740. 4-*Aminosalicylic Acid and its Derivatives. Part III.** *Some Reactions of 2-Acetoxy-4-nitrobenzoyl Chloride and the Synthesis of some Aryl Esters of 4-Aminosalicylic Acid.*

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Further derivatives of 4-aminosalicylic acid have been made for examination as antituberculous compounds. A series of substituted amides and aryl esters of 4-aminosalicylic acid has been obtained from 4-nitrosalicylic acid.

Use of 4-aminosalicylic acid in the treatment of tuberculosis led to the preparation of many of its derivatives (*e.g.*, Doub, Schaefer, Bambas, and Walker, *J. Amer. Chem. Soc.*, 1951, **73**, 903; Drain, Martin, Mitchell, Seymour, and Spring, *J.*, 1949, 1498; Hirt and Hurni, *Helv. Chim. Acta*, 1949, **32**, 378; Rosdahl, *Svensk Kem. Tidskr.*, 1948, **60**, 12). This paper records a further series of derivatives, the pharmacological and tuberculostatic properties of which have been or will be published elsewhere (cf. Drain, Goodacre, and Seymour, *J. Pharm. Pharmacol*, 1949, **1**, 784).

Treatment of 2-acetoxy-4-nitrobenzoic acid with thionyl chloride in benzene gave the chloride which by reaction with the amine, followed by deacetylation and reduction, afforded a series of amides. The chloride was converted into 4-amino-2-hydroxyphenylacetic acid by Wolff rearrangement of the intermediate diazo-ketone.

The report by Friere (*Compt. rend.*, 1950, **231**, 728) that phenyl 4-aminosalicylate is a more active tuberculostatic agent than either the acid or chloramphenicol prompted us to synthesise a series of aryl esters. These were obtained by reaction of 4-nitrosalicylic acid

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with the phenol in the presence of phosphoryl chloride, and subsequent reduction by hydrogen in the presence of Adams's catalyst or by zinc and ammonium chloride.

4-Amino-3 : 5-di-iodosalicylic acid was obtained from the amino-acid by iodine and hydrogen peroxide or by treatment of methyl 4-aminosalicylate with iodine chloride followed by hydrolysis.

4-Benzylsulphonamidosalicylic acid was prepared from methyl 4-aminosalicylate by standard methods.

Experimental

2-*Acetoxy*-4-*nitrobenzoyl Chloride*.—2-Acetoxy-4-nitrobenzoic acid (4·5 g.). thionyl chloride (9 ml.), and benzene (30 ml.) were refluxed for 30 minutes and concentrated under reduced pressure to give a pale yellow syrup which crystallised. The chloride separated from benzene–light petroleum (b. p. 40—60°) in pale yellow needles, m. p. 56°. Doub, Schaefer, Bambas, and Walker (*J. Amer. Chem. Soc.*, 1951, **73**, 903) give m. p. 57°.

2-*Acetoxy*-4-*nitrobenzo*-p-*toluidide*.—2-Acetoxy-4-nitrobenzoyl chloride (from 1·5 g. of acid) was heated with *p*-toluidine (1·5 g.) in ether (50 ml.) under reflux for 30 minutes. The solution was extracted with dilute hydrochloric acid, and the ethereal layer dried ($MgSO_4$) and evaporated. 2-*Acetoxy*-4-*nitrobenzo*-p-*toluidide* separated from ethanol in pale yellow needles, m. p. 131° (Found : C, 60·4; H, 4·3; N, 8·9. $C_{16}H_{14}O_5N_2$ requires C, 61·1; H, 4·45; N, 8·9%).

2-*Hydroxy*-4-*nitrobenzo*-p-*toluidide*.—2-Acetoxy-4-nitrobenzo-*p*-toluidide (0·7 g.) was heated under reflux for 30 minutes with methanol (50 ml.) containing 20% aqueous potassium hydroxide (10 ml.) and the mixture poured into ice-water (200 ml.) and 20% hydrochloric acid (15 ml.). The precipitated 2-*hydroxy*-4-*nitrobenzo*-p-*toluidide* (0·5 g.) separated from dioxan in pale yellow needles, m. p. 251° (Found : C, 61·6; H, 4·4; N, 10·2. $C_{14}H_{12}O_4N_2$ requires C, 61·75; H, 4·4; N, 10·3%).

Similarly, 2-*hydroxy*-4-*nitrobenzanilide* was obtained (without purification of the intermediate acetoxy-compound) as pale yellow needles (from aqueous dioxan), m. p. 238° (Found : C, 60·8; H, 3·8; N, 10·8. Calc. for $C_{13}H_{10}O_4N_2$: C, 60·45; H, 3·9; N, 10·85%). Doub *et al.* (*loc. cit.*) report m. p. 234—235°.

4-*Amino*-2-*hydroxybenzo*-p-*toluidide*.—The nitro-toluidide (1·45 g.) in 50% aqueous methanol (100 ml.) containing 5N-sodium hydroxide (1·1 ml.) was hydrogenated over Adams's catalyst at room temperature and pressure until absorption ceased. The catalyst was removed, the filtrate neutralised with acetic acid, and the product (0·9 g.) collected.

4-*Amino*-2-*hydroxybenzo*-p-*toluidide* separated from aqueous methanol as pale cream-coloured needles, m. p. 172° (Found : C, 69·3; H, 5·9; N, 11·6. $C_{14}H_{14}O_2N_2$ requires C, 69·4; H, 5·8; N, 11·6%).

Similarly, 4-*amino*-2-*hydroxybenzanilide* was obtained as colourless needles (from aqueous methanol), m. p. 151° (Found : C, 68·4; H, 5·3; N, 12·4. Calc. for $C_{13}H_{12}O_2N_2$: C, 68·4; H, 5·3; N, 12·3%). Doub *et al.* (*loc. cit.*) report m. p. 144—145°.

2-*Hydroxy*-4-*nitrohippuric Acid*.—2-Acetoxy-4-nitrobenzoyl chloride (from 4·5 g. of acid) in dry benzene (30 ml.) was added dropwise during 30 minutes to a vigorously stirred solution of glycine (1·5 g.) in 20% aqueous sodium hydroxide (4 ml.) and 10% aqueous sodium hydrogen carbonate (80 ml.). After 2 hours the mixture was diluted with water (100 ml.) and extracted with ether (50 ml.). The aqueous layer was acidified with hydrochloric acid, to yield a pale yellow solid (2·78 g.) which was extracted for 15 minutes with boiling ether (25 ml.) to remove 4-nitrosalicylic acid. The insoluble residue (1·28 g.) separated from dilute ethanol as a pale yellow microcrystalline powder, m. p. 203—205° (Found : C, 45·1; H, 3·35; N, 11·8. Calc. for $C_9H_8O_6N_2$: C, 45·0; H, 3·3; N, 11·7%). Doub *et al.* (*loc. cit.*) report m. p. 211°.

Similarly prepared was 2-*hydroxy*-4-*nitrobenzoyl*-DL-*alanine* which separated from aqueous ethanol in pale yellow crystals, m. p. 226—227° (Found : C, 47·4; H, 4·0; N, 11·4. $C_{10}H_{10}O_6N_2$ requires C, 47·2; H, 3·9; N, 11·0%), and 2-*hydroxy*-4-*nitrobenzoyl*-DL-*aspartic acid*, a pale yellow microcrystalline powder (from aqueous ethanol), m. p. 203—205° (Found : C, 44·5; H, 3·4; N, 9·4. $C_{11}H_{10}O_8N_2$ requires C, 44·3; H, 3·35; N, 9·4%).

4-*Amino*-2-*hydroxyhippuric Acid*.—2-Hydroxy-4-nitrohippuric acid (2·4 g.) in 50% ethanol (100 ml.) containing sodium hydrogen carbonate (0·84 g.) was hydrogenated over Adams's catalyst at atmospheric pressure and temperature until absorption ceased. Removal of catalyst followed by addition of hydrochloric acid (9·7 ml. of 1·03N) and evaporation to dryness yielded a solid which was triturated with water to remove sodium chloride. From the residue (1·3 g.), 4-*amino*-2-*hydroxyhippuric acid* separated as colourless crystals, m. p. 170—175°

(decomp.) (from water) (Found : C, 51·4; H, 4·7; N, 13·2. $C_9H_{10}O_4N_2$ requires C, 51·4; H, 4·75; N, 13·3%).

Similarly prepared were 4-*amino*-2-*hydroxybenzoyl*-DL-*alanine*, pale brown (from water), m. p. 168—170° (decomp.) (Found : C, 53·4; H, 5·5; N, 12·5. $C_{10}H_{12}O_4N_2$ requires C, 53·6; H, 5·4; N, 12·5%), and 4-*amino*-2-*hydroxybenzoyl*-DL-*aspartic acid*, pale brown (from water), m. p. 204° (decomp.) (Found : C, 49·1; H, 4·5; N, 10·5. $C_{11}H_{12}O_6N_2$ requires C, 49·2; H, 4·5; N, 10·4%).

2-*Acetoxy*-4-*nitrophenyl Diazomethyl Ketone*.—2-Acetoxy-4-nitrobenzoyl chloride (from 9 g. of acid) in dry ether was added gradually to an ethereal solution of diazomethane (from 17 g. of methyl-*N*-nitrosourea) with swirling at 0°. The solution was kept for 2 hours at 0°, then overnight at room temperature. Removal of the ether yielded the diazo-ketone (7·9 g.), m. p. 90—94°, sufficiently pure for Wolff rearrangement. A sample recrystallised 3 times from benzene–light petroleum yielded pale yellow prisms of *diazo-ketone*, m. p. 110° (decomp.) (Found : C, 48·1; H, 2·9; N, 16·6. $C_{10}H_7O_5N_3$ requires C, 48·2; H, 2·8; N, 16·85%).

Methyl 2-*Acetoxy*-4-*nitrophenylacetate*.—2-Acetoxy-4-nitrophenyl diazomethyl ketone (6·4 g.) in methanol (100 ml.) was warmed to 60° and a methanolic suspension of silver oxide (from 20 ml. of 10% aqueous silver nitrate) added in portions during 30 minutes. The mixture was refluxed for 30 minutes and filtered whilst hot (charcoal). Evaporation under reduced pressure to 25 ml. yielded colourless needles (2·9 g.); a further 0·65 g. was obtained by evaporating the mother-liquors to dryness and triturating the residue with methanol. *Methyl* 2-*acetoxy*-4-*nitrophenylacetate* separated from methanol in colourless feathery needles, m. p. 85·5° (Found : C, 52·1; H, 4·45; N, 5·55. $C_{11}H_{11}O_6N$ requires C, 52·2; H, 4·35; N, 5·5%).

The ester (3·55 g.) was heated under reflux for 45 minutes with glacial acetic acid (12 ml.) and hydrochloric acid (18 ml.). The hot solution was filtered (charcoal) and diluted with water (60 ml.). On cooling, the crude acid (2·1 g.) separated, and the mother-liquors yielded a further 0·6 g. on ether-extraction. 2-Hydroxy-4-nitrophenylacetic acid separated from water in pale yellow needles as a *monohydrate*, m. p. 147—148° (Found : C, 44·8; H, 4·2; N, 6·35. $C_8H_7O_5,H_2O$ requires C, 44·7; H, 4·2; N, 6·5%).

4-*Amino*-2-*hydroxyphenylacetic Acid*.—The nitro-acid (2·1 g.) in methanol (50 ml.), hydrogenated at atmospheric temperature and pressure over Adams's catalyst, gave 4-*amino*-2-*hydroxyphenylacetic acid* (1·4 g.) as pale yellow prisms (from water), m. p. 188—189° (Found : C, 57·5; H, 5·4; N, 8·1. $C_8H_9O_3N$ requires C, 57·5; H, 5·4; N, 8·4%).

4-(2-*Acetoxy*-4-*nitrobenzamido*)*salicylic Acid*.—2-Acetoxy-4-nitrobenzoyl chloride (from 5·62 g. of acid) in dry benzene (100 ml.) was added dropwise with stirring to a suspension of 4-aminosalicylic acid (7·64 g.) in dry ether (250 ml.). After 2 hours the solvents were removed under reduced pressure and the residue boiled with alcohol (200 ml.) and filtered from 4-aminosalicylic acid hydrochloride. The filtrate was concentrated and on refrigeration the product (6·7 g.) separated. 4-(2-*Acetoxy*-4-*nitrobenzamido*)*salicylic acid* crystallised from ethyl acetate–light petroleum (b. p. 60—80°) as clusters of pale yellow needles, m. p. 240—242° (decomp.) (Found : C, 53·1; H, 3·35; N, 7·6. $C_{16}H_{12}O_8N_2$ requires C, 53·35; H, 3·35; N, 7·8%).

This (2·0 g.) in alcohol (150 ml.) was kept at room temperature for 5 minutes with alcoholic potassium hydroxide (50 ml. of 4%). On acidification, and dilution with water (200 ml.), the product separated as a yellow amorphous solid (1·8 g.). Reprecipitation from aqueous alkali gave a pale yellow jelly which on dilution with two volumes of alcohol gave a clear solution from which 4-(2-*hydroxy*-4-*nitrobenzamido*)*salicylic acid* separated as small yellow needles, m. p. 279—280° (decomp.) (Found : C, 52·8; H, 3·2; N, 8·4. $C_{14}H_{10}O_7N_2$ requires C, 52·85; H, 3·15; N, 8·8%).

4-(4-*Amino*-2-*hydroxybenzamido*)*salicylic Acid*.—4-(2-Hydroxy-4-nitrobenzamido)salicylic acid (1·4 g.) in water containing sodium hydrogen carbonate (1·1 g.) was hydrogenated at atmospheric temperature and pressure over Adams's catalyst, the theoretical amount of hydrogen being absorbed in about 20 minutes. After removal of the catalyst the filtrate was acidified with acetic acid. The product was a yellow amorphous solid (1·2 g.). Two recrystallisations from aqueous acetone gave the *amino-acid* as yellow needles, m. p. 251° (decomp.) (Found : C, 58·8; H, 4·85; N, 9·3. $C_{14}H_{12}O_5N_2$ requires C, 58·4; H, 4·2; N, 9·7%).

Phenyl 4-*nitrosalicylate*.—4-Nitrosalicylic acid (18·3 g., 0·1 mole), phenol (9·4 g., 0·1 mole), and phosphorus oxychloride (6·16 g., 0·04 mole) were heated at 120° for 3 hours. After cooling, the mixture was ground with water, then with sodium hydrogen carbonate solution. The solid was dried and crystallised from acetone, from which *phenyl* 4-*nitrosalicylate* (13·1 g.) separated as pale yellow prisms, m. p. 148—150° (Found : C, 60·4; H, 3·5; N, 5·8. $C_{13}H_9O_4N$ requires C, 60·2; H, 3·7; N, 5·8%).

Similarly prepared were o-, pale yellow prisms (from 50% alcohol), m. p. 94° (Found: C, 61·7; H, 4·04; N, 5·2. $C_{14}H_{11}O_5N$ requires C, 61·5; H, 4·0; N, 5·1%), m-, pale yellow needles (from acetone), m. p. 94—95° (Found: C, 61·5; H, 4·2; N, 5·3%), and p-*tolyl*, pale yellow needles (from 50% alcohol), m. p. 122° (Found: C, 61·2; H, 4·2; N, 6·2%), β-*naphthyl*, pale yellow crystals (from ethyl acetate), m. p. 189—190° (Found: C, 66·1; H, 3·65; N, 4·7. $C_{17}H_{11}O_5N$ requires C, 66·0; H, 3·55; N, 4·5%), m-, pale yellow needles (from aqueous acetone), m. p. 166·5—167° (Found: C, 51·35; H, 2·55; N, 9·3. $C_{13}H_8O_7N_2$ requires C, 51·30; H, 2·65; N, 9·2%), and p-*nitrophenyl* 4-*nitrosalicylate*, yellow prismatic needles (from acetone), m. p. 154—154·5° (Found: C, 51·75; H, 2·75; N, 9·4%).

Phenyl 4-*aminosalicylate*.—(*a*) Phenyl 4-nitrosalicylate (2·5 g.) in ethyl acetate (250 ml.) was shaken with Adams's catalyst under hydrogen at atmospheric pressure until absorption ceased. After removal of the catalyst the solution was evaporated to dryness under reduced pressure and the residue crystallised from alcohol, from which *phenyl* 4-*aminosalicylate* separated in pale cream-coloured needles, m. p. 145—146° (Found: C, 68·2; H, 4·8; N, 6·2. $C_{13}H_{11}O_3N$ requires C, 68·1; H, 4·8; N, 6·1%).

(*b*) Phenyl 4-nitrosalicylate (20 g.) and ammonium chloride (10 g.) in 50% aqueous alcohol (1 l.) were refluxed with zinc dust (200 g.) for 4 hours. After removal of the zinc, the filtrate was concentrated under reduced pressure to *ca.* 350 ml. and cooled. The solid was collected and recrystallised from alcohol, giving needles of phenyl 4-aminosalicylate (16 g.), m. p. 145—146° undepressed on admixture with a specimen prepared by method (*a*) above.

Similarly prepared were o-, colourless plates (from alcohol), m. p. 86—88° (Found: C, 68·9; H, 5·15; N, 5·75. $C_{14}H_{13}O_3N$ requires C, 69·1; H, 5·35; N, 5·8%), m-, colourless needles (from 60% acetone), m. p. 129—130° (Found: C, 69·1; H, 5·2; N, 5·55%), and p-*tolyl* 4-*aminosalicylate*, colourless needles (from 50% alcohol), m. p. 112° (Found: C, 68·9; H, 5·6; N, 5·9%), β-*naphthyl*, colourless needles (from 80% alcohol), m. p. 160—161° (Found: C, 72·85; H, 4·5; N, 5·2. $C_{17}H_{13}O_3N$ requires C, 73·1; H, 4·65; N, 5·0%), m- (method *a* only), colourless needles (from 40% acetone), m. p. 157° (Found: C, 64·4; H, 5·0; N, 11·5. $C_{13}H_{12}O_3N$ requires C, 63·9; H, 4·9; N, 11·5%), and p-*aminophenyl* 4-*aminosalicylate*, colourless needles (from aqueous alcohol), m. p. 181° (Found: C, 63·7; H, 4·9; N, 10·9%).

Methyl 4-*Benzylsulphonamidosalicylate*.—Methyl 4-aminosalicylate (16·7 g.) in dry pyridine (150 ml.) was heated with toluene-ω-sulphonyl chloride (19·0 g.) at 100° for 30 minutes. The solution was poured into ice-water (1 l.) containing hydrochloric acid (200 ml.) and after 2 hours at 0° the solid product (27·3 g.) was collected, washed with cold water, and dried. *Methyl* 4-*benzylsulphonamidosalicylate* separated from methanol in colourless stout rods, m. p. 172—173° (Found: C, 56·4; H, 4·3; N, 4·6; S, 9·8. $C_{15}H_{15}O_5NS$ requires C, 56·1; H, 4·7; N, 4·4; S, 10·0%).

The ester (22·6 g.) was heated under reflux for 30 minutes with 4% sodium hydroxide solution (250 ml.), cooled, and acidified with dilute hydrochloric acid. 4-*Benzylsulphonamidosalicylic acid* separated from 50% ethanol in colourless needles (18·1 g.), m. p. 224° (decomp.) (Found: C, 54·3; H, 4·2; N, 4·6; S, 10·15. $C_{14}H_{13}O_5NS$ requires C, 54·7; H, 4·2; N, 4·55; S, 10·4%).

4-*Amino*-3 : 5-*di-iodosalicylic Acid*.—(*a*) Methyl 4-aminosalicylate (1 g.) in hot carbon tetrachloride (50 ml.) was treated with a solution of iodine chloride (2 g.) in carbon tetrachloride (10 ml.). The gummy solid which separated was triturated with 10% aqueous sodium hydrogen carbonate, to yield the crude ester (1·1 g.) as a pale brown solid. *Methyl* 4-*amino*-3 : 5-*di-iodosalicylate* separated from methanol in colourless feathery needles, m. p. 159° (Found: C, 23·5; H, 1·8; N, 3·3; I, 60·3. $C_8H_7O_3NI_2$ requires C, 22·9; H, 1·7; N, 3·3; I, 60·6%). Hydrolysis with boiling 10% sodium hydroxide (20 ml.) for 10 minutes afforded 4-*amino*-3 : 5-*di-iodosalicylic acid* as colourless needles, m. p. 180° (decomp.) (from aqueous ethanol) (Found: C, 21·3; H, 1·2; N, 3·5; I, 62·5. $C_7H_5O_3NI_2$ requires C, 20·7; H, 12·1; N, 3·5; I, 62·7%).

(*b*) To 4-aminosalicylic acid (36 g.) suspended in 95% alcohol (200 ml.) was added sulphuric acid (24 ml.), the temperature being kept below 50°. Iodine (59·2 g.) was added, and then hydrogen peroxide (36 ml. of 30%) dropwise with stirring during 30 minutes. The mixture was cooled and the product (89 g.) collected. Crystallisation from alcohol gave colourless needles, m. p. 180° (decomp.) undepressed on admixture with a specimen prepared by method (*a*) above.

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