402. *Aminohydroxynaphthoic Acids. Part I. Synthesis of 6-Amino-4-hydroxy-2-naphthoic Acid ("Carboxy γ-Acid").*

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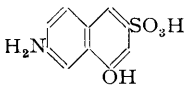
Nitration of 4-keto-1 : 2 : 3 : 4-tetrahydro-2-naphthoic acid in concentrated sulphuric acid at −10° to −5° yields principally 6-nitro-4-keto-1 : 2 : 3 : 4-tetrahydro-2-naphthoic acid.* This substance is readily converted into 6-amino-4-hydroxy-2-naphthoic acid, the carboxylic analogue of the technically important γ-acid, by bromination, dehydrobromination, and subsequent reduction of the nitro-group.

Although the aminonaphtholsulphonic acids represent one of the most important types of intermediate in dye chemistry, very few members of the corresponding series bearing carboxyl in place of the sulphonic acid groups, *i.e.*, aminohydroxynaphthoic acids, are known. The majority of those which have been described in the literature have the hydroxyl and amino-groups situated in the same ring of the naphthalene molecule, whereas those aminonaphthol-sulphonic acids which have proved of greatest interest are derived from heteronuclear aminonaphthols.

Aminonaphtholsulphonic acid γ ["γ-acid" (I)] is typical of the class in which the hydroxyl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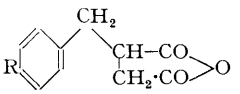
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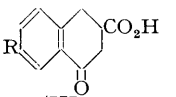
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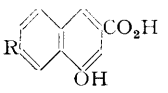
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and amino-groups are situated in different rings, and is a substance of great technical importance. It is clear that the synthesis of the carboxylic analogue (IV; R = NH_2) of γ-acid or the synthesis of any other acid with heteronuclear hydroxyl and amino-groups must differ fundamentally from that employed for the corresponding sulphonic acid, as it is not possible to introduce carboxyl groups into β-naphthylamine by any process strictly analogous to that of sulphonation. Moreover, the conversion of a sulphonic acid into a hydroxyl group by alkali fusion, a reaction frequently employed in preparing aminonaphtholsulphonic acids, has no counterpart in the carboxylic acid series.

The methods available for preparing substituted 4-hydroxy-2-naphthoic acids have been discussed by Haworth, Jones, and Way (*J.*, 1943, 10), who conclude that the best general synthesis is that in which a benzylsuccinic anhydride (II) is subjected to ring-closure, the resulting 4-keto-1 : 2 : 3 : 4-tetrahydro-2-naphthoic acid (III) being subsequently converted into a 4-hydroxy-2-naphthoic acid (IV) by successive bromination and dehydrobromination. The benzylsuccinic acids required for this synthesis were obtained by condensing benzyl halides with ethyl sodio-α-acetosuccinate, but, since Haworth *et al.* were unable to obtain 4-nitrobenzyl-succinic acid by this method, they failed to obtain 6-nitro-4-hydroxy-2-naphthoic acid (IV; R = NO_2).

* Patent protection pending.

Ring-closure of 4-nitrobenzylsuccinic anhydride would probably be difficult to achieve on account of the deactivating effect of the nitro-group, but, since this obstacle might be overcome by previous reduction and acetylation, *i.e.*, ring closure of (II; R = NHAc), the condensation of 4-nitrobenzyl chloride with ethyl sodio-α-acetosuccinate was re-investigated (cf. Haworth *et al.*, *loc. cit.*), but without success. Attempts to obtain the required substance by successive condensation of 4-nitrobenzyl chloride with ethyl sodioacetoacetate and ethyl chloroacetate in ethanol, followed by hydrolysis, did not give 4-nitrobenzylsuccinic acid.

The direct nitration of 4-keto-1 : 2 : 3 : 4-tetrahydro-2-naphthoic acid (III; R = H), however, offers a method of preparation for 6-nitro-4-keto-1 : 2 : 3 : 4-tetrahydro-2-naphthoic acid in which the difficulties discussed above are avoided. This substance is smoothly nitrated in concentrated sulphuric acid at −10° to −5°, a 95% yield of crude mononitration product, probably a mixture of 6- and 8-nitro-4-keto-1 : 2 : 3 : 4-tetrahydro-2-naphthoic acid, being obtained. Several recrystallisations of this mixture from water yielded *6-nitro-4-keto-1 : 2 : 3 : 4-tetrahydro-2-naphthoic acid* (III; R = NO_2). Bromination in chloroform then gave *3-bromo-6-nitro-4-keto-1 : 2 : 3 : 4-tetrahydro-2-naphthoic acid*, which was readily dehydrobrominated to *6-nitro-4-hydroxy-2-naphthoic acid* (IV; R = NO_2) by heating it with diethylaniline. Reduction of this nitro-compound with hydrogen at room temperature and pressure in the presence of Raney nickel afforded *6-amino-4-hydroxy-2-naphthoic acid* (IV; R = NH_2), the carboxylic analogue of γ-acid.

Oxidation of 6-nitro-4-keto-1 : 2 : 3 : 4-tetrahydro-2-naphthoic acid with alkaline permanganate gave 4-nitrophthalic acid, from which it is evident that the nitro-group is in position 6 or 7. In order to establish the position of this group with certainty, 6-amino-4-hydroxy-2-naphthoic acid was diazotised and the diazonium solution treated with cuprous chloride. The product, *6-chloro-4-hydroxy-2-naphthoic acid*, was decarboxylated by heating it with quinoline in the presence of copper bronze, the chloronaphthol thus obtained being identical with an authentic sample of 7-chloro-1-naphthol. The latter was prepared from 8-nitro-2-naphthylamine (Saunders and Hamilton, *J. Amer. Chem. Soc.*, 1932, **54**, 638) by diazotisation and the Sandmeyer reaction, yielding 7-chloro-1-nitronaphthalene, reduction of which afforded 7-chloro-1-naphthylamine; this was converted into 7-chloro-1-naphthol by boiling the diazonium salt with 50% sulphuric acid.

Experimental.

(Analyses by Mr. E. S. Morton. M. p.s are uncorrected.)

Benzylsuccinic Acid.—The following method gave a somewhat higher yield than that of Haworth *et al.* (*loc. cit.*) and is more convenient for large-scale preparations. A solution of ethyl sodioacetoacetate, prepared from sodium (115 g.) in ethanol (1375 c.c.) and ethyl acetoacetate (1300 g.), was treated with benzyl chloride (633 g.) at 25—30° and the reaction mixture subsequently boiled under reflux until neutral to litmus. Fractionation in a vacuum, after removal of sodium chloride and ethanol, gave ethyl acetoacetate and ethyl benzylacetoacetate (890 g.), b. p. 136°/2 mm. The latter product (110 g.) was added to a solution of sodium (11·5 g.) in ethanol (150 c.c.), and ethyl chloroacetate (65 g.) run in at 25—30°. After the mixture had been heated under reflux until neutral to litmus, sodium chloride and ethanol were removed. Fractionation in a vacuum yielded ethyl α-aceto-α-benzylsuccinate (82 g.), b. p. 170—180°/1·3 mm. Hydrolysis by boiling 2N-sodium hydroxide (3 mols.) for 18 hours and subsequent acidification then afforded benzylsuccinic acid (80%), which was purified by recrystallisation from hot water; m. p. 160°.

Benzylsuccinic Anhydride (II; R = H).—Benzylsuccinic acid was heated under reflux with an equal weight of acetic anhydride for 15 minutes; acetic acid and excess of anhydride were then removed by distillation. Vacuum distillation of the residue afforded benzylsuccinic anhydride, m. p. 95—97° (90—95%), b. p. 185°/2 mm.

4-Keto-1 : 2 : 3 : 4-tetrahydro-2-naphthoic Acid (III; R = H).—Benzylsuccinic anhydride (100 g.) was added to aluminium chloride (143 g.), dissolved in nitrobenzene (500 c.c.), the temperature being kept at 20—25° (ice-bath). After 24 hours at ordinary temperature, the solution was poured on a mixture of ice and hydrochloric acid. Removal of the nitrobenzene by steam-distillation yielded crude 4-keto-1 : 2 : 3 : 4-tetrahydro-2-naphthoic acid, which was purified by crystallisation from hot water. This method is more convenient than that of Haworth *et al.* for large-scale work.

6-Nitro-4-keto-1 : 2 : 3 : 4-tetrahydro-2-naphthoic Acid (III; R = NO_2).—The foregoing acid (38 g.) was dissolved in sulphuric acid (190 c.c., *d* 1·84) at 10°. A mixture of nitric acid (14·4 c.c.; *d* 1·4) and sulphuric acid (30 c.c., *d* 1·84) was dropped into the stirred solution at −10° to −5°. After being stirred for 1 hour at 0° the reaction mixture was poured on ice, and the product (44·5 g.) collected, washed with water until free from acid, and dried at 50°. Several crystallisations of this crude product, m. p. 154—163°, from hot water gave *6-nitro-4-keto-1 : 2 : 3 : 4-tetrahydro-2-naphthoic acid* (24 g.), m. p. 179° (Found: C, 56·2; H, 4·0; N, 6·2. $C_{11}H_9O_5N$ requires C, 56·15; H, 3·85; N, 5·95%).

Permanganate Oxidation of 6-Nitro-4-keto-1 : 2 : 3 : 4-tetrahydro-2-naphthoic Acid.—The nitro-compound (1·1 g.) in a slight excess of dilute sodium carbonate solution was treated with potassium permanganate (4 g.; 2·5% solution) at the boil. When oxidation was complete, the solution was filtered from manganese dioxide, and the filtrate concentrated to 50 c.c., acidified with concentrated hydrochloric acid, and extracted with ether (2 × 25 c.c.). After removal of the ether, the residue was

heated under reflux with acetic anhydride (2 c.c.) for 5 minutes, and the latter then removed under reduced pressure. Sublimation under 2 mm. pressure and crystallisation of the sublimate from benzene–ligroin yielded 4-nitrophthalic anhydride, m. p. 119°, not depressed by admixture with an authentic sample.

3-*Bromo*-6-*nitro*-4-*keto*-1 : 2 : 3 : 4-*tetrahydro*-2-*naphthoic Acid*.—6-Nitro-4-keto-1 : 2 : 3 : 4-tetrahydro-2-naphthoic acid (20 g.), suspended in chloroform (60 c.c.), was treated gradually with a solution of bromine (4·6 c.c.) in chloroform (40 c.c.). The reaction mixture was warmed to 40° after addition of the first portion of bromine solution to initiate the reaction and then instantly cooled to 15°, the remainder of the bromine being added at 15—20°. After removing the solvent in a vacuum, the crude *bromo*-compound (22·5 g.) was purified by crystallisation from acetone–benzene. It then melted at 188°, with evolution of hydrogen bromide (Found : C, 42·5; H, 2·85; Br, 24·8. $C_{11}H_8O_5NBr$ requires C, 42·05; H, 2·55; Br, 25·4%).

6-*Nitro*-4-*hydroxy*-2-*naphthoic Acid* (IV; R = NO_2).—The foregoing bromo-compound (26 g.) and diethylaniline (260 c.c.) were heated on the steam-bath for 6 hours. After addition of excess of sodium hydrogen carbonate, the diethylaniline was removed by steam-distillation, and the residual solution poured into an excess of 2N-hydrochloric acid. The solid product (18·2 g.) was collected, washed with water, and dried at 50°. It was dissolved in ethanol, and the resulting solution clarified (carbon) and evaporated to dryness. Crystallisation of the residue from acetone yielded 6-*nitro*-4-*hydroxy*-2-*naphthoic acid* as orange prisms (Found : C, 56·8; H, 3·3; N, 6·2. $C_{11}H_7O_5N$ requires C, 56·65; H, 3·0; N, 6·0%).

6-*Amino*-4-*hydroxy*-2-*naphthoic Acid* (IV; R = NH_2).—6-Nitro-4-hydroxy-2-naphthoic acid (25 g.) and Raney nickel catalyst (*ca.* 2 g.) (prepared as described below) in ethanol (350 c.c.) were shaken with hydrogen at room temperature and pressure. When absorption of hydrogen had ceased, the catalyst was filtered off, and the filtrate immediately added to 10N-hydrochloric acid (15 c.c.) mixed with ethanol (40 c.c.). The ethanol was removed in a vacuum, the residual solid (25 g.) dissolved in warm 0·1N-hydrochloric acid (50 c.c.), and the solution clarified (carbon) and cooled to 10°. Addition of an equal volume of concentrated hydrochloric acid precipitated 6-*amino*-4-*hydroxy*-2-*naphthoic acid hydrochloride*, which was dried in a vacuum (NaOH) (Found : C, 55·35; H, 4·5; N, 6·4; Cl, 14·85. $C_{11}H_9O_3N,HCl$ requires C, 55·1; H, 4·2; N, 5·9; Cl, 14·8%). Cautious addition of dilute aqueous ammonia to an aqueous solution of the hydrochloride yielded the free *amino-acid* as a cream-coloured precipitate which darkened in air (Found : C, 65·45; H, 4·5; N, 7·3. $C_{11}H_9O_3N$ requires C, 65·05; H, 4·45; N, 6·9%).

6-*Chloro*-4-*hydroxy*-2-*naphthoic Acid* (IV; R = Cl).—6-Amino-4-hydroxy-2-naphthoic acid hydrochloride (2·5 g.) was dissolved in water (10 c.c.) and 10N-hydrochloric acid (2·5 c.c.) by warming, and diazotised at 0° by addition of 2N-sodium nitrite (5 c.c.) with stirring. The diazonium salt suspension was added to cuprous chloride (1·2 g.) in hydrochloric acid (20 c.c., *d* 1·18), and the reaction mixture stirred for 1 hour at 20°, after which the temperature was raised to 80° during 15—30 minutes. After cooling, the product was filtered off and dissolved in dilute sodium carbonate, and the clarified (carbon) solution poured into an excess of dilute hydrochloric acid. Crystallisation from methanol gave the *acid*, m. p. 302—304° (Found : Cl, 16·1. $C_{11}H_7O_3Cl$ requires Cl, 15·95%).

Decarboxylation of 6-*Chloro*-4-*hydroxy*-2-*naphthoic Acid*.—The acid (0·5 g.) was heated under reflux with quinoline (5 c.c.) and copper bronze (0·5 g.) for 2¼ hours, and, after the mixture had been cooled, 5N-sodium hydroxide (10 c.c.) was added. After removal of the quinoline by steam-distillation, the liquors were concentrated to 40—50 c.c., clarified (carbon), and treated with carbon dioxide until precipitation was complete. The precipitate was collected and re-dissolved in 0·2N-sodium hydroxide (5 c.c.), the solution filtered, and the filtrate poured into an excess of 2N-hydrochloric acid. The product, purified by crystallisation from hot water, had m. p. 120—121°, not depressed by admixture with an authentic sample of 7-chloro-1-naphthol.

7-*Chloro*-1-*nitronaphthalene*.—A solution of 8-nitro-2-naphthylamine (Saunders and Hamilton, *loc. cit.*) (9·4 g.) in glacial acetic acid (50 c.c.) was added to sodium nitrite (3·5 g.) in sulphuric acid (50 c.c., *d* 1·84) with stirring, the temperature being kept at 15—25° (ice bath). After a further 15 minutes the diazonium salt solution was added with stirring to a solution of cuprous chloride (23·5 g.) in hydrochloric acid (190 c.c., *d* 1·18). After 1 hour, water (470 c.c.) was added, and the product collected and dried at 50°. It was purified by crystallisation from ethanol (carbon); yield, 4·8 g.; m. p. 112° (lit., m. p. 116°).

7-*Chloro*-1-*naphthylamine*.—Raney nickel catalyst (1 g.) was added to 7-chloro-1-nitronaphthalene (4·16 g.) in ethanol (200 c.c.). Reduction was effected by shaking with hydrogen at room temperature and pressure until absorption ceased. After removal of the catalyst and the ethanol, the residue was added to an excess of 10N-hydrochloric acid. The hydrochloride of 7-chloro-1-naphthylamine (m. p. 258°) separated on cooling (Schroeter, *Ber.*, 1930, **63**, 1318, gives m. p. 235—239°).

7-*Chloro*-1-*naphthol*.—7-Chloro-1-naphthylamine (as hydrochloride, 4·28 g.) was diazotised at 0—5° in sulphuric acid (3 c.c., *d* 1·84) and water (20 c.c.) by addition of 2N-sodium nitrite (10 c.c.). The diazonium salt solution was added dropwise to boiling sulphuric acid (150 c.c.; 50% w/w), the product being simultaneously removed by steam-distillation. The aqueous distillate was cooled and the product collected. It was purified by crystallisation from hot water, m. p. 121—122° (lit., m. p. 123°).

Raney nickel catalyst. Catalyst, of activity suitable for the above reactions, was prepared as follows. 11N-Sodium hydroxide (270 c.c.) and water (360 c.c.) were heated to 50° and Raney nickel alloy (150 g.) added during 2 hours with stirring, the temperature being kept below 98°. More 11N-sodium hydroxide (100 c.c.) and water (50 c.c.) were added and the temperature raised to 115°. After 4 hours at 115°, the mixture was cooled, and the catalyst washed twice by decantation, filtered, and washed with water (4 l.) on the filter.

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