318. 4-*Aminosalicylic Acid and Its Derivatives.*

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The acid obtained by carboxylation of 3-aminophenol is shown to be 4-aminosalicylic acid. A synthesis of the isomeric 4-hydroxyanthranilic acid is described. A number of derivatives of 4-aminosalicylic acid has been prepared for test against pathogenic strains of *M. tuberculosis*.

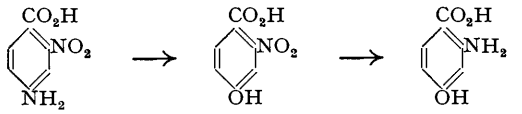
Following upon Bernheim's observation (*Science*, 1940, **92**, 204; *J. Bact.*, 1941, **41**, 387) that derivatives of benzoic and salicylic acids cause considerable increase in the oxygen uptake of tubercle bacilli, Lehmann (*Lancet*, 1946, I, 14, 15) examined a number of derivatives of benzoic acid in order to test their inhibitory effect upon the growth of tubercle bacilli. Of the compounds tested, 4-aminosalicylic acid was the most interesting, *in vitro* tests showing 50—75% inhibition of growth at a dilution of 1 : 650,000. This early promise was supported by limited clinical trial. Subsequent experience has shown that Lehmann's original claim is well founded, and that a *prima facie* case is established for a detailed clinical examination of the acid and its derivatives. This paper is a preliminary report upon the chemistry of 4-aminosalicylic acid, which was undertaken with the object of preparing derivatives of the acid for test against pathogenic strains of the tubercle bacillus; a study of the inhibitory effects of some of the derivatives described in this paper, has been reported (Goodacre, Mitchell, and Seymour, *Quart. J. Pharm. Pharmacol.*, 1948, **21**, 301). In addition, a convenient method for the preparation of the acid is described; a preliminary note upon the development of this method appeared in *Nature* (1948, **161**, 435) and this has been followed by a number of publications from other laboratories describing the same method (Sheehan, *J. Amer. Chem. Soc.*, 1948, **70**, 1665; Erlenmeyer, Prijs, Sorkin, and Suter, *Helv. Chim. Acta*, 1948, **31**, 988; Rosdahl, *Sartryck ur Svensk. Kemisk Tidsk.*, 1948, **60**, 12; Wessely, Benedikt, and Benger, *Monatsh.*, 1948, **79**, 185).

4-Aminosalicylic acid was first described by Seidel and Bittner (*Monatsh.*, 1902, **23**, 423), who prepared it by the reduction of 4-nitrosalicylic acid by means of tin and hydrochloric acid. We find that the reduction can be effected by using ferrous sulphate, Raney alloy and alkali, or hydrogen with a platinum catalyst.

The doses of 4-aminosalicylic acid used for clinical cases are relatively large (15—30 g. per day). The preparation of 4-aminosalicylic acid *via* 4-nitrosalicylic acid does not lend itself to large-scale application. Alternative methods for the preparation of 4-aminosalicylic acid were therefore sought. Of the methods examined, direct carboxylation of 3-aminophenol proved most successful. Treatment of 3-aminophenol with sodium or potassium hydrogen carbonate,

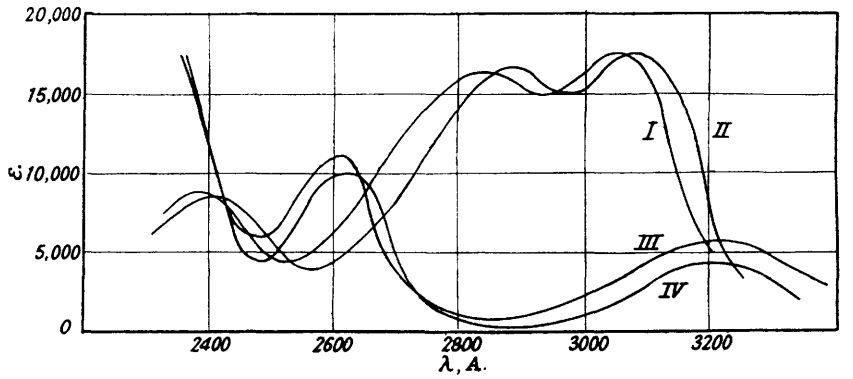
or ammonium carbonate, and carbon dioxide at 100—140° gave an aminohydroxybenzoic acid in yields of 40—50%.

This acid is most probably either 4-aminosalicylic acid or 4-hydroxyanthranilic acid. The latter structure was excluded as follows : An unambiguous synthesis of 4-hydroxyanthranilic acid was completed (cf. Rodionow and Fedorowa, *Bull. Soc. chim.*, 1939, **6**, 478) starting from 2-nitro-4-aminobenzoic acid (Schofield and Simpson, J., 1945, 512; Bogert and Kropff, *J. Amer. Chem. Soc.*, 1909, **31**, 841). The latter was converted into 2-*nitro*-4-*hydroxybenzoic acid*, catalytic reduction of which gave 4-*hydroxyanthranilic acid* characterised as its *hydrochloride* :



Methyl and *ethyl* 4-*hydroxyanthranilate* were prepared by similar reduction of *methyl* and *ethyl* 2-*nitro*-4-*hydroxybenzoate*. 4-Hydroxyanthranilic acid is different from the acid obtained by carboxylation of 3-aminophenol. The latter acid was converted into its *methyl* and *ethyl* esters, and these proved to be different from the corresponding esters of 4-hydroxyanthranilic acid.

Final proof that the acid obtained by carboxylation of 3-aminophenol is 4-aminosalicylic acid was obtained by comparison of its methyl, ethyl, n-*propyl*, n-*butyl*, and iso*butyl* esters with the esters prepared by reduction of the corresponding *esters* of 4-nitrosalicylic acid. Corresponding members of the two series of esters were identical.



(*I*) 4-*Aminosalicylic acid.*
(*II*) *Methyl* 4-*aminosalicylate.*
(*III*) 4-*Hydroxyanthranilic acid.*
(*IV*) *Methyl* 4-*hydroxyanthranilate.*
} *In ethanol.*

4-Aminosalicylic acid exhibits a characteristic intense absorption spectrum in the ultra-violet, with maxima at approximately 2390, 2840, and 3040 A.; methyl 4-aminosalicylate shows a similar absorption spectrum. 4-Hydroxyanthranilic acid and its methyl ester, on the other hand, exhibit maxima at approximately 2600 and 3200 A. (see Fig.). Way, Smith, Howie, Weiss, and Swanson (*J. Pharmacol.*, 1948, **93**, 368) have described the ultra-violet absorption spectrum of 4-aminosalicylic acid " obtained from different commercial houses ". For this material they observed maxima at 2660 and 2980 A. Although the nature of the solvent used for the determination is not stated, the values given by these authors are demonstrably not those of 4-aminosalicylic acid since they also report that an ether extract of the sample of acid employed exhibits an absorption spectrum which is quite different from that of the original sample. The absorption spectrum of the ether extract appears to be similar to that of pure 4-aminosalicylic acid shown in the figure, but a close comparison is not possible since the solvent employed for the measurement of the ultra-violet absorption spectrum of the ether extract is not disclosed, nor is the concentration employed. We find exact correspondence in the absorption spectra of specimens of 4-aminosalicylic acid prepared by carboxylation of 3-aminophenol and by reduction of 4-nitrosalicylic acid.

After the method for the preparation of 4-aminosalicylic acid described above had been developed, we found a reference in Beilstein (4th Edn., **14**, 592) to " 2-amino-4-hydroxybenzoic acid (?), m. p. 148° with decomp. to carbon dioxide and *m*-aminophenol," obtained by treatment

of 3-aminophenol with ammonium carbonate solution. Reference to the patent cited by Beilstein (D.R.-P. 50,835) showed that this structure was not ascribed to the reaction product which was simply described as "*m*-aminophenol carboxylic acid."

Acetylation of 4-aminosalicylic acid using one molecular proportion of acetyl chloride gives 4-acetamidosalicylic acid, which gives a positive reaction with aqueous ferric chloride. After oral administration of sodium 4-aminosalicylate, this compound has been isolated from human urine (cf. Bray, Ryman, and Thorpe, *Nature*, 1948, **162**, 64) and from the urine of rabbits (Venkataraman, Venkataraman, and Lewis, *J. Biol. Chem.*, 1948, **173**, 641). Using an excess of acetic anhydride, acetylation of 4-aminosalicylic acid gives *4-acetamido-2-acetoxybenzoic acid* which does not give a coloration with aqueous ferric chloride. Similarly, acetylation of methyl 4-aminosalicylate gives first *methyl 4-acetamidosalicylate* and then *methyl 4-acetamido-2-acetoxybenzoate*. Treatment of the latter with cold potassium carbonate solution gives the 4-monoacetyl derivative. 4-Aminosalicylic acid has been further characterised by the preparation of its *amide*, *hydrazide*, and 3 : 5-*dibromo*-derivative. These and other derivatives are described in the Experimental section.

Experimental.

4-Aminosalicylic Acid.—(i) A mixture of 3-aminophenol (40 g.), potassium hydrogen carbonate (110 g.), and water (260 c.c.) in an autoclave was treated with carbon dioxide (initial pressure, 5 atm.) and then heated for 6 hours at 100°. After filtration, the cold mixture was adjusted to pH approx. 6·5 by addition of hydrochloric acid, and then continuously extracted with ether. Evaporation of the extract gave 3-aminophenol (20·2 g.). The aqueous solution (charcoal) was acidified with acetic acid. The solid (18·8 g.) was collected and crystallised from aqueous methanol, from which 4-aminosalicylic acid separated as needles, m. p. 142—143° (decomp.) (Found: C, 55·1; H, 4·6; N, 8·9. Calc. for $C_7H_7O_3N$: C, 54·9; H, 4·6; N, 9·15%) The ultra-violet absorption spectrum is shown in the figure. Treatment of the mother-liquors with concentrated hydrochloric acid gave 4-aminosalicylic acid as its hydrochloride (2·5 g.). Sodium hydrogen carbonate or ammonium carbonate can be used instead of potassium hydrogen carbonate. The m. p. of 4-aminosalicylic acid is not a reliable criterion of purity since it varies considerably with the rate of heating, and m. p.s varying between 140° and 150° have been observed for the same specimen of acid under apparently identical conditions (Oberweger, Seymour, and Simmonite, *Quart. J. Pharm. Pharmacol.*, 1948, **21**, 292). The value 220° given by Seidel and Bittner (*loc. cit.*) for the m. p. of 4-aminosalicylic acid is in error; it probably refers to the hydrochloride (m. p. 224—225°, see below). Kondo and his co-workers (*loc. cit.*) give m. p. 145—151° for 4-aminosalicylic acid. The acid gives a violet coloration with aqueous ferric chloride.

(ii) A mixture of 3-aminophenol (20 g.), glycerol (80 c.c.), and potassium hydrogen carbonate (80 g.) was gradually heated to 130°. When frothing had subsided, a stream of carbon dioxide was passed through the mixture for 4 hours. The hot solution was slowly poured into 5% hydrochloric acid (500 c.c.), and the hydrochloride collected, washed with alcohol and ether, and dried (m. p. 217—222°; 16 g.). The hydrochloride (16 g.) was added to a solution of potassium hydrogen carbonate (8·4 g.) in water (100 c.c.), and the mixture extracted repeatedly with ether. The ethereal extract was treated with charcoal, concentrated, and diluted with light petroleum (b. p. 40—60°), whereupon 4-aminosalicylic acid separated as needles, m. p. 138—140°.

(iii) A solution of 4-nitrosalicylic acid (m. p. 235—236° decomp.) (18·3 g.) in a mixture of ammonia (*d* 0·88; 140 c.c.) and water (140 c.c.) was added slowly to a boiling solution of hydrated ferrous sulphate (195 g.) in water (400 c.c.). The solution was kept alkaline by addition of aqueous ammonia during the course of the reaction. When the addition was complete, the mixture was boiled for 10 minutes. The hot solution was filtered, and the filtrate concentrated to approximately half bulk under reduced pressure in an atmosphere of nitrogen. The cold solution was acidified to Congo-red with concentrated hydrochloric acid, and the crystalline hydrochloride was collected and washed with alcohol and acetone. The hydrochloride was treated with excess of sodium hydrogen carbonate solution, and the solution filtered (charcoal) and acidified with acetic acid. 4-Aminosalicylic acid separated as needles, m. p. 142—143° (decomp.) (yield 60—70%) (Found: C, 54·8; H, 4·5; N, 9·2. Calc. for $C_7H_7O_3N$: C, 54·9; H, 4·6; N, 9·15%).

The *hydrochloride* can be obtained by treatment of a solution of the acid in dry acetone or ether with dry hydrogen chloride. It is obtained as scintillating needles, m. p. 224—225° (Found: C, 44·8; H, 4·2; N, 7·6; Cl, 18·4. $C_7H_8O_3NCl$ requires C, 44·3; H, 4·2; N, 7·4; Cl, 18·7%).

(iv) A solution of 4-nitrosalicylic acid (1·8 g.) in dry ethyl acetate (50 c.c.) was shaken with hydrogen in the presence of platinum (from 100 mg. of PtO_2, H_2O) for two hours, hydrogen absorption (740 c.c. at 18° and 750 mm.) then being complete. The mixture was filtered, and the filtrate evaporated to dryness in an atmosphere of carbon dioxide. 4-Aminosalicylic acid (1·5 g., m. p. 140°) was crystallised from aqueous methanol, from which it separated as needles, m. p. 137—138° (Found: N, 9·3. Calc. for $C_7H_7O_3N$: N, 9·15%). Light absorption in alcohol: Maxima at 2390 A., $\varepsilon = 6800$; 2850 A., $\varepsilon = 14{,}800$; 3040 A., $\varepsilon = 16{,}400$.

(v) A solution of 4-nitrosalicylic acid (5 g.) in 10% sodium hydroxide (150 c.c.) was treated at 90° with Raney alloy (15 g.) added during 20 minutes, and the mixture heated for an hour at the same temperature. The hot mixture was filtered, and the cold filtrate poured into concentrated hydrochloric acid (110 c.c.) with stirring and cooling. The hydrochloride was collected and washed with alcohol and then had m. p. 224—225° (decomp.) undepressed when mixed with the specimens described above (yield, 60%) (Found: C, 44·5; H, 4·6; N, 7·3%).

Decomposition of the hydrochloride as described above gave 4-aminosalicylic acid, m. p. 141·5° (decomp.) undepressed when mixed with the previously described specimens.

4-*Aminosalicylamide.*—A solution of 4-nitrosalicylamide (1 g.) in ethanol (100 c.c.) was shaken with hydrogen in the presence of platinum from platinum oxide (50 mg.) for 3 hours at room temperature, gas absorption then being complete. The product was recrystallised (charcoal) from hot water, from which 4-*aminosalicylamide* (0·75 g.) separated as hexagonal plates, m. p. 160—161° (Found: C, 55·2; H, 5·3; N, 18·4. $C_7H_8O_2N_2$ requires C, 55·3; H, 5·3; N, 18·4%).

4-*Aminosalicylhydrazide.*—Methyl 4-aminosalicylate (4·0 g.) was heated on the water-bath with hydrazine hydrate (90%, 3 c.c.) for 30 minutes. More hydrazine hydrate (2 c.c.) was added, and heating continued for 1 hour. The mixture was diluted with water, and the solid (1·8 g.) crystallised from aqueous ethanol to yield 4-*aminosalicylhydrazide* as felted needles, m. p. 197° (decomp.) (Found: C, 50·3; H, 5·5; N, 24·9. $C_7H_9O_2N_3$ requires C, 50·3; H, 5·4; N, 25·1%).

4-*Acetamidosalicylic Acid.*—(*a*) A solution of 4-aminosalicylic acid (1·53 g.) in pyridine (8 c.c.) was heated at 100° for 2 hours with acetyl chloride (0·84 g.). The cold solution was poured on a mixture of ice and hydrochloric acid, and the mixture filtered. The solid (1·5 g., m. p. 220—222°, decomp.) was crystallised from glacial acetic acid, from which 4-acetamidosalicylic acid separated as a microcrystalline powder, m. p. 220—222°. The m. p. varies with the rate of heating; with rapid heating, it is 232° (Found: C, 55·1; H, 5·2; N, 7·1. Calc. for $C_9H_9O_4N$: C, 55·3; H, 4·6; N, 7·2%). With aqueous ferric chloride the acid gives a purple coloration. Light absorption in alcohol: Maxima at 2690 A., $\varepsilon = 19{,}200$; 3040 A., $\varepsilon = 9100$.

(*b*) A 24-hour specimen of urine (*ca.* 750 c.c.), collected during oral administration of sodium 4-aminosalicylate (25 g. per day) to a woman, was adjusted to pH approx. 5·0 by addition of hydrochloric acid and continuously extracted with ether for 48 hours. The extract was washed with 10% hydrochloric acid, dried (Na_2SO_4), and evaporated. The solid residue was dissolved in cold sodium hydrogen carbonate solution, the mixture filtered, and the filtrate acidified with dilute hydrochloric acid. The solid (2 g.) was crystallised from glacial acetic acid, from which 4-acetamidosalicylic acid separated as microprisms, m. p. 224° undepressed when mixed with the specimen described above (Found: C, 55·5; H, 4·8; N, 7·1%). Light absorption in ethanol: Maxima at 2690 A., $\varepsilon = 17{,}000$; 3050 A., $\varepsilon = 7000$.

4-*Acetamido*-2-*acetoxybenzoic Acid.*—4-Aminosalicylic acid (3·06 g.) was heated at 100° with acetic anhydride (6 c.c.) for 1 hour. The mixture was diluted with water, and the solid collected and crystallised from glacial acetic acid, from which 4-*acetamido*-2-*acetoxybenzoic acid* separated as needles, m. p. 189—190·5° (Found: C, 55·4; H, 4·6; N, 6·2. $C_{11}H_{11}O_5N$ requires C, 55·7; H, 4·6; N, 5·9%).

4-*Benzamidosalicylic acid.*—4-Aminosalicylic acid (6·1 g.) in aqueous sodium hydroxide (20%; 20 c.c.) was treated with benzoyl chloride (5·6 g.) added slowly with shaking. After acidification with mineral acid, the solid was collected and crystallised from aqueous ethanol, from which 4-*benzamidosalicylic acid* separated as needles, m. p. 253°. It gives a purple colour with ferric chloride (Found: C, 65·5; H, 4·2; N, 5·4. $C_{14}H_{11}O_4N$ requires C, 65·4; H, 4·3; N, 5·45%).

4-*Succinamidosalicylic Acid.*—A solution of 4-aminosalicylic acid (3 g.) in acetone (60 c.c.) was refluxed with succinic anhydride (2·6 g.) for 1½ hours. The solid was collected and crystallised from aqueous ethanol, from which 4-succinamidosalicylic acid separated as a *monohydrate*, m. p. 230° (decomp.) (Found: C, 48·7; H, 4·5; N, 5·2; equiv., 275. $C_{11}H_{11}O_6N,H_2O$ requires C, 48·7; H, 4·8; N, 5·2%; equiv., 271). It gives a purple coloration with aqueous ferric chloride.

3 : 5-*Dibromo*-4-*aminosalicylic Acid.*—A solution of 4-aminosalicylic acid (4·6 g.) in glacial acetic acid (90 c.c.) was treated at room temperature with a solution of bromine (9·6 g.) in glacial acetic acid (120 c.c.). The solid separating (5·3 g.) was triturated with water and crystallised from 50% acetic acid, from which 3 : 5-*dibromo*-4-*aminosalicylic acid* separated as needles, m. p. 205° (decomp.) (Found: C, 27·0; H, 1·6; N, 4·1; Br, 51·5. $C_7H_5O_3NBr_2$ requires C, 27·0; H, 1·6; N, 4·5; Br, 51·4%).

Methyl 4-*nitrosalicylate*, obtained by 20 hours' heating under a reflux of a solution of 4-nitrosalicylic acid (5·0 g.) with methanol (100 c.c.) either containing concentrated sulphuric acid (5 c.c.) or saturated with dry hydrogen chloride, separates from aqueous methanol as elongated yellow plates and from light petroleum (b. p. 60—80°) as yellow prisms, m. p. 99·5—100° (Found: C, 49·0; H, 3·7; N, 7·5. $C_8H_7O_5N$ requires C, 48·7; H, 3·55; N, 7·1%). Ethyl 4-nitrosalicylate was obtained by the method described by Borsche (*Annalen*, 1912, **390**, 18); it separates from ethanol as needles, m. p. 87°.

The following 4-nitrosalicylic esters were obtained by the same methods. n-*Propyl*, flat yellow needles from aqueous *n*-propanol, m. p. 32—33° (Found: C, 53·5; H, 5·1; N, 6·3. $C_{10}H_{11}O_5N$ requires C, 53·3; H, 4·9; N, 6·2%); iso*propyl*, pale yellow needles, m. p. 72°, from aqueous *iso*propanol (Found: C, 53·3; H, 4·7; N, 6·5%); n-*butyl*, pale yellow needles, m. p. 34°, from methanol (Found: C, 55·4, 55·4; H, 5·7, 5·5; N, 6·0. $C_{11}H_{13}O_5N$ requires C, 55·2; H, 5·4; N, 5·9%); iso*butyl*, pale yellow needles, m. p. 62—63°, from light petroleum (Found: C, 55·1; H, 5·3; N, 5·8%).

2-*Hydroxyethyl* 4-*nitrosalicylate* (obtained by the sulphuric acid method) separates from benzene as pale yellow needles, m. p. 121—122° (Found: C, 47·5; H, 4·0; N, 6·5. $C_9H_9O_6N$ requires C, 47·5; H, 4·0; N, 6·2%).

Methyl 4-*Aminosalicylate.*—(*a*) A solution of 4-aminosalicylic acid [prepared by method (i) above; 1·5 g.] in dry methanol (40 c.c.) and concentrated sulphuric acid (2 c.c.) was heated under reflux for 8 hours. The solution was concentrated to a bulk of 10 c.c. and neutralised by addition of 10% sodium carbonate solution. The solid was collected and crystallised from aqueous methanol, from which *methyl* 4-*aminosalicylate* (0·75 g.) separated as needles, m. p. 120—121° (Found: C, 57·3, 57·3; H, 5·5, 5·4; N, 8·6. $C_8H_9O_3N$ requires C, 57·5; H, 5·4; N, 8·4%). The ultra-violet absorption spectrum is shown in the figure.

(*b*) A solution of 4-aminosalicylic acid in dry ether was treated with a solution of diazomethane (1 mole) in ether at 0° until nitrogen evolution ceased. The solution was washed with aqueous sodium hydrogen carbonate, dried (Na_2SO_4), and evaporated. Recrystallisation of the crystalline residue from light petroleum (b. p. 100—120°) gave the methyl ester as needles or plates, m. p. 119—120° either alone or mixed with the specimen described above (Found: C, 57·7; H, 5·8; N, 8·4%).

(*c*) A solution of methyl 4-nitrosalicylate (7·5 g.) in ethanol (250 c.c.) was shaken with hydrogen and platinum oxide until hydrogen absorption ceased. The filtered solution was evaporated, and the residue crystallised from light petroleum (b. p. 60—80°) to give methyl 4-aminosalicylate (4·5 g.) as needles, m. p. 119—120° undepressed when mixed with the specimens described above (Found: C, 57·3; H, 5·5;

N, 8·4, 8·6%). Light absorption in alcohol: Maxima at 2410 A., ε = 9000; 2890 A ε = 15,600; 3070 A., ε = 18,000.

The following 4-aminosalicylates were prepared by suitable adaptation of methods (*a*) and (*c*) above. The esters obtained by the two methods are identical: *Ethyl*, needles, m. p. 111·5—113°, from light petroleum (b. p. 100—120°) or from aqueous acetone (Found: C, 59·5; H, 5·8; N, 7·5. $C_9H_{11}O_3N$ requires C, 59·7; H, 6·1; N, 7·7%); n-*propyl*, needles, m. p. 102—103°, from light petroleum (b. p. 60—80°) or from aqueous alcohol (Found: C, 61·7; H, 6·7; N, 6·8. $C_{10}H_{13}O_3N$ requires C, 61·5; H, 6·7; N, 7·2%); iso*propyl* [method (*c*) only], needles, m. p. 75—76°, from light petroleum (b. p. 60—80°) (Found: C, 61·8, 61·7; H, 6·8, 6·6; N, 7·3, 7·1%); n-*butyl*, needles, m. p. 92·5—93°, from light petroleum (b. p. 60—80°) or aqueous ethanol (Found: C, 63·2; H, 7·1; N, 6·6. $C_{11}H_{15}O_3N$ requires C, 63·2; H, 7·2; N, 6·7%); iso*butyl*, needles, m. p. 84°, from light petroleum (b. p. 60—80°) (Found: C, 63·3; H, 7·4; N, 6·8%).

n-*Amyl* 4-*Aminosalicylate*.—*n*-Amyl 4-nitrosalicylate was prepared by the method described for its homologues; it was obtained as an oil which was catalytically reduced without further purification. n-*Amyl* 4-*aminosalicylate* was obtained as plates, m. p. 70°, from light petroleum (b. p. 100—120°) (Found: C, 64·4; H, 7·5; N, 6·4. $C_{12}H_{17}O_3N$ requires C, 64·5; H, 7·6; N, 6·3%). 2-*Hydroxyethyl* 4-*aminosalicylate*.—This [method (*c*) only] formed plates, m. p. 130—131°, from water (Found: C, 54·7; H, 5·5; N, 7·2. $C_9H_{11}O_4N$ requires C, 54·9; H, 5·6; N, 7·1%).

Methyl 4-*Acetamidosalicylate*.—A solution of methyl 4-aminosalicylate (1·67 g.) in chloroform (20 c.c.) and acetic anhydride (1 c.c.) was heated under reflux for 2 hours. The mixture was evaporated under reduced pressure, and the residue crystallised from aqueous ethanol to yield *methyl* 4-*acetamidosalicylate* as needles, m. p. 150°, which gave a purple coloration with aqueous ferric chloride (Found: C, 57·7; H, 5·2; N, 6·9. $C_{10}H_{11}O_4N$ requires C, 57·4; H, 5·3; N, 6·7%). The ester was also obtained by treatment of 4-acetamidosalicylic acid in ethereal solution with diazomethane.

Methyl 4-*Acetamido*-2-*acetoxybenzoate*.—A solution of methyl 4-aminosalicylate (3·34 g.) in acetic anhydride (3·75 c.c.) and acetic acid (2 c.c.) was heated on the water-bath for 1 hour. The solution was poured into water, and the solid collected and crystallised from aqueous ethanol, from which *methyl* 4-*acetamido*-2-*acetoxybenzoate* (3·2 g.) separated as needles, m. p. 145—147°; it does not give a coloration with aqueous ferric chloride solution (Found: C, 57·8; H, 5·7; N, 5·5. $C_{12}H_{13}O_5N$ requires C, 57·4; H, 5·2; N, 5·6%).

A solution of methyl 4-acetamido-2-acetoxybenzoate (0·5 g.) in methanol (20 c.c.) was treated with one of potassium carbonate (0·5 g.) in water (2 c.c.) and the mixture kept at room temperature for 60 hours. The mixture was evaporated (reduced pressure) and the residue extracted with ether. Evaporation of the ethereal solution and crystallisation of the residue from aqueous methanol gave methyl 4-acetamidosalicylate as needles, m. p. 150°, undepressed when mixed with the specimen above.

Methyl 4-*benzamidosalicylate*, prepared by treatment of 4-benzamidosalicylic acid with diazomethane in ether–methanol, separates from benzene as needles, m. p. 168° (Found: C, 65·9; H, 4·9; N, 5·3. $C_{15}H_{13}O_4N$ requires C, 66·4; H, 4·8; N, 5·2%).

Methyl 4-*benzamido*-2-*benzoyloxybenzoate* was obtained by benzoylation of methyl 4-aminosalicylate or of methyl 4-benzamidosalicylate by means of benzoyl chloride and sodium hydroxide solution. It separates from aqueous ethanol as needles, m. p. 158—159° (Found: C, 69·8; H, 4·7; N, 3·4. $C_{22}H_{17}O_5N$ requires C, 70·4; H, 4·5; N, 3·7%).

Methyl 4-*Acetylsulphanilamidosalicylate*.—A solution of methyl 4-aminosalicylate (3·36 g) in dry pyridine (25 c.c) was treated with acetylsulphanilyl chloride (5·12 g). The solution was heated on a steam-bath for 90 minutes and poured on crushed ice (100 g.). The solid was collected and crystallised from aqueous alcohol, from which *methyl* 4-*acetylsulphanilamidosalicylate* (3·2 g.) separated as plates, m. p. 238° (Found: C, 52·3; H, 4·5; N, 7·5. $C_{16}H_{16}O_6N_2S$ requires C, 52·7; H, 4·4; N, 7·7%).

Methyl 4-*Sulphanilamidosalicylate*.—A solution of the acetyl compound (1·6 g.) in 75% ethanol (10 c.c.) was heated under reflux with 10% hydrochloric acid (5 c.c.) for 2 hours. The solution was evaporated under reduced pressure, and the residue crystallised from aqueous ethanol to yield *methyl* 4-*sulphanilamidosalicylate* (1·2 g.) as plates, m. p. 210° (Found: C, 52·5; H, 4·4; N, 9·1. $C_{14}H_{14}O_5N_2S$ requires C, 52·2; H, 4·3; N, 8·7%), insoluble in sodium hydrogen carbonate solution.

4-*Sulphanilamidosalicylic Acid*.—A solution of the methyl ester (1·2 g.) in excess of alcoholic potassium hydroxide solution (10%) was heated under reflux for 2 hours. The mixture was adjusted to pH 4·0 by addition of hydrochloric acid. The solid was collected and crystallised from aqueous ethanol, from which 4-*sulphanilamidosalicylic acid* (0·7 g.) separates as prisms, m. p. 220° (decomp.) (Found: C, 51·1; H, 4·2; N, 8·8. $C_{13}H_{12}O_5N_2S$ requires C, 50·65; H, 3·9; N, 9·1%). It is soluble in cold sodium hydrogen carbonate solution with effervescence. The same acid was also obtained by treatment of 4-aminosalicylic acid with acetylsulphanilyl chloride, followed by hydrolysis of the product (Found: C, 50·8; H, 4·2; N, 8·9; S, 10·6%).

2-*Nitro*-4-*hydroxybenzoic Acid*.—A warm solution of 2-nitro-4-aminobenzoic acid (18·2 g.) in water (30 c.c.) and concentrated sulphuric acid (22 c.c.) was rapidly chilled to 0°. After the addition of crushed ice (50 g.), a solution of sodium nitrite (7·5 g.) in water (16 c.c.) was added during 1 hour at 0—5°. The mixture was stirred for a further hour at this temperature, treated with urea (10 g.), and filtered. The solution was slowly added (1 hour) to a boiling solution of sulphuric acid (70 c.c., conc.) in water (50 c.c.), and the mixture heated under reflux for 3 hours. On cooling, 2-*nitro*-4-*hydroxybenzoic acid* (7·5 g.) separated as light yellow plates, m. p. 230° (decomp.) (Found: C, 46·1; H, 3·0; N, 7·4. $C_7H_5O_5N$ requires C, 45·9; H, 2·7; N, 7·65%).

Methyl 2-*nitro*-4-*hydroxybenzoate* was obtained by heating a solution of the acid (3·7 g.) with methanol (80 c.c.) containing concentrated sulphuric acid (2 c.c.) under reflux for 18 hours. It separated from water as needles, m. p. 168° (Found: C, 49·0; H, 3·5; N, 6·9. $C_8H_7O_5N$ requires C, 48·7; H, 3·55; N, 7·1%).

Ethyl 2-*nitro*-4-*hydroxybenzoate*, prepared in a similar manner, separates from water as needles, m. p. 157° (Found: C, 51·3; H, 4·2; N, 6·5. $C_9H_9O_5N$ requires C, 51·2; H, 4·3; N, 6·6%).

4-*Hydroxyanthranilic Acid*.—A solution of 2-nitro-4-hydroxybenzoic acid (4·6 g.) in ethyl alcohol

(100 c.c.) was shaken with hydrogen and platinum (from platinum oxide) at room temperature and pressure, until hydrogen absorption was complete. The filtered solution was evaporated, and the solid recrystallised from water to give 4-*hydroxyanthranilic acid* (3 g.) as prismatic needles, m. p. 158° (decomp.). The m. p. varied with the rate of heating (Found : C, 55·2; H, 4·8; N, 9·4. $C_7H_7O_3N$ requires C, 54·9; H, 4·5; N, 9·15%). The *hydrochloride* crystallised from concentrated hydrochloric acid in needles (Found : C, 44·1; H, 4·3; N, 7·4. $C_7H_8O_3NCl$ requires C, 44·3; H, 4·2; N, 7·4%). It decomposes at 155° and finally melts above 220°, a behaviour which may indicate preliminary decomposition to 3-aminophenol hydrochloride (m. p. 237°).

Methyl 4-*hydroxyanthranilate*, obtained by similar catalytic reduction of methyl 2-nitro-4-hydroxybenzoate, separates as needles from water, m. p. 134·5—135° (Found : C, 57·9; H, 5·5; N, 8·25. $C_8H_9O_3N$ requires C, 57·5; H, 5·4; N, 8·4%). A mixture with methyl 4-aminosalicylate (m. p. 119—120°) melted at 100—104°.

Ethyl 4-*hydroxyanthranilate* separates as needles from water, m. p. 119—120°. A mixture with ethyl 4-aminosalicylate (m. p. 110—112°) has m. p. 95—100° (Found : C, 59·7; H, 6·1; N, 7·6. $C_9H_{11}O_3N$ requires C, 59·7; H, 6·1; N, 7·7%).

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