

DERIVATIVES OF SALICYLIC ACID.

Part XIII. Chlorosalicylic Acids and Their Methyl Ethers.

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3-SUBSTITUTED salicylic acids are difficult to obtain by direct substitution; the orienting influence is favourable to position 5. Chlorination¹ of salicylic acid has so far given a mixture consisting mainly of 5-chlorosalicylic acid, and small quantities of 3-chloro- and 3:5-dichlorosalicylic acids and chlorophenols; no conditions were known which would give each of these substances alone and separately. The methyl ethers of these acids had also not received proper attention; that of 3-chlorosalicylic acid being yet unknown, and those of 5-chloro- and 3:5-dichlorosalicylic acids² obtained indirectly from 2-methyl-4-chlorophenyl methyl ether and 2-methyl-4:6-dichlorophenyl methyl ether.

As the amides of these acids were required for some other work, convenient methods had to be worked out for the preparation of the above acids, which together with some new derivatives form the subject-matter of the present paper.

3-Chlorosalicylic acid.—This acid has now been prepared in good yield by two different methods. Sulphonic acid group in 5-sulphosalicylic acid is unstable and can be substituted with hydrogen by superheated steam.³ This acid when chlorinated gave *3-chloro-5-sulphosalicylic acid* which on desulphonation at 160°–70° gave 3-chlorosalicylic acid.

In previous work with chloralsalicylamide, it has been found that the substitution of carboxyl group by chloralamide group changes the main orienting influence from position 5 to position 3. In agreement with this observation a good yield of *chloral-3-chlorosalicylamide* is obtained by the chlorina-

¹ Heubner and Brenken, *Ber.*, 1873, 6, 174; Lassar-Cohn and Schultze, *ibid.*, 1905, 38, 3300; Ullmann and Kopetschni, *ibid.*, 1911, 44, 428.

² Paratoner and Condorelli, *Gaz.*, 1898, 281, 211–12; Martini, *ibid.*, 1899, 29, II, 62.

³ Meldrum and Shah, *J.C.S.*, 1923, 123, 1986; Hirwe and Patil, *Proc. Ind. Acad. Sci.*, 1937, 5 (4), 321–25.

tion of chloralsalicylamide, which yields 3-chloro-salicylic acid in good quantity on hydrolysis.

Methylation of the chloroacid with dimethyl sulphate and concentrated alkali affords a good yield of the *methyl ether*, hitherto unknown.

5-Chlorosalicylic acid.—This acid is obtained alone and not in a mixture, as obtained by previous workers⁴ if the rate of passing chlorine and the temperature is controlled, as described in the experimental section.

3 : 5-Dichlorosalicylic acid.—The rate of passing chlorine is not very important in this case. Chlorination of salicylic acid at 0°–5° gives pure dichloro acid.

The *methyl ethers* of the above two acids have been obtained by chlorination of the corresponding 2-methoxy-benzoic acids; they could not be obtained by the direct methylation of the acids.

The *amides* of some of the above compounds have been prepared by the usual methods.

Experimental.

3-Chlorosalicylic acid has been prepared by two different methods.

Method I.—By using (a) molecular chlorine or (b) nascent chlorine. (a) Chlorine (35 g., 1 mol.) was slowly passed at 0°–5° into a glacial acetic acid solution of 5-sulphosalicylic acid (100 g.). The mixture was kept at room temperature overnight during which time, much hydrogen chloride was evolved and a sticky mass separated. This was filtered on glass-wool, and dried on a porous plate. It was then dissolved in a little hot water to which syrupy phosphoric acid was added to raise the boiling point; superheated steam was passed in the liquid mass, the temperature finally reaching 170°. On cooling, 3-chlorosalicylic acid separated and was filtered off and the filtrate repeatedly heated with superheated steam as before until no further yield of 3-chlorosalicylic acid was obtained. The solid was collected, washed with water and crystallised from dilute alcohol: white needles, m.p. 180°–182° (178°–Varnholt⁵; 180°–Anschutz, Anspach⁶): yield about 72 per cent. It gave with ferric chloride an intense violet colouration.

Part of the 3-chloro acid probably decomposes to chlorophenol, as indicated by the smell, during desulphonation. (b) Powdered potassium permanganate (17 g.) was added slowly with constant stirring to concentrated hydrochloric acid (200 c.c.) in which was dissolved 5-sulphosalicylic acid

⁴ Heubner and Brenken and others (*loc. cit.*).

⁵ *J. Prakt. Chem.*, 1887, 36 (2), 22.

⁶ *Ann.*, 1906, 346, 312.

(50 g.). The reaction mixture was kept overnight and the resulting clear solution was concentrated and then heated in a strong round-bottomed flask with addition of syrupy phosphoric acid. Superheated steam was then passed into the liquid mass for about an hour, the temperature finally reaching 170° . The smell of chlorophenol was observed also in this process. The operation was stopped when a solid product started separating. The solid was washed with water to remove potassium and manganese salts; the chloro-acid crystallised from alcohol in white needles: m.p. and mixed m.p. with product from (a) $180-182^{\circ}$.

Chloral-3-chlorosalicylamide (chlorination of chlorosalicylamide).—Chlorine (5 g.) was slowly passed into a solution of chlorosalicylamide (20 g.) in glacial acetic acid, keeping the temperature below 15° . When the required amount of chlorine had been absorbed, the solution was kept overnight at room temperature. No solid had separated by next day. On dilution with water a pinkish powder (18 g.) was precipitated which was filtered. The crude product, m.p. $132-136^{\circ}$, on crystallisation from alcohol gave colourless needles m.p., $159-160^{\circ}$: the alcoholic solution gave a red colouration with ferric chloride.

(Found: N, 4.5; Cl, 44.7; $C_9H_7O_3NCl_4$ requires N, 4.4; Cl, 44.5 per cent.)

3-Chlorosalicylic acid (Hydrolysis of Chloral-3-chlorosalicylamide).—Chloral-3-chlorosalicylamide (20 g.) was dissolved in sodium hydroxide (10 per cent. 200 c.c.) and the solution refluxed on a sand-bath for about six hours. After cooling, the solution was acidified with dilute hydrochloric acid, when a paste resulted. It was washed with water several times until it solidified. The solid crystallised from dilute alcoholic white needles with m.p. $180-81^{\circ}$. The mixed melting point of this substance with that obtained by *Method I* above showed no lowering. Yield about 86 per cent.

Potassium-3-chlorosalicylate crystallised from water in needles. (Found: K, 18.9; $C_7H_4O_3ClK$ requires K, 18.5 per cent.)

Calcium-3-chlorosalicylate—crystallised from water in white plates. (Found: Ca, 9.0; H_2O , 12.2; $C_{14}H_8O_6Cl_2Ca, 3H_2O$ requires Ca, 9.2; H_2O , 12.4 per cent.)

Silver-3-chlorosalicylate—crystallised from water in minute needles turning dark on exposure. (Found: Ag, 38.4; $C_7H_4O_3ClAg$ requires Ag, 38.6 per cent.)

3-Chlorosalicylamide: Method I.—A mixture of methyl-3-chlorosalicylate (20 g.) and liquor ammonia (200 c.c.; D. 0.888) was put in a spring-stoppered bottle and mechanically shaken for six hours when a clear

solution was obtained which on evaporation on a water-bath gave a solid. It was triturated with dilute hydrochloric acid, filtered, washed and dried. (It is soluble in hot water, alcohol, acetone and acetic acid.) The amide crystallised from dilute alcohol in white needles, m.p. 174–175°; it gave as violet-red colouration with ferric chloride. (Found: Cl, 20.8; $C_7H_6O_2NCl$ requires Cl, 20.7 per cent.)

Method II.—A mixture of 3-chlorosalicylic acid (10 g.) and phosphorous pentachloride (12 g.) suspended in low-boiling petroleum ether was refluxed at 30–40° for four hours (Anschutz and Anspach⁷), the cool reaction mixture was poured into liquor ammonia (D. 0.888), kept cool by surrounding ice, with constant stirring. The solid (8.5 g.) crystallised from dilute alcohol: prisms, m.p. 174–176°. Mixed melting point with the amide prepared by *Method I* above showed no lowering.

5-Chlorosalicylic acid.—Salicylic acid (14 g.) was dissolved in glacial acetic acid and the container surrounded with ice. Into the ice-cold solution chlorine (7 g.) was gradually passed, so that the bubbles could be counted (about 60–70 bubbles per minute). The resulting solution was allowed to stand overnight at the room temperature, during which hydrogen chloride was evolved. On diluting the solution with water, a solid was obtained which crystallised from dilute alcohol in fine needles, m.p. 172–173°; yield 15 g.; it gave with alcoholic ferric chloride a violet colouration (m.p., 167.5°—Beilstein⁸; 172.5°—Huebner, Brenken⁹; 176°—Lassar-Cohn, Schultze¹⁰).

3 : 5-Dichlorosalicylic acid.—Salicylic acid (14 g., 1 mol.) was dissolved in glacial acetic acid and the container surrounded with ice. Into the ice-cold solution, chlorine (14 g., 2 mols.) was slowly passed, the rate of bubbling chlorine did not require to be specially controlled as in the above experiment. The resulting solution was kept overnight at room temperature and then heated on a water-bath for about an hour to complete the reaction. Hydrogen chloride was profusely evolved. The reaction mixture gave a solid on dilution with water; this crystallised from dilute alcohol in thick needles, m.p. 219–220°; yield 16.5 g.; it gave with alcoholic ferric chloride a reddish-violet colouration (m.p. 219.5°—Martini¹¹; 223°—Lassar-Cohn, Schultze¹²).

⁷ *Ibid.*

⁸ *Ber.*, 1875, 8, 816; *Ann.*, 1875, 179, 285.

⁹ *Ibid.*, 1873, 6, 174.

¹⁰ *Ibid.*, 1905, 38, 3300.

¹¹ *Gaz.*, 1899, 29, II, 62.

¹² *Ber.*, 1905, 38, 3300.

Calcium-3:5-dichlorosalicylate—crystallised from water in white plates. Found: Ca, 7.4; H₂O, 14.0; C₁₄H₆O₆Cl₄Ca, 4H₂O requires Ca, 7.6; H₂O, 13.7 per cent.)

3-Chloro-2-methoxybenzoic acid.—3-Chlorosalicylic acid (17 g.) was dissolved in cold potassium hydroxide (75 c.c.—40 g. KOH in 150 c.c. H₂O) and dimethyl sulphate (100 g.) gradually added with constant shaking and cooling under tap. It was then kept overnight and then heated on a water-bath for half an hour, when further quantity of potassium hydroxide (75 c.c. remaining from above) was added and the heating continued for quarter of an hour more. The cooled solution on acidification gave a solid (16 g.) which crystallised from alcohol: white needles; m.p. 120–21°: it gave no colouration with alcoholic ferric chloride. (Found: equivalent weight, 187.4; Cl, 19.1; C₈H₇O₃Cl requires equivalent weight, 186.5; Cl, 19.0 per cent.) It is soluble in alcohol, acetone, benzene and acetic acid.

Sodium-3-chloro-2-methoxybenzoate—crystallised from water: needles. (Found: Na, 10.4; H₂O, 8.1; C₈H₆O₃ClNa, H₂O requires Na, 10.2; H₂O, 8.0 per cent.)

Barium-3-chloro-2-methoxybenzoate—crystallised from water: white needles. (Found: Ba, 23.8, 23.8; C₁₆H₁₂O₃Cl₂Ba, 4H₂O requires Ba, 23.6 per cent.)

Silver-3-chloro-2-methoxybenzoate.—Difficultly soluble in hot water: darkens. (Found: Ag, 37.1; C₈H₆O₃ClAg requires Ag, 36.8 per cent.)

3-Chloro-2-methoxybenzamide.—A mixture of 3-chloro-2-methoxybenzoic acid (6 g.) and phosphorous pentachloride (7 g.) was treated as above, until a yellowish-white solid (5 g.) was obtained. It crystallised from alcohol: flakes, m.p., 99–100°: it gave no colouration with alcoholic ferric chloride. (Found: Cl, 19.3; C₈H₅O₂NCl requires Cl, 19.1 per cent.) It is soluble in alcohol, acetone, benzene and acetic acid.

5-Chloro-2-methoxybenzoic acid.—2-Methoxybenzoic acid (14 g.) was dissolved in glacial acetic acid and the solution kept cool by surrounding ice whilst chlorine (7 g.) was passed into it. The resulting solution was allowed to stand overnight at room temperature. On dilution a solid was obtained (15.5 g.) which crystallised from dilute alcohol: white needles, m.p. 80–81°: it gave no colouration with alcoholic ferric chloride (m.p. 81–82°—Peratoner, Condorelli¹³).

Silver-5-chloro-2-methoxybenzoate—crystallised from water: minute needles turning brownish. (Found: Ag, 36.9; C₈H₆O₃ClAg requires Ag, 36.8 per cent.)

¹³ *Gaz.*, 1898, 28, I, 211.

5-Chloro-2-methoxybenzamide.—A mixture of 5-chloro-2-methoxybenzoic acid (6 g.) and phosphorous pentachloride (7 g.) was treated as above. A solid (5 g.) was obtained. It crystallised from alcohol : prisms, m.p. 137–138°; it gave no colouration with alcoholic ferric chloride. (Found : Cl, 19.2; $C_8H_8O_2NCl$ requires Cl, 19.1 per cent.) It is soluble in alcohol, acetone, benzene and acetic acid.

3 : 5-Dichloro-2-methoxybenzoic acid.—2-Methoxybenzoic acid (15 g.) was dissolved in glacial acetic acid and the solution kept cool by surrounding ice, whilst chlorine (15 g.) was passed into it. The resulting solution was kept overnight at room temperature. Next day a solid (11 g.) had separated which was filtered off, washed with acetic acid and then with water and dried. It crystallised from alcohol : white prisms, m.p. 166–167°. A further quantity (4 g.) of the substance was recovered by diluting the mother-liquor with water. It gave no colouration with alcoholic ferric chloride (m.p. 166.5–167° Martini¹⁴).

Sodium-3 : 5-dichloro-2-methoxybenzoate—crystallised from water : white plates. (Found : Na, 8.0; H_2O , 13.2; $C_8H_5O_3Cl_2Na, 2H_2O$ requires Na, 8.2; H_2O , 12.90 per cent.)

Barium-3 : 5-dichloro-2-methoxybenzoate—crystallised from water : needles. (Found : Ba, 20.3; H_2O , 13.2; $C_{16}H_{10}O_6Cl_4Ba, 5H_2O$ requires Ba, 20.5; H_2O , 13.5 per cent.)

Silver-3 : 5-dichloro-2-methoxybenzoate.—Very difficultly soluble in water : turns grey. (Found : Ag, 33.1; $C_8H_5O_3Cl_2Ag$ requires Ag, 32.9 per cent.)

3 : 5-Dichloro-2-methoxybenzamide.—A mixture of 3 : 5-dichloro-2-methoxybenzoic acid (20 g.) and phosphorous pentachloride (25 g.) was treated as above, when a solid (19.5 g.) was obtained. It crystallised from alcohol : white prisms; m.p. 152–153°; it gave no colouration with alcoholic ferric chloride. (Found : N, 6.0; $C_8H_7O_2NCl_2$ requires N, 6.4 per cent.) It is soluble in alcohol, acetone, benzene and acetic acid.

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¹⁴ *Ibid.*, 1899, 29, II, 62.