

3 : 3'-DIHYDROXYAZOBENZENE-4 : 4'-DICARBOXYLIC ACID AND 4-AMINOSALICYLIC ACID

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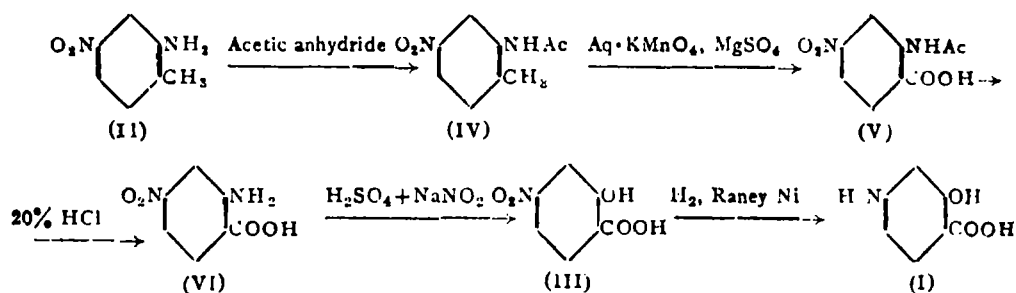
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LEHMANN¹ first observed that 4-(or *p*)-aminosalicylic acid (I) had an inhibitory action on tubercle bacilli *in vitro*, and other workers² have confirmed and extended his observation to experimental tuberculosis. Clinical trials also appear to have given promising results. It has been reported² that 4-aminosalicylic acid even prevents the growth of tubercle bacilli made resistant to streptomycin. It may be stated in this connection that 5-aminosalicylic acid has sometimes been referred to in the literature³ as *p*-aminosalicylic acid which has incidentally been shown to be ineffective in tuberculosis.¹ In view of the possible chemotherapeutic value of 4-aminosalicylic acid, available methods for its preparation have been examined, and a convenient procedure is now described, starting from the commercially available 4-nitro-*o*-toluidine (Fast Scarlet G Base; II), which is prepared⁴ by nitration of *o*-toluidine.

Seidel and Bittner⁵ obtained 4-aminosalicylic acid by reduction of 4-nitrosalicylic acid with tin and hydrochloric acid. Reduction of this nitroacid in almost quantitative yield by means of sodium sulphide has been recorded by Popov,⁶ and later by Kartzner⁷ who employed hydrogen under pressure and nickel as catalyst; the melting points of their products have not been mentioned. The observation that 4-aminosalicylic acid has valuable properties as an antitubercular agent has led several workers to attempt its synthesis by newer and better methods. Martin, *et al.*⁸ and Sheehan⁹ independently found that *m*-aminophenol and ammonium carbonate when heated at 110° under pressure for twelve hours give 4-aminosalicylic acid, and not 4-hydroxyanthranilic acid as tentatively assumed¹⁰ in a patent claim.¹¹ Martin, *et al.*⁸ have prepared the acid by "direct carboxylation of *m*-aminophenol using modified Kolbe conditions", but further details and yield have not been mentioned. According to Sheehan⁹ the yield of 4-aminosalicylic acid is about 25 per cent., half of the aminophenol remaining unconverted. It appeared to us that the preparation of 4-aminosalicylic acid from the corresponding nitrocompound offers some advantages, of which one is the readier accessibility of certain

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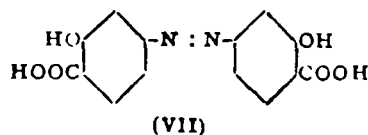
derivatives of 4-aminosalicylic acid. The recorded methods² for the synthesis of 4-nitrosalicylic acid (III) lack preparative value, and the acid has now been prepared in excellent yield, from 4-nitro-*o*-toluidine.



4-Nitro-*o*-toluidine (II) was acetylated, and the amide (IV) oxidised with potassium permanganate solution under neutral conditions to the carboxylic acid (V) in 80 per cent yield. Oxidation of (IV) with alkaline potassium permanganate has been reported by Wheeler and Barnes,¹³ but the yield has not been mentioned. The acid (V) was deacetylated by boiling with hydrochloric acid. The anthranilic acid (VI) was diazotised and the diazonium salt decomposed to produce 4-nitrosalicylic acid, m.p. 235°. Seidel and Bittner⁵ have obtained this acid (III) from (VI) by the same method and recorded its m.p. as 235°, while Ullmann and Wagner¹⁴ who have prepared it from 2-chloro-4-nitrobenzoic acid quote the m.p. 226° (darkens 220°). 4-Nitrosalicylic acid was reduced with hydrogen in presence of Raney nickel at forty pounds pressure to 4-aminosalicylic acid in ninety-five per cent yield. The crystallised acid melted at 133° with decomposition. We have found that the rate of heating is important, and by raising the temperature rapidly, melting points as high as 148–49° can be observed. Varying melting points have been recorded for the acid by different workers: Seidel and Bittner,⁵ 220°; Sheehan,⁹ 146–7°; Rosdahl,¹⁵ 130°; while Martin, *et al.*⁸ have made no reference to the melting point of 4-aminosalicylic acid obtained by them. As suggested by Sheehan,⁹ Seidel and Bittner⁵ have probably mistaken the hydrochloride for its base. O'Connor¹⁶ quotes the m.p. 150–1° (decomp.); Whittet¹⁷ has obtained a sample decomposing at 137°, but not finally melting until 150°, as well as a sample melting at 139–41° (decomp.); McAnally and Seymour¹⁸ suggest that the m.p. is variable from 140° to 150–1° on account of decarboxylation to *m*-aminophenol.

Diazotised 4-aminosalicylic acid has been coupled with β -naphthol and hexylresorcinol to yield the corresponding monoazo dyes, the dye in the second case being formulated as 4-*n*-hexyl-6-(3'-hydroxy-4'-carboxy) benzeneazoresorcinol.

3: 3'-Dihydroxyazobenzene-4: 4'-dicarboxylic acid (VII) has been prepared by reduction of 4-nitrosalicylic acid with glucose or zinc dust in alkaline solution. The azosalicylic acid (VII) is of interest on account of its



reducibility *in vivo* to two molecules of 4-aminosalicylic acid; of further interest from this point of view is the *O*-diacetyl derivative of (VII).

Salts of sulphanilamides and sulphonic acids have been found to be more active *in vitro* than the parent sulpha drugs.¹⁶ Salts of 4-aminosalicylic acid with naphthalene- β -sulphonic acid and with a wetting agent, sodium dibutyl-naphthalene sulphonate, have now been prepared.

The synthesis of other derivatives of 4-aminosalicylic acid and the azosalicylic acid (VII), and an examination of their properties as anti-bacterial agents, are in progress.

EXPERIMENTAL

4-Nitro-*o*-toluidine, obtained as the commercial Fast Scarlet G Base (m.p. 99–100°; the pure substance melts at 104–5°) was used without purification as the starting material.

4-Nitro-*N*-acetylanthranilic acid (V)

To a suspension of 4-nitro-acet-*o*-toluidide (25 g.) in boiling water (300 c.c.) containing magnesium sulphate (90 g.), under mechanical agitation, was added potassium permanganate solution (4%; 1600 c.c.) in small quantities during one hour. Boiling was continued for 15 minutes, the reaction mixture filtered hot, and the precipitate washed with hot water. The filtrate and washings were acidified with hydrochloric acid when (V) separated in crystalline form (23 g.; 80% yield). Recrystallised from water, the very pale yellow needles had m.p. 215° (Wheeler and Barnes,¹³ 215°; Ullmann and Uzbachian,¹³ 221°).

4-Nitro-anthranilic acid (VI)

Hydrolysis of (V) (25 g.) was effected by means of boiling hydrochloric acid (20%; 250 c.c.) during 30 minutes. The reaction liquid was cooled, basified with 30% ammonia in order to decompose the hydrochloride of the base and the solution was then filtered. The filtrate on acidification with glacial acetic acid yielded nitro-anthranilic acid (20 g.). The orange red needles from alcohol melted at 266·5° (Wheeler and Barnes,¹³ 264°;

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Ullmann and Uzbachian,¹³ 269·5°) (Found: N, 15·6. $C_7H_6O_4N_2$ requires N, 15·4%).

4-Nitrosalicylic acid (III)

4-Nitroanthranilic acid (20 g.) was suspended in 50% sulphuric acid (50 c.c.) and diazotised at 0° C. with sodium nitrite solution (15 g. in 20 c.c. water). The solution was poured in a thin stream into 80% boiling sulphuric acid (500 c.c.) and boiling continued (5–10 mins.) until decomposition of the diazonium salt was complete. On cooling (III) separated in crystalline form (17·5 g.; 87% yield). It crystallised from water in pale yellow needles, m.p. 235° (darkens at 220°) (Ullmann and Wagner,¹⁴ 226°, darkens at 220°); (Seidel and Bittner,⁵ 235°) (Found: N, 7·8. $C_7H_5O_5N$ requires N, 7·7%). It gives a brownish-red colouration with ferric chloride.

Acetate of (III).—Was formed by treating (III) with acetyl chloride and a drop of pyridine. Crystallised from benzene, m.p. 144·5° (Found: N, 6·2. $C_9H_7O_8N$ requires N, 6·2%).

4-Aminosalicylic Acid (I)

To a solution of 4-nitrosalicylic acid (10 g.) in sodium bicarbonate solution (12·5%; 40 c.c.) was added a suspension of Raney nickel (about 1 g. in 10 c.c. alcohol), and the mixture shaken in a bottle with hydrogen under 40 lbs. pressure for 4 hours. On filtering, removing alcohol from the filtrate and making acid (pH 3) with hydrochloric acid, 4-aminosalicylic acid separated in crystalline form (7 g.). Further acidification of the mother-liquor precipitated the hydrochloride of (I) (1 g.). The total yield from the reaction calculated as 4-aminosalicylic acid amounts to 95% of the theoretical. 4-Aminosalicylic acid crystallised from alcohol in brown needles, m.p. 133° (decomp.); (Seidel and Bittner,⁵ 220°; Sheehan,⁹ 146–7°; Rosdahl,¹⁵ 130°) (Found: N, 9·1. $C_7H_7O_3N$ requires N, 9·2%). It gives a reddish-brown colouration with alcoholic ferric chloride.

The hydrochloride crystallised from water containing a little hydrochloric acid in shining colourless plates, m.p. 219·5° (Sheehan,⁹ 223°) (Found: N, 7·1. $C_7H_8O_3NCl$ requires N, 7·3%). Longer boiling during crystallisation causes decarboxylation.

3'-Hydroxy-4'-carboxybenzeneazo-2-naphthol

The dye obtained by coupling diazotised 4-aminosalicylic acid with β -naphthol in the usual manner crystallised from 50% alcohol in curved red needles, m.p. 259° (decomp.) (Found: N, 9·1. $C_{17}H_{13}O_4N_2$ requires N, 9·1%).

4-n-Hexyl-6-(3'-hydroxy-4'-carboxy) benzeneazoresorcinol

The dye obtained by adding diazotised 4-aminosalicylic acid (1 mol.) to a solution of 4-*n*-hexylresorcinol (1 mol.) dissolved in 50% alcohol to which sodium acetate had been added in excess, crystallised from glacial acetic acid in red needles, m.p. 194° (decomp.) (Found: N, 7.8. $C_{19}H_{22}O_5N_2$ requires N, 7.9%).

3:3'-Dihydroxyazobenzene-4:4'-dicarboxylic acid (VII)

Method (1).—4-Nitrosalicylic acid (15 g.) in 22% caustic soda solution (225 c.c.) was warmed to 50°, and a solution of glucose (100 g.) in water (150 c.c.) was slowly added during one hour. The reaction mixture was then warmed on the steam-bath for 15 minutes, when the solution which was reddish-brown in colour turned to deep brown. On cooling, air was bubbled through the solution for about 4 hours for oxidation of the hydrazo-compound and the solution then acidified with hydrochloric acid. The precipitated acid was collected and dissolved in the minimum amount of 10% sodium carbonate solution (about 150 c.c.) by warming. On cooling, the disodium salt of the acid (VII) separated (6 g.). It crystallised from water in orange needles (Found: N, 8.0. $C_{14}H_8O_6N_2Na_2$ requires N, 8.1%).

Method (2).—To a mixture of 4-nitrosalicylic acid (7.2 g.), sodium hydroxide (7.2 g.), water (20 c.c.) and methanol (35 c.c.), zinc dust (6 g.) was added, and the mixture was refluxed on the water-bath for 10 hours. It was then cooled to 60° and filtered hot. The residue of sodium zincate was washed on the filter with a little hot methanol. The methanol was distilled off from the filtrate and washings, and the aqueous solution acidified with hydrochloric acid. The acid which separated was filtered, washed, dried and dissolved in hot 25% sodium carbonate solution (50 c.c.). On cooling, the disodium salt of the acid (VII) separated (6.1 g.; 89% yield).

Acidification of the disodium salt gave the free acid which crystallised from nitrobenzene in needles, which did not melt below 325°. The substance gives a red colouration with concentrated sulphuric acid and the alcoholic solution gives a dark violet colour with ferric chloride (Found: N, 9.2. $C_{14}H_{10}O_6N_2$ requires N, 9.3%).

The *acetate* of (VII), prepared by heating (VII) (1 g.), pyridine (3 drops) and acetyl chloride (4 c.c.) for 15 minutes on the water-bath, crystallised from alcohol in needles, which did not melt below 325° (Found: N, 7.3. $C_{18}H_{14}O_8N_2$ requires N, 7.2%).

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Salt of 4-aminosalicylic acid hydrochloride with sodium naphthalene- β -sulphonate

Boiling aqueous solutions of 4-aminosalicylic acid hydrochloride (0.5g. in 7 c.c. water) and sodium naphthalene- β -sulphonate (0.65 g. in 6 c.c. water) were mixed together, boiled further for 2-3 minutes and allowed to cool. A crystalline salt separated, which was crystallised from water acidulated with hydrochloric acid. The chocolate coloured crystals melted at 252°. (Found: N, 4.5. $C_{17}H_{15}O_6SN$ requires N, 4.0%).

Salt of 4-aminosalicylic acid hydrochloride and sodium dibutyl-naphthalene sulphonate

The salt was prepared as described in the previous experiment by mixing the equimolecular aqueous solutions at the boil. It separated from water as a powder, m.p. 238° (Found: N, 2.8. $C_{25}H_{32}O_6NS$ requires N, 3.0%).

SUMMARY

Starting from 4-nitro-*o*-toluidine, a commercially available dyestuff intermediate, 4-aminosalicylic acid has been prepared in an overall yield of 60 per cent. New derivatives of the acid are described. 3:3'-Dihydroxyazobenzene-4:4'-dicarboxylic acid has been obtained from 4-nitrosalicylic acid, an intermediate in the synthesis of 4-aminosalicylic acid. This azo salicylic acid and its *O*-acetyl derivative are of interest on account of their *in vivo* reducibility to 4-aminosalicylic acid and 4-aminoaspirin.

ACKNOWLEDGEMENT

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