829. *Sporidesmins. Part IV.*[1] *The Synthesis of 2-Amino-5-chloro-3,4-dimethoxybenzoic Acid and Related Compounds.*

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2-Amino-5-chloro-3,4-dimethoxybenzoic acid, a possible biogenetic precursor of the sporidesmins, its *N*-methyl derivative, and three other chlorodimethoxyanilines or their related isatins have been synthesised.

The preparation from sporidesmin and the synthesis of 5-chloro-6,7-dimethoxy-1-methylisatin and 5-chloro-3,4-dimethoxy-2-methylaminobenzoic acid have been described.[2] In view of the possible biogenetic significance of 5-chloro-3,4-dimethoxyanthranilic acid,[3]

[1] Part III, Hodges, Ronaldson, Shannon, Taylor, and White, *J.*, 1964, 26.
[2] Hodges, Ronaldson, Taylor, and White, *J.*, 1963, 5332.
[3] Done, Mortimer, Taylor, and Russell, *J. Gen. Microbiol.*, 1961, **26**, 207.

its synthesis in quantity was required. It was also desirable that the synthesis should be adaptable to the preparation of anthranilic acids isotopically labelled in known positions.

4-Acetoxy-5-chloro-3-methoxy-2-nitrobenzaldehyde can be obtained by nitration of acetyl-5-chlorovanillin,[4] and we considered that further elaboration should yield the required anthranilic acid. However, we were unable, under a variety of conditions, to obtain a satisfactory yield of acetyl-5-chlorovanillin since, when 5-chlorovanillin was acetylated as described in the literature, only the triacetyl derivative was isolated. To overcome this difficulty, 5-chlorovanillin was converted into the corresponding nitrile [5] which, on nitration, gave a mononitro-derivative in high yield. This nitro-derivative resisted hydrolysis and was not investigated further, though it was probably 4-acetoxy-5-chloro-3-methoxy-2-nitrobenzonitrile. No pure product was obtained from nitration of 4-acetoxy-5-chloro-3-methoxybenzoic acid; but the corresponding methyl ester gave a mixture from which two products were isolated. The major component was shown to be methyl 4-acetoxy-5-chloro-3-methoxy-2-nitrobenzoate, by hydrolysing it to the phenolic acid, decarboxylating and methylating the resulting phenol, and reducing to give 2,3-dimethoxyaniline. The minor isomeric component must therefore be methyl 4-acetoxy-3-chloro-5-methoxy-2-nitrobenzoate. Methyl 4-acetoxy-5-chloro-3-methoxy-2-nitrobenzoate was then transformed unambiguously into the required anthranilic acid. Isotopic or radioactive chlorine, carbon, hydrogen, or nitrogen can be introduced at the appropriate synthetic step and the synthesis has the additional merit that a radioactive 4-methoxy-group, after incorporation into sporidesmin, can be specifically removed.[2] After acetylation and *N*-methylation, 5-chloro-3,4-dimethoxyanthranilic acid gave the chlorodimethoxymethylacetanilide which was obtained as a sporidesmin degradation product.[2]

Before the orientation of the aromatic substituents in sporidesmin was known, it was thought that it might be similar to that in griseofulvin. Hence 2-chloro-3,5-dihydroxytoluene was methylated, oxidised to 2-chloro-3,5-dimethoxybenzoic acid, and converted into the corresponding aniline by a Schmidt reaction. The toluene-*p*-sulphonate of the aniline was methylated and the product shown to differ from the toluene-*p*-sulphonate of the chlorodimethoxymethylaniline isolated from sporidesmin. The alternative orientation, similar to that present in griseofulvin, was also prepared by conversion, in high overall yield, of 1,3-dimethoxybenzene into 5-chloro-2,4-dimethoxyhydroxyiminoacetanilide. The latter compound resisted cyclisation under the usual conditions and gave only a low yield of 4-chloro-5,7-dimethoxyisatin, together with small quantities of an indigo-like material which was not characterised.

7-Chloro-4,5-dimethoxyisatin was prepared by the Sandmeyer hydroxyiminoacetanilide synthesis because of the similarity of the ultraviolet spectrum of sporidesmin and 2,3-dimethoxybenzaldehyde.[6]

Experimental

4-Acetoxy-5-chloro-3-methoxybenzoic Acid.—Treatment of vanillin (450 g.) with t-butyl hypochlorite gave 5-chlorovanillin [7] (452 g.) which was converted *via* its oxime into 4-acetoxy-5-chloro-3-methoxybenzonitrile (408 g.). Alkaline hydrolysis gave 5-chloro-4-hydroxy-3-methoxybenzoic acid (390 g.),[5] which, on acetylation using acetic anhydride in pyridine, yielded *4-acetoxy-5-chloro-3-methoxybenzoic acid*, needles, m. p. 155—157° (from aqueous methanol) (Found: C, 49·15; H, 3·75. $C_{10}H_9ClO_5$ requires C, 49·1; H, 3·7%).

Nitration of 4-Acetoxy-5-chloro-3-methoxybenzonitrile.—The nitrile (420 mg.) was added to stirred nitric acid (*d* 1·42; 5 ml.) at −5°, set aside at 20° for 20 min., and poured on to ice

[4] Raiford and Lichty, *J. Amer. Chem. Soc.*, 1930, **52**, 4576.
[5] Raiford and Potter, *J. Amer. Chem. Soc.*, 1933, **55**, 1682.
[6] Ronaldson, Taylor, White, and Abraham, *J.*, 1963, 3172.
[7] Ginsberg, *J. Amer. Chem. Soc.*, 1951, **73**, 2723.

The product crystallised from aqueous methanol as hexagonal plates (430 mg.) of *4-acetoxy-5-chloro-3-methoxy-2(6)-nitrobenzonitrile*, m. p. 81—82° (Found: C, 44·05; H, 2·7; Cl, 13·1; N, 10·75. $C_{10}H_7ClN_2O_5$ requires C, 44·25; H, 2·6; Cl, 13·1; N, 10·35%).

Methyl 5-Chloro-4-hydroxy-3-methoxybenzoate.—5-Chloro-4-hydroxy-3-methoxybenzoic acid (330 g.), sulphuric acid (*d* 1·84, 20 ml.) and methanol (2 l.) were heated under reflux for 20 hr. Methanol (1 l.) was distilled off, the residue added to ice–water (3 l.), the precipitate collected, dissolved in sodium hydrogen carbonate solution (5%), and the solution filtered and acidified. The precipitate (209 g.) gave the *ester*, plates, m. p. 137—138° (from methanol) (Found: C, 49·65; H, 4·1; Cl, 17·35. $C_9H_9ClO_4$ requires C, 49·9; H, 4·2; Cl, 16·35%).

Methyl 4-Acetoxy-5-chloro-3-methoxybenzoate.—The above ester (209 g.) acetic anhydride (600 ml.), and sodium acetate (20 g.) were heated under reflux for 1 hr. The mixture was stirred with ice–water (3 l.) and the product collected (250 g.), m. p. 76°. Recrystallisation from light petroleum gave prisms of the *acetate*, m. p. 81—82° (Found: C, 50·8; H, 4·55; O, 30·9. $C_{11}H_{11}ClO_5$ requires C, 51·05; H, 4·3; O, 30·95%).

Methyl 4-Acetoxy-5-chloro-3-methoxy-2-nitrobenzoate.—Nitric acid (*d* 1·42; 1·5 l.) was stirred at −15° and the above acetate (250 g.) added at such a rate that the temperature did not exceed −5°. Stiring was continued for 1 hr., the mixture was poured on to ice (3 kg.), and the yellow precipitate was recrystallised from methanol giving prisms (220 g.) of the *nitro-derivative*, m. p, 89—90° (Found: C, 43·2; H, 3·2; Cl, 12·1; N, 4·75. $C_{11}H_{10}ClNO_7$ requires C, 43·6; H, 3·25; Cl, 11·7; N, 4·6%). Recrystallisation of the material in the mother-liquors from the above reaction from light petroleum–carbon tetrachloride gave *methyl 4-acetoxy-3-chloro-5-methoxy-2-nitrobenzoate* as prisms (1·24 g.), m. p. 140—141° (Found: C, 43·75; H, 3·75; O, 36·95%).

5-Chloro-4-hydroxy-3-methoxy-2-nitrobenzoic Acid.—Methyl 4-acetoxy-5-chloro-3-methoxy-2-nitrobenzoate (1·54 g.), methanol (10 ml.), and 4N-sodium hydroxide (8 ml.) were heated under reflux for 2 hr. The *acid* crystallised from acetone–benzene as prisms (1·11 g.), m. p. 197—199° (Found: C, 39·2; H, 2·65; O, 38·8. $C_8H_6ClNO_6$ requires C, 38·8; H, 2·45; O, 38·75%).

6-Chloro-2-methoxy-3-nitrophenol.—The above acid (720 mg.) was heated at 200°/10 mm. until distillation ceased. The most volatile condensate crystallised from light petroleum as needles (85 mg.) of the *phenol*, m. p. 92—94° (Found: C, 41·65; H, 3·0; O, 31·85. $C_7H_6ClNO_4$ requires C, 41·3; H, 2·95; O, 31·45%).

2,3-Dimethoxyaniline Hydrochloride.—The above phenol (254 mg.), potassium t-butoxide (200 mg.), dimethyl sulphate (300 mg.), and toluene (10 ml.) were heated together under reflux for 1 hr. The products were adsorbed in light petroleum on alumina and eluted with light petroleum–benzene (9 : 1) as an oil (143 mg.) which had no absorption in the region 3100—3600 $cm.^{-1}$. Hydrogenation of this oil in methanol, using 5% palladised charcoal catalyst, gave 2,3-dimethoxyaniline hydrochloride (81 mg.), identical with an authentic sample.[8]

Methyl 5-Chloro-4-hydroxy-3-methoxy-2-nitrobenzoate.—Methyl 4-acetoxy-5-chloro-3-methoxy-2-nitrobenzoate (210 g.), methanol (1 l.), and 4N-hydrochloric acid (1 l.) were heated under reflux for 3 hr., then left at room temperature for 16 hr. The product (163 g., m. p. 128°, was recrystallised from methanol as plates of the *phenol*, m. p. 132—134° (Found: C, 41·1; H, 3·45; O, 37·2. $C_9H_8ClNO_6$ requires C, 41·3; H, 3·1; O, 36·7%).

Methyl 5-Chloro-3,4-dimethoxy-2-nitrobenzoate.—The above phenol (87 g.) in toluene (500 ml.) was treated with triethylamine (100 g.) when the phenol dissolved as its yellow triethylammonium salt. Dimethyl sulphate (131 g.) was added and the solution heated under reflux until it was colourless. The addition of triethylamine (10 g.) and dimethyl sulphate (10 g.) was repeated until the solution remained colourless on addition of the triethylamine. The *methyl 5-chloro-3,4-dimethoxy-2-nitrobenzoate* (100 g.) was recrystallised from hexane as needles, m. p. 64° (Found: C, 43·9; H, 4·0; N, 4·7. $C_{10}H_{10}ClNO_6$ requires C, 43·6; H, 3·6; N, 5·1%). Alkaline hydrolysis of this ester gave *5-chloro-3,4-dimethoxy-2-nitrobenzoic acid* as needles, m. p. 143—144° (from light petroleum–carbon tetrachloride) (Found: C, 41·75; H, 3·2; O, 36·7. $C_9H_8ClNO_6$ requires C, 41·3; H, 3·1; O, 36·7%).

Methyl 2-Amino-5-chloro-3,4-dimethoxybenzoate.—Methyl 5-chloro-3,4-dimethoxy-2-nitrobenzoate (11 g.) in ethanol (300 ml.) at 60° was treated with 2N-hydrochloric acid (200 ml.), heated to boiling, and the stirred mixture treated with a solution of stannous chloride dihydrate (30 g.) in concentrated hydrochloric acid (250 ml.). The mixture became yellow, then red, and finally colourless as a precipitate separated. After boiling for a further 5 min. the mixture

[8] Gulland, Robinson, Scott, and Thornley, *J.*, 1929, 2924.

was poured on to ice and sodium hydroxide solution (20%), and extracted with ether. The extract was evaporated and the residue (7·4 g.), m. p. 30°, recrystallised from light petroleum as prisms of the *amine*, m. p. 37—39° (Found: C, 49·1; H, 5·05; O, 26·1. $C_{10}H_{12}ClNO_4$ requires C, 48·9; H, 4·95; O, 26·05%).

2-Amino-5-chloro-3,4-dimethoxybenzoic Acid.—A suspension of the above ester (10 g.) in sodium hydroxide (10%; 100 ml.) was heated under reflux until a clear solution was obtained (1·5 hr.). Acidification with acetic acid gave the *anthranilic acid* (7·5 g.), needles, m. p. 142—143° (from light petroleum–carbon tetrachloride) (Found: C, 47·1; H, 4·7; O, 27·55. $C_9H_{10}ClNO_4$ requires C, 46·75; H, 4·65; O, 27·65%).

Acetylation of Methyl 2-Amino-5-chloro-3,4-dimethoxybenzoate.—The amine (730 mg.), acetic anhydride (3 ml.), and sodium acetate (200 mg.) were heated under reflux for 1 hr. Water was added and the mixture heated at 90° for 30 min. Crystallisation of the product from light petroleum–chloroform gave *methyl 5-chloro-2-diacetylamino-3,4-dimethoxybenzoate* as prisms (670 mg.), m. p. 110—112° (Found: C, 50·4; H, 4·9; O, 29·45. $C_{14}H_{16}ClNO_6$ requires C, 50·0; H, 4·9; O, 29·1%). On heating with aqueous methanolic hydrochloric acid (30%; 4N), the diacetyl derivative gave *methyl 2-acetamido-5-chloro-3,4-dimethoxybenzoate*, needles, m. p. 100—101° (from light petroleum) (Found: C, 50·15; H, 5·1; O, 28·2. $C_{12}H_{14}ClNO_5$ requires C, 50·1; H, 4·9; O, 27·8%).

4-Chloro-2,3-dimethoxy-N-methylacetanilide.—2-Amino-5-chloro-3,4-dimethoxybenzoic acid (580 mg.) was dissolved in hydrazine hydrate and the solution evaporated to dryness. The crude hydrazine salt decomposed smoothly at 140—150°/1 mm., giving a basic liquid (330 mg.). This base was acetylated using acetic anhydride in pyridine and the resulting acetanilide was treated in benzene with sodium hydride (200 mg.). After heating under reflux for 20 min. methyl iodide (300 mg.) was added, the heating continued for 2 hr., and the product then adsorbed from benzene on silica gel. Elution with benzene–ether (4 : 1) gave the unmethylated acetanilide (170 mg.) and further elution with benzene–ether (2 : 3) gave *4-chloro-2,3-dimethoxy-N-methylacetanilide*, needles (22 mg.), m. p. 82—83·5° (from water), undepressed on admixture with a sample from sporidesmin [2] (Found: C, 54·1; H, 5·85; O, 20·15. $C_{11}H_{14}ClNO_3$ requires C, 54·2; H, 5·8; O, 19·7%).

2-Chloro-3,5-dimethoxytoluene.—Methylation of 2-chloro-3,5-dihydroxytoluene [9] (7·1 g.) with dimethyl sulphate in aqueous sodium hydroxide gave the *dimethyl ether* as prisms (5·8 g.), m. p. 40—41° (from light petroleum) (Found: C, 58·25; H, 6·1; O, 16·7. $C_9H_{11}ClO_2$ requires C, 57·9; H, 5·95; O, 17·15%).

2-Chloro-3,5-dimethoxybenzoic Acid.—2-Chloro-3,5-dimethoxytoluene (4·6 g.) was heated under reflux in water while potassium permanganate (15 g.) was added in portions over 12 hr. *2-Chloro-3,5-dimethoxybenzoic acid* crystallised from acetone–chloroform as needles (740 mg.), m. p. 184—185° (Found: C, 49·75; H, 4·35; O, 30·05. $C_9H_9ClO_4$ requires C, 49·9; H, 4·2; O, 29·55%).

2-Chloro-3,5-dimethoxy-N-methyl-N-toluene-p-sulphonylaniline.—Sulphuric acid (*d* 1·84; 1·5 ml.) was added dropwise to a stirred solution of 2-chloro-3,5-dimethoxybenzoic acid (350 mg.) in chloroform containing hydrogen azide (0·16N; 25 ml.) at 20°. The mixture was stirred at 45° until no more nitrogen was evolved. Water (20 ml.) was added, the aqueous phase separated, and the chloroform washed with water (2 × 10 ml.). The combined aqueous phases were washed with chloroform, basified with ammonium hydroxide, extracted with ether, the extract dried and saturated with hydrogen chloride. *2-Chloro-3,5-dimethoxyaniline hydrochloride* separated from butanol as colourless needles (145 mg.), m. p. 229—230° (Found: Cl, 32·4; N, 6·3. $C_8H_{11}Cl_2NO_2$ requires Cl, 31·7; N, 6·25%). The base was converted into its toluene-p-sulphonyl derivative, which was methylated aqueous sodium hydroxide by shaking with dimethyl sulphate. *2-Chloro-3,5-dimethoxy-N-methyl-N-toluene-p-sulphonylaniline* separated from light petroleum or methanol as prisms (7 mg.), m. p. 125—140° (decomp.) (Found: C, 54·0; H, 4·8; O, 17·8. $C_{16}H_{18}ClNO_4S$ requires C, 54·0; H, 5·1; O, 18·0%).

1,3-Dimethoxy-4-nitrobenzene.—1,3-Dimethoxybenzene (35 g.) and acetic anhydride (250 g.) were stirred together and treated at 20—30° with cupric nitrate trihydrate (25 g.). The mixture was stirred for 2·5 hr. after the exothermic reaction ceased, then water (1·5 l.) was added and stirring continued for 18 hr. The product separated from cyclohexane as colourless blades (41 g.), m. p. 74°.[10]

[9] Hitosa and Inoue, *J. Pharm. Soc. Japan*, 1954, **74**, 1122.
[10] Hodgson and Handley, *J.*, 1928, 162.

2-Chloro-1,5-dimethoxy-4-nitrobenzene.—t-Butyl hypochlorite (9 g.) was added dropwise to stirred 1,3-dimethoxy-4-nitrobenzene (10 g.) in t-butyl alcohol (150 ml.) at 30—35°. After 10 min. the chloro-derivative (11·8 g.) separated, m. p. 118—120°.[11]

5-Chloro-2,4-dimethoxyaniline.[11] The above chloronitrobenzene (10 g.) in methanol (200 ml.) was hydrogenated using Raney nickel catalyst at 20°/50 atm. 5-Chloro-2,4-dimethoxyaniline hydrochloride (10 g.), m. p. 219—220°, was precipitated from ether with hydrogen chloride. The free *base* crystallised from cyclohexane as needles, m. p. 90° (Found: C, 51·0; H, 5·5; Cl, 19·0; N, 7·3. $C_8H_{10}ClNO_2$ requires C, 51·2; H, 5·3; Cl, 19·0; N, 7·5%).

5-Chloro-2,4-dimethoxyhydroxyiminoacetanilide.—The above hydrochloride (1 g.), chloral hydrate (1 g.), and water (2 ml.) were treated with sodium sulphate decahydrate until the solution was saturated, when the sulphate of the base separated. A solution of hydroxylamine hydrochloride (1·4 g.) in water (2 ml.) was added and the stirred mixture heated to boiling. An oil separated after 2 min. which crystallised on cooling, giving the *acetanilide* as colourless blades (0·65 g.), m. p. 198° [from ethanol–water (1 : 19) or di-2-propyl ether] (Found: C, 46·5; H, 4·75; Cl, 14·2; N, 10·5. $C_{10}H_{11}ClN_2O_4$ requires C, 46·8; H, 4·3; Cl, 13·8; N, 10·9%).

4-Chloro-5,7-dimethoxyisatin.—The above hydroxyimino-compound (0·6 g.) was added to sulphuric acid (*d* 1·84; 6 ml.) at 45—50°. The stirred mixture was heated at 70—80° for 10 min., then poured on to ice (20 g.). The blue mixture was extracted with ethyl acetate (5 × 5 ml.) and the combined extracts were evaporated and adsorbed from benzene on silica gel (35 g.). A blue zone (0·1 g.) was eluted with ether–benzene (1 : 1). The eluate was evaporated, the residue digested with benzene (10 ml.) and the colourless hydroxyimino-acetanilide (85 mg.) collected. Further elution provided a red zone which was rechromatographed and recrystallised from methanol as very dark red prisms (20 mg.) of *4-chloro-5,7-dimethoxyisatin*, m. p. 280—282° (Found: 50·1; H, 4·3. $C_{10}H_8ClNO_4$ requires C, 49·7; H, 3·3%), $\lambda_{max.}$ (EtOH) 203, 255, 304, 499 mμ (log ε 4·56, 3·94, 3·45, 2·52), $\nu_{max.}$ (KBr) 1730, 1620, 970, 885 cm.$^{-1}$.

7-Chloro-4,5-dimethoxyisatin.—2-Chloro-4,5-dimethoxyaniline [12] (prepared by a Schmidt reaction on 2-chloro-4,5-dimethoxybenzoic acid) (120 mg.) and chloral hydrate (110 mg.) were dissolved in warm 2N-sulphuric acid (1 ml.) and the solution saturated with sodium sulphate decahydrate. Hydroxylamine hydrochloride (140 mg.) in water (1 ml.) was added and the stirred mixture boiled 5 min., allowed to cool, and the precipitate collected. The product (60 mg.), m. p. 180—182°, was added to sulphuric acid (*d* 1·84; 2 ml.) at 50°, heated at 80° for 10 min., and the resulting green-blue liquid poured on to ice. The red mixture was extracted with ethyl acetate (4 × 10 ml.), the extract evaporated, and the residue (15 mg.), m. p. 251—256° adsorbed from benzene on silica gel (5 g.). A red band, eluted with benzene–ether (9 : 1), gave *7-chloro-4,5-dimethoxyisatin* as blue-red needles (10 mg.), m. p. 258—259° (from aqueous ethanol) (Found: C, 50·0; H, 3·7%), $\lambda_{max.}$ (EtOH) 208, 256, 329, 481 mμ (log ε 4·35, 4·21, 3·79, 2·56), $\nu_{max.}$ (KBr) 1757, 1720, 1620, 995, 965, 870 cm.$^{-1}$.

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[11] Badische Aniline und Soda Fabrik, G.P., 135,331.
[12] Holmes, Conrady, Guthrie, and McKay, *J. Amer. Chem. Soc.*, 1954, **76**, 2400.