gel [11] did not facilitate these reactions. *p*-Nitrophenylsulphenyl chloride reacted with a number of alkylsalicylic acids to give the expected 5-*p*-nitrophenylthio derivatives in moderate yield, and similarly *o*-nitrophenylsulphenyl chloride and 2,4-dinitrophenylsulphenyl chloride with (7) gave good yields of the nitrophenylthio derivatives (8a and b). When (7) was treated with *m*-nitrophenylsulphenyl chloride, however, the *m*-nitrophenylthio derivative (yield 80%) was accompanied by 7% of 3-t-butyl-5-chloro-6-methylsalicylic acid (9). Formation of a chlorosalicylic acid was more marked when arylsulphenyl chlorides devoid of nitro groups were used. 4-Chlorophenylsulphenyl chloride with 3-methylsalicylic acid gave 5-*p*-chlorophenylthio-3-methylsalicylic acid (40%) and 5-chloro-3-methylsalicylic acid (9%), but with (7) the results were variable; the chloro acid (9) was formed in up to 75% yield, and the arylthio derivative (8c) was obtained, in small yield, in only a few experiments.

Under similar conditions the reactions of methanesulphenyl chloride with (7) were varied and irreproducible. The usual product was (9), but in some experiments the 5-methylthio derivative (10) was formed. A third product that was isolated was identified as the pyridinium salt (11). The formation of this compound requires an attack by pyridine, and furthermore sulphenyl halide may be lost by formation of the methylthiopyridinium ion (12).[12] To prevent this the sterically hindered base 2,6-lutidine was used instead of pyridine. It gave consistent but small yields of (10).

The use of 2,6-lutidine or the hindered base ethyldiisopropylamine in the reaction of *p*-chlorophenylsulphenyl chloride with (7) gave consistent and good yields of (8c) (Table 1), whereas with triethylamine only the chloro compound (9) was formed. Arylthio derivatives have been obtained from several salicylic acids and numerous arylsulphenyl chlorides using 2,6-lutidine,

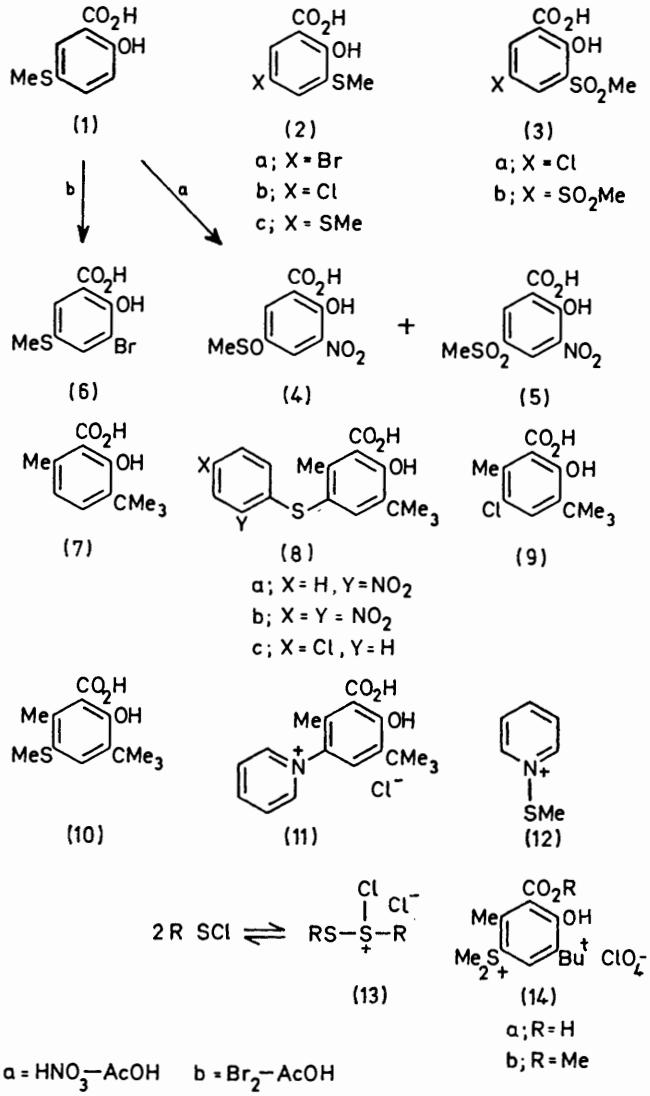

TABLE 1

Reaction of 4-chlorophenylsulphenyl chloride with (7)

Base	Yield (%) Aryl-S-	Cl
Pyridine	0–10	75
2,6-Lutidine	50	2
Pr^i_2NEt	33	18
NEt_3	0	74

but chloromethanesulphenyl chloride and trichloromethanesulphenyl chloride did not react with (7) under these conditions.

There have been a few reports [13] of chlorination by sulphenyl chlorides, but in most cases the evidence was equivocal because free chlorine was present during the reactions. The sulphenyl chlorides used in our experi-

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[11] M. Hojo and R. Masuda, *Synth. Comm.*, 1975, **5**, 173.

[12] G. K. Helmkamp, D. C. Owsley, W. M. Barnes, and H. N. Cassey, *J. Amer. Chem. Soc.*, 1968, **90**, 1635; V. J. Traynelis and J. N. Rieck, *J. Org. Chem.*, 1973, **38**, 4334.

[13] R. T. Wragg, *J. Chem. Soc.*, 1964, 5482; M. Oki and K. Kobayashi, *Bull. Chem. Soc. Japan*, 1973, **46**, 687; *Synthesis*, 1975, 196; R. M. Scribner, *J. Org. Chem.*, 1966, **31**, 3671.

ments were free from excess of chlorine but in some instances they gave high yields of chlorination products. Modena and his co-workers [14] have shown that sulphenyl chlorides form ionic dimers (13) in certain solvents, and it is conceivable that these dimers are chlorinating agents, the formation of stable disulphides being the driving force. The failure of *o*- and *p*-nitroarylsulphenyl chlorides to chlorinate salicylic acids may reflect a failure to dimerise. However, the presence of dimers in our reaction mixtures has not been demonstrated. An attempt to suppress the postulated dimerisation by adding chloride ions (as tetrabutylammonium chloride) in the reaction of *p*-chlorophenylsulphenyl chloride and (7) with pyridine stopped both the chlorination and the sulphenylation reactions. We have regarded the sulphenylation as a straightforward electrophilic substitution, but it is possible that the reaction occurs through formation of a sulphenic ester and subsequent rearrangement by cleavage of the sulphenate ion and nucleophilic attack in the *para*-position.* This would explain the formation of (11) and the chlorination reactions as well as the formation of the thio derivatives, and would accord with the greater difficulty of sulphenylating sterically hindered acids such as (7). T.l.c. examination of our reaction mixtures, however, gave evidence only of the starting materials and the final products.

Methylthio derivatives of (7) are obtained more readily by reaction of (7) or its methyl ester with dimethyl sulphoxide and perchloric acid [15] to give the 5-dimethylsulphonium perchlorates (14) which may be demethylated with aqueous potassium chloride. Esterification of (7) is conveniently done in hexamethylphosphoramide–alcohol mixtures.[16] The alkyl and arylthio compounds were oxidised with hydrogen peroxide in acetic acid, reaction at room temperature affording sulphoxides whereas at 100° sulphones were usually produced. Sulphones were also obtained directly from arylsulphonyl chlorides and 3-methylsalicylic acid and thymotic acid under Friedel–Crafts conditions at lower temperatures than those reported [5] for Fries rearrangements. Separation of the arylthio and arylsulphonylsalicylic acids from starting materials or other reaction products was often facilitated by the solubility of their sodium salts in organic solvents.

EXPERIMENTAL

5-Bromo-3-chlorosulphonylsalicylic Acid.—5-Bromosalicylic acid (97.6 g) was added gradually with stirring to chlorosulphonic acid (179 ml) at 15—20°. The mixture was heated for 3 h at 65° and was then cooled and poured on to crushed ice (2 kg) with vigorous stirring. The gummy product was rapidly extracted with ether and the solution was dried (Na_2SO_4) and evaporated. The residue was crystallised from toluene, giving the *sulphonyl chloride* (44 g), m.p. 196—198° (Found: C, 27.1; H, 1.5. $C_7H_4BrClO_5S$ requires C, 26.6; H, 1.3%).

5,5′-Dibromo-3,3′-dicarboxy-2,2′-dihydroxydiphenyl Disulphide.—5-Bromo-3-chlorosulphonylsalicylic acid (44 g) dissolved in ethanol (312 ml) was stirred at 0—5° and zinc dust (91 g) was added gradually. Concentrated hydrochloric acid (220 ml) was added with cooling during 15 min, and the mixture was stirred for 2.5 h at 15—20°. Some white solid that precipitated was redissolved by addition of ethanol and the filtered solution was treated with a 25% solution of iron(III) chloride in ethanol (307 ml) with addition of concentrated hydrochloric acid to prevent formation of a purple iron complex. After 1 h the *disulphide* was precipitated with water and was purified by solution in aqueous sodium carbonate and reprecipitation with hydrochloric acid, yield 28 g, m.p. 276—277° (Found: C, 34.4; H, 1.9. $C_{14}H_8Br_2O_6S_2$ requires C, 33.9; H, 1.6%).

3,3′-Dicarboxy-5,5′-dichloro-2,2′-dihydroxydiphenyl disulphide, m.p. 275—278°, was prepared similarly from 5-chloro-3-chlorosulphonylsalicylic acid (Found: C, 41.6; H, 2.2. $C_{14}H_8Cl_2O_6S_2$ requires C, 41.3; H, 2.0%). 3,5-Bis(chlorosulphonyl)salicylic acid was reduced similarly and the filtered solution was concentrated (without oxidation) to yield the crude dithiol as a yellow solid that could not be purified.

5-Chloro-3-methylthiosalicylic Acid (2b).—3,3′-Dicarboxy-5,5′-dichloro-2,2′-dihydroxydiphenyl sulphide (4 g) and N-sodium hydroxide solution (30 ml) were boiled under reflux for 0.5 h and the solution was cooled and was shaken with dimethyl sulphate (2 ml). Methylation was rapid and the sodium salt crystallised out. After acidification with concentrated hydrochloric acid the *methylthio acid* was collected and crystallised from water, yield 1.8 g, m.p. 185—187° (Found: C, 44.0; H, 3.3. $C_8H_7ClO_3S$ requires C, 43.9; H, 3.2%).

Similar fission and alkylation of appropriate disulphides using butyl iodide instead of dimethyl sulphate, with acetone added to give a homogeneous solution, afforded *5-bromo-2-n-butylthiosalicylic acid*, m.p. 132—134° (from benzene) (Found: C, 42.7; H, 4.2. $C_{11}H_{13}BrO_3S$ requires C, 43.3; H, 4.3%), and *5-isobutylthiosalicylic acid*, m.p. 101—103° (from water) (Found: C, 58.2; H, 6.2. $C_{11}H_{14}O_3S$ requires C, 58.4; H, 6.2%).

3,5-Bis(methylthio)salicylic Acid.—Crude 3,5-dimercaptosalicylic acid (2 g) dissolved in N-sodium hydroxide (30 ml) was stirred with dimethyl sulphate (3.76 g). After 3 min the solution was acidified with hydrochloric acid to precipitate the *product* (1.0 g), m.p. 181—183° (from toluene) (Found: C, 47.4; H, 4.3. $C_9H_{10}O_3S_2$ requires C, 47.0; H, 4.35%). Samples of the starting material having a high disulphide content were best reduced with glucose and sodium hydroxide before methylation.

3-Bromo-5-methylthiosalicylic Acid (2a).—5-Methylthiosalicylic acid (1) (18.4 g) in glacial acetic acid (180 ml) was stirred and treated dropwise with bromine (16 g) in acetic acid (20 ml). After 16 h the solution was concentrated under reduced pressure to give the *bromo acid* (11.3 g), m.p. 162—164° (from acetic acid–water) (Found: C, 37.1; H, 2.6. $C_8H_7BrO_3S$ requires C, 36.5; H, 2.7%), τ[$CDCl_3$–$(CD_3)_2SO$] 2.1 (2 H, q, *J* 2 Hz) and 7.1 (3 H, s).

Nitration of 5-Methylthiosalicylic Acid.—Nitric acid (8.0 g, *d* 1.5) in acetic acid (20 ml) was added cautiously to (1) (23 g) dissolved in acetic acid (120 ml), and the mixture was

* We are indebted to Dr. D. R. Hogg for this suggestion.

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[16] P. E. Pfeffer, T. A. Foglia, P. A. Barr, I. Schmeltz, and L. S. Silbert, *Tetrahedron Letters*, 1972, 4063.

stirred and heated under reflux for 2 h and was allowed to cool overnight. *5-Methylsulphinyl-3-nitrosalicylic acid* (4) (6.4 g) was filtered off and gave pale yellow crystals (from methanol), m.p. 233° (Found: C, 38.5; H, 2.9; N, 5.5. $C_8H_7NO_6S$ requires C, 39.2; H, 2.9; N, 5.7%), *m/e* 245 (M^+), τ[$(CD_3)_2SO$] 1.55—1.65 (2 H, q, *J* 2 Hz) and 7.2 (3 H, s). The filtrate was heated with 27.5% hydrogen peroxide (80 ml) at 90° for 40 min, and after dilution with water the solution was evaporated under reduced pressure to give *5-methylsulphonyl-3-nitrosalicylic acid* (5) (7 g), pale yellow crystals, m.p. 242—244: (from water) (Found: C, 36.8; H, 2.9; N, 5.3. $C_8H_7NO_7S$ requires C, 36.8; H, 2.7; N, 5.4%), τ[$(CD_3)_2SO$] 1.6 (2 H, q, *J* 2.5 Hz) and 6.8 (3 H, s). This compound was obtained in 34% yield by nitrating 5-methylsulphonylsalicylic acid under similar conditions. 5-Isobutylthiosalicylic acid was nitrated similarly (95° for 5 h) and the reaction mixture was oxidised with hydrogen peroxide to give *5-isobutylsulphonyl-3-nitrosalicylic acid*, pale yellow crystals, m.p. 196—198° (from water) (Found: C, 43.6; H, 4.4; N, 4.3. $C_{11}H_{13}NO_7S$ requires C, 43.6; H, 4.3; N, 4.6%).

5-Methylsulphonylsalicylic Acid.—Compound (1) (5 g), acetic acid (50 ml), and 27.5% hydrogen peroxide (20 ml) were heated at 90—95° for 40 min, and after dilution with water the solution was evaporated to small bulk under reduced pressure to give the *sulphone* (4.9 g), m.p. 201—203° (from water) (Found: C, 44.0; H, 3.8. $C_8H_8O_5S$ requires C, 44.4; H, 3.7%), τ[$(CD_3)_2SO$] 1.7—3.0 (3 H, m) and 6.84 (3 H, s).

The following were prepared similarly: *3,5-bis(methylsulphonyl)salicylic acid* (3b), m.p. 264—266° (from acetic acid) (Found: C, 36.2; H, 3.4. $C_9H_{10}O_7S_2$ requires C, 36.7; H, 3.4%), τ[$(CD_3)_2SO$] 2.65 (2 H, q, *J* 2.6 Hz), 6.65 (3 H, s), and 6.75 (3 H, s); *5-chloro-3-methylsulphonylsalicylic acid* (3a), m.p. 205—207° (from water) (Found: C, 38.0; H, 2.9. $C_8H_7ClO_5S$ requires C, 38.3; H, 2.8%); *3-bromo-5-methylsulphonylsalicylic acid*, m.p. 257—259° (from water) (Found: C, 32.1; H, 2.4. $C_8H_7BrO_5S$ requires C, 32.5; H, 2.4%), τ[$(CD_3)_2SO$] 1.72 (2 H, s) and 6.74 (3 H, s); *5-bromo-3-n-butylsulphonylsalicylic acid*, m.p. 169—170° (from water) (Found: C, 38.5; H, 3.9. $C_{11}H_{13}BrO_5S$ requires C, 39.2; H, 3.9%), τ[$(CD_3)_2SO$] 1.9 (2 H, q, *J* 2.5 Hz), 6.5 (2 H, t), 8.5 (4 H, m), and 9.1 (3 H, t).

2-Acetoxy-5-methylsulphonylbenzoic Acid.—5-Methylsulphonylsalicylic acid (1 g) and acetyl chloride (7 ml) were boiled under reflux for 7 h and cooled to give the *acetyl derivative*, m.p. 159—160°, which was rapidly hydrolysed by moisture (Found: C, 46.6; H, 4.0. $C_{10}H_{10}O_6S$ requires C, 46.5; H, 3.9%).

Reactions with Sulphenyl Chlorides.—*5-p-Chlorophenylthio-6-methyl-3-t-butylsalicylic acid* (8c) (*method* a). 4,4′-Dichlorodiphenyl disulphide (18.9 g, *M*/16 + 5%) was suspended in dry chloroform (185 ml) and was treated with chlorine at 10° until it dissolved. A slow stream of chlorine was passed into the solution for a further 10 min and the solution was then evaporated to 5/6 of its volume at 20—25° under reduced pressure. It was then added at 10—15° to a stirred solution of (7) (26 g, *M*/8) and 2,6-lutidine (26.8 g, *M*/4) in tetrachloroethane (300 ml) with careful exclusion of moisture. Stirring was continued overnight at room temperature and the solution was washed in water (2 × 80 ml), N-NaOH solution (4 × 150 ml), and 6N-hydrochloric acid (2 × 100 ml). Acidification of the alkaline extract gave 5-chloro-6-methyl-3-t-butylsalicylic acid (9) (0.5 g), m.p. 209—211° (lit.,[17] 208—211°). The organic phase was treated with N-NaOH solution (3 × 150 ml), each addition causing the separation of a red oily gum at the interface. This gum was collected and was triturated with concentrated hydrochloric acid with cooling, giving a paste that was filtered, dried, and crystallised from acetic acid to yield the *product* (19.6 g) (Table 2).

6-Methyl-5-m-nitrophenylthio-3-t-butylsalicylic acid (*method* b). The sulphenyl chloride prepared from 3,3′-dinitrodiphenyl disulphide (10 g) in dry chloroform (100 ml) as in the foregoing preparation was added during 5 min to a solution of (7) (13 g) and pyridine (10.8 ml) in tetrachloroethane (150 ml) at 10—15° with exclusion of moisture and the mixture was stirred overnight at room temperature. It was then washed with water (2 × 70 ml) and treated with N-NaOH solution (4 × 200 ml) which caused the precipitation of a gum at the interface. The gum was separated by decantation and was triturated with concentrated hydrochloric acid to yield the *product* which was crystallised from xylene (Table 2). Acidification of the alkaline extract gave the chloro acid (9) (1.0 g). In some analogous preparations, *e.g.* with *p*-nitrophenylsulphenyl chloride, the sodium salt of the product was not precipitated by the sodium hydroxide solution and the product was recovered by acidification of this solution.

5-Methanesulphonyl-6-methyl-3-t-butylsalicylic acid (10). Dimethyl disulphide (17.7 g, 3M/16) cooled to −20° was treated with chlorine until 8.8 g (*M*/8) had been absorbed. The temperature of the solution was allowed to rise to 0° and the sulphenyl chloride was used immediately (chlorination of the disulphide with sulphuryl chloride, or the use of distilled methanesulphenyl chloride gave similar results). The sulphenyl chloride was added below 0° to a well stirred solution of (7) (26 g) and pyridine (20 ml) in tetrachloroethane (130 ml) protected from moisture. The mixture was stirred at 0° for 1 h and then at room temperature for 2 h and it was then poured into water (*ca.* 150 ml). The solid that separated was collected and crystallised from acetic acid to give *1-(5-carboxy-4-hydroxy-6-methyl-3-t-butylphenyl)pyridinium chloride* (11) (1.1 g), m.p. 254° (decomp.) (Found: C, 63.5; H, 6.2; N, 4.3; Cl, 11.0. $C_{17}H_{20}ClNO_3$ requires C, 63.45; H, 6.2; N, 4.35; Cl, 11.0%), τ(CF_3CO_2D) 1.12 (3 H, m), 1.54—1.7 (2 H, m), 2.35 (1 H, s), 7.6 (3 H, s), and 8.47 (9 H, s), *m/e* 242 (M − Cl − CO_2). A solution of this compound (0.2 g) in hot water treated with sodium acetate (0.2 g) gave the *betaine hydrate* (0.15 g), m.p. 288° (decomp.) (Found: C, 68.0; H, 7.0; N, 4.7. $C_{17}H_{19}NO_3,H_2O$ requires C, 67.3; H, 6.9; N, 4.6%), τ[$(CD_3)_2SO$] 0.75 (2 H, d), 1.1 (1 H, t), 1.63 (2 H, t), 2.65 (1 H, s), 7.64 (3 H, s), and 8.62 (9 H, s). The organic phase from the reaction mixture was extracted with N-NaOH solution (2 × 100 ml) and the extract was acidified with hydrochloric acid to give a solid from which the methylthio derivative (10) could not readily be separated. The crude mixture (*ca.* 11 g) was therefore oxidised with 27.5% hydrogen peroxide (50 ml) in acetic acid (100 ml) for 40 min at 90—100°. After cooling and dilution with water the *methylsulphonyl derivative* (1.3 g) crystallised, pale yellow crystals, m.p. 232° (decomp.) (from chlorobenzene) (Found: C, 54.3; H, 6.2. $C_{13}H_{18}O_5S$ requires C, 54.5; H, 6.3%), τ[$(CD_3)_2SO$] 2.02 (1 H, s), 6.8 (3 H, s), 7.28 (3 H, s), 8.6 (9 H, s). In other experiments only the chloro acid (9) was isolated; the use of 2,6-lutidine instead of pyridine consistently gave the methylthio acid (isolated as the sulphone). Similarly, methanesulphenyl

[17] Monsanto, U.K. 1,139,638.

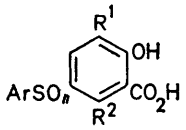
chloride with salicylic acid and 2,6-lutidine gave (1) (34%), m.p. 123—126°, which was characterised by oxidation to the sulphone, m.p. 201—203°.

5-p-*Chlorophenylsulphonyl*-3-*isopropyl*-6-*methylsalicylic acid* (*method* d). Thymotic acid (5.7 g) was added to aluminium chloride (8.1 g) in dry nitrobenzene (35 ml). After gas evolution had ceased *p*-chlorobenzenesulphonyl chloride (6.3 g) was added and the mixture was heated for 4 h at 90—100°. The mixture was cooled, decomposed with dilute hydrochloric acid, and extracted with ethyl acetate. The organic phase was washed with saturated $NaHCO_3$ solution, separated, and steam distilled. The residue was acidified with hydrochloric acid and the oily product was collected and crystallised from xylene–light petroleum to give the *sulphone* (1.9 g), m.p. 165—166° (Table 2). Under similar conditions salicylic acid gave 5-p-*chlorophenylsulphonylsalicylic acid* (Table 2) in which the proton in the 3-position was characterised by the doublet at τ 2.8 at higher field than the other aromatic protons [in $(CD_3)_2SO$].

6-*Methyl*-5-p-*nitrophenylsulphonyl*-3-*t*-*butylsalicylic acid*

TABLE 2

Arylthio-, arylsulphinyl-, and arylsulphonyl-salicylic acids (A)



Ar	*n*	R^1	R^2	Formula	M.p. (°C)	Found (%) C	H	N	Required (%) C	H	N	Method	Yield (%)
C_6H_5	0	Bu^t	Me	$C_{18}H_{20}O_3S$	169—170	68.0	6.4		68.4	6.3		a	31
C_6H_5	2	Bu^t	Me	$C_{18}H_{20}O_5S$	172—174	61.9	5.7		62.1	5.7		c	36
4-MeC_6H_4	2	Me	H	$C_{15}H_{14}O_5S,0.5H_2O$	250—252	57.5	4.7		57.2	4.7		d	12
4-MeC_6H_4	0	Bu^t	Me	$C_{19}H_{22}O_3S,0.5H_2O$	163—164	67.7	6.6		67.3	6.8		a	25
4-MeC_6H_4	2	Bu^t	Me	$C_{19}H_{22}O_5S$	187—188	62.4	6.1		63.0	6.1		c	67
4-ClC_6H_4	0	Me	H	$C_{14}H_{11}ClO_3S$	175—176	56.8	3.7		57.0	3.7		b	40
4-ClC_6H_4	2	Me	H	$C_{14}H_{11}ClO_5S$	237—238	52.0	3.8		51.5	3.4		c d	67 12
4-ClC_6H_4	2	H	H	$C_{13}H_9ClO_5S$	218—219	49.6	2.9		49.9	2.9		d	15
4-ClC_6H_4	2	Pr^i	Me	$C_{17}H_{17}ClO_5S$	165—166	55.9	4.7		55.4	4.6		d	17
4-ClC_6H_4	0	Bu^t	Me	$C_{18}H_{19}ClO_3S$	172—174	61.3	5.4		61.6	5.4		a	50
4-ClC_6H_4	2	Bu^t	Me	$C_{18}H_{19}ClO_5S$	196—197	56.6	5.0		56.5	5.0		c	67
4-BrC_6H_4	0	Bu^t	Me	$C_{18}H_{19}BrO_3S$	172—174	54.4	4.8		54.7	4.8		a	40
4-Br-3-MeC_6H_3	0	Bu^t	Me	$C_{19}H_{21}BrO_3S$	193—195	55.3	5.1		55.7	5.1		a	50
4-Br-3-MeC_6H_3	2	Bu^t	Me	$C_{19}H_{21}BrO_5S$	192—194	51.5	4.8		51.7	4.8		c	45
3,4-$Cl_2C_6H_3$	0	Bu^t	Me	$C_{18}H_{18}Cl_2O_3S$	163—164	55.9	4.7		56.1	4.7		a	33
3,4-$Cl_2C_6H_3$	2	Bu^t	Me	$C_{18}H_{18}Cl_2O_5S$	191—192	51.7	4.3		51.8	4.3		c	54
2,5-$Cl_2C_6H_3$	0	Bu^t	Me	$C_{18}H_{18}Cl_2O_3S$	202—204	55.5	4.6					a	52
2,5-$Cl_2C_6H_3$	2	Bu^t	Me	$C_{18}H_{18}Cl_2O_5S$	252—253	51.5	4.3					c	37
2,4,5-$Cl_3C_6H_2$	0	Bu^t	Me	$C_{18}H_{17}Cl_3O_3S,0.5H_2O$	216—218	50.4	4.0		50.4	4.2		a	67
2,4,5-$Cl_3C_6H_2$	1	Bu^t	Me	$C_{18}H_{17}Cl_3O_4S$	207—209	49.5	3.9		49.6	3.9		c	33
4-BrC_6H_4	2	Me	H	$C_{14}H_{11}BrO_5S$	233—235	45.4	3.2		45.3	3.0		d	16
2-$NO_2C_6H_4$	0	Bu^t	Me	$C_{18}H_{19}NO_5S$	218—220	59.9	5.3	3.8	59.8	5.3	3.9	b	69
2-$NO_2C_6H_4$	2	Bu^t	Me	$C_{18}H_{19}NO_7S$	237—238	55.1	5.0	3.5	55.0	4.8	3.6	c	65
3-$NO_2C_6H_4$	0	Bu^t	Me	$C_{18}H_{19}NO_5S$	185—188	59.8	5.4	3.9				b	80
3-$NO_2C_6H_4$	2	Bu^t	Me	$C_{18}H_{19}NO_7S$	190—191	55.1	4.9	3.5				c	69
4-$NO_2C_6H_4$	0	Me	H	$C_{14}H_{11}NO_5S$	199—201	54.9	3.5	4.1	55.1	3.6	4.6	b	37
4-$NO_2C_6H_4$	1	Me	H	$C_{14}H_{11}NO_6S$	253—255	52.1	3.5	4.2	52.3	3.4	4.4	e	61
4-$NO_2C_6H_4$	2	Me	H	$C_{14}H_{11}NO_7S$	258—260	50.0	3.4	4.1	49.9	3.3	4.2	c	70
4-$NO_2C_6H_4$	0	Pr^i	Me	$C_{17}H_{17}NO_5S$	177—179	58.8	4.9	3.8	58.8	4.9	4.0	b	8
4-$NO_2C_6H_4$	1	Pr^i	Me	$C_{17}H_{17}NO_6S$	133—135	56.1	4.9	3.9	56.2	4.7	3.9	e	80
4-$NO_2C_6H_4$	2	Pr^i	Me	$C_{17}H_{17}NO_7S$	214—216	53.8	4.6	3.6	53.8	4.5	3.7	c	92
4-$NO_2C_6H_4$	0	Bu^t	H	$C_{17}H_{17}NO_5S$	184—185	58.7	5.0	3.6				b	35
4-$NO_2C_6H_4$	2	Bu^t	H	$C_{17}H_{17}NO_7S$	199—201	53.9	4.5	3.5				c	76
4-$NO_2C_6H_4$	0	Bu^t	Me	$C_{18}H_{19}NO_5S$	195—197	59.9	5.4	3.9				b	53
4-$NO_2C_6H_4$	1	Bu^t	Me	$C_{18}H_{19}NO_6S$	201—202	57.3	5.2	3.7	57.3	5.0	3.7	e	40
4-$NO_2C_6H_4$	2	Bu^t	Me	$C_{18}H_{19}NO_7S$	222—224	55.6	5.0	3.1				c	85
2,4-$(NO_2)_2C_6H_3$	0	Bu^t	Me	$C_{18}H_{18}N_2O_7S$	258 (decomp.)	53.3	4.5	6.7	53.2	4.4	6.9	b	51
2,4-$(NO_2)_2C_6H_3$	1	Bu^t	Me	$C_{18}H_{18}N_2O_8S$	228 (decomp.	51.2	4.3	6.5	51.2	4.3	6.6	e	74
2,4-$(NO_2)_2C_6H_3$	2	Bu^t	Me	$C_{18}H_{18}N_2O_9S$	240 (decomp.)	49.5	4.1	6.3	49.3	4.1	6.4	c	59
2-Cl-5-$NO_2C_6H_3$	0	Bu^t	Me	$C_{18}H_{18}ClNO_5S$	220—221	54.3	4.5	3.4	54.6	4.6	3.5	b	37
2-Cl-5-$NO_2C_6H_3$	1	Bu^t	Me	$C_{18}H_{18}ClNO_6S$	224—225	52.2	4.4	3.3	52.5	4.4	3.4	c	
2-Cl-5-$NO_2C_6H_3$	2	Bu^t	Me	$C_{18}H_{18}ClNO_7S$	275 (decomp.)	50.5	4.4	3.2	50.5	4.2	3.3	c	
4-Cl-2-$NO_2C_6H_3$	0	Bu^t	Me	$C_{18}H_{18}ClNO_5S$	223—225	54.3	4.6	3.3				b	65
4-Cl-2-$NO_2C_6H_3$	2	Bu^t	Me	$C_{18}H_{18}ClNO_7S$	244—245	50.0	4.3	3.0				c	60
4-Cl-3-$NO_2C_6H_3$	0	Bu^t	Me	$C_{18}H_{18}ClNO_5S$	173—174	54.8	4.6	3.5				b	64
4-Cl-3-$NO_2C_6H_3$	2	Bu^t	Me	$C_{18}H_{18}ClNO_7S$	206—208	50.4	4.2	3.2				c	69

[a] Sulphenyl chloride and 2,6-lutidine. [b] Sulphenyl chloride and pyridine. [c] H_2O_2–acetic acid, 90—95°. [d] Friedel–Crafts. [e] H_2O_2–acetic acid, 15—20°.

(*method* c). 6-Methyl-5-*p*-nitrophenylthio-3-t-butylsalicylic acid (3 g) in acetic acid (30 ml) and 27.5% hydrogen peroxide (18.5 ml) was heated 40 min at 90—95° and the mixture was poured into water (100 ml). The *product* was filtered off and crystallised from toluene (Table 2).

6-*Methyl*-5-p-*nitrophenylsulphinyl*-3-*t-butylsalicylic acid* (*method* e). 3-t-Butyl-6-methyl-5-*p*-nitrophenylthiosalicylic acid (2 g) dissolved in acetic acid (200 ml) was stirred for 6 h at room temperature with 27.5% hydrogen peroxide (11 ml) and then added to water (700 ml). The *product* was filtered off and crystallised from acetic acid (Table 2).

Methyl 6-*methyl*-3-*t-butylsalicylate*. The acid (7) (10.4 g) dissolved in hexamethylphosphoramide (50 ml) and ethanol (50 ml) was treated with powdered potassium hydroxide (3 g), the mixture was stirred and heated to 50° and methyl iodide (14.5 g) was added. Stirring at 50° was continued for 3 h, and the mixture was cooled and added to 3N-hydrochloric acid (500 ml). The *ester* separated as an oil which solidified and was crystallised from ethanol, yield 6.2 g, m.p. 72—73° (Found: C, 70.3; H, 8.4. $C_{13}H_{18}O_3$ requires C, 70.3; H, 8.1%), τ[$(CD_3)_2SO$] 2.95 (2 H, q, *J* 8 Hz), 6.0 (3 H, s), 7.5 (3 H, s), and 8.55 (9 H, s). *Ethyl* 6-*methyl*-3-*t-butylsalicylate* was made similarly, using ethyl iodide, and had m.p. 45—46° (Found: C, 71.2; H, 8.5. $C_{14}H_{20}O_3$ requires C, 71.2; H, 8.5%).

4-*Hydroxy*-3-*methoxycarbonyl*-2-*methyl*-5-*t-butylphenyldimethylsulphonium perchlorate* (14b). Methyl 6-methyl-3-t-butylsalicylate (4.25 g) was added with stirring and cooling (<5°) to phosphoryl chloride (8 ml) and 70% perchloric acid (10 ml). Dimethyl sulphoxide (1.6 g) was added dropwise below 5° and the mixture was stirred for 1 h at 5—10° and for 2 h at 15—20°, and was allowed to stand overnight. The solution was poured into ice and water (100 g) and the precipitated *sulphonium salt* (4.8 g) was collected and crystallised from ethanol, forming white needles, m.p. 200—201° (Found: C, 47.0; H, 6.0; S, 8.4. $C_{15}H_{23}ClO_7S$ requires C, 47.1; H, 6.0; S, 8.4%), τ[$(CDCl_3$–$(CD_3)_2SO$] 2.2 (1 H, s), 4.1 (3 H, s), 4.77 (6 H, s), 7.47 (3 H, s), and 8.6 (9 H, s).

Methyl 6-*methyl*-5-*methylthio*-3-*t-butylsalicylate*. The foregoing sulphonium salt (2 g) and saturated potassium chloride solution (30 ml) were boiled under reflux for 5 h, The cooled mixture was diluted with water (50 ml) and the *product* was recovered by extraction with ether, yield 1 g. m.p. 95—96° (from acetic acid) (Found: C, 63.1; H, 7.7, $C_{14}H_{20}O_3S$ requires C, 62.7; H, 7.5%), τ($CDCl_3$) 2.55 (1 H. s), 6.1 (3 H, s), 7.45 (3 H, s), 7.75 (3 H, s), and 8.7 (9 H, s).

3-*Carboxy*-4-*hydroxy*-2-*methyl*-5-*t-butylphenyldimethylsulphonium perchlorate* (14a), m.p. 274° (decomp.), was prepared in the same way as the ester (Found: C, 45.6; H, 5.8; S, 8.4. $C_{14}H_{21}ClO_7S$ requires C, 45.6; H, 5.7; S, 8.7%), τ[$(CD_3)_2SO$] 2.25 (1 H, s), 6.75 (6 H, s), 7.53 (3 H, s), and 8.65 (9 H, s).

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