

696. *The Hydroxynaphthoate Series. Part I. A Synthesis of 4-Hydroxynaphthoic Acid and its Simple Esters.*

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The synthesis of some potentially fungistatic 4-hydroxynaphthoates is described. The parent acid is obtained by direct oxidation of the aldehyde with alkaline silver oxide, and the *n*-alkyl esters are synthesised by an indirect route *via* 4-benzyloxynaphthaldehyde and the corresponding acid.

THE inhibitory action of the esters of 4-hydroxybenzoic acid against micro-organisms including bacteria, moulds, and yeasts is well known; more recently these compounds have found considerable use as preservatives, and further systematic investigations on the fungistatic activity of the simple and substituted *p*-hydroxybenzoates have been undertaken (Cavill and Vincent, *J. Soc. Chem. Ind.*, 1947, **66**, 175; Cavill, Phillips, and Vincent, *ibid.*, 1949, **68**, 12). Likewise the fungistatic activity of the *p*-aminobenzoates has been demonstrated (Cavill and Vincent, *ibid.*, p. 189) and similarly it is intended to investigate the 4-hydroxynaphthoates.

The present communication reports a new synthesis of 4-hydroxynaphthoic acid and its simple esters.

4-Hydroxynaphthoic acid was first obtained by Heller (*Ber.*, 1912, **45**, 675) by fusion of 4-hydroxynaphthaldehyde with potassium hydroxide. The naphthoic acid was readily decarboxylated; even heating it in aqueous solution for a short time caused evolution of carbon dioxide. An attempt was made to obtain the acid by oxidative fusion with sodium hydroxide in the presence of lead dioxide, but only α -naphthol was identified in the reaction mixture. Ultimately the more recent oxidative procedure described by Pearl (*J. Amer. Chem. Soc.*, 1946, **68**, 431) was adopted, and we now report the controlled oxidation of 4-hydroxynaphthaldehyde with silver oxide in excess of sodium hydroxide solution in conversions of up to 47% of the naphthoic acid, which has been characterised by the formation of the *O*-acetyl derivative. However, the product of this oxidation was difficult to purify and would appear to be contaminated by quinonoid materials.

There is no reference to the preparation of the esters from the parent acid, but Montmollin and Spieler (U.S.P. 1,474,928) synthesised the methyl and the ethyl ester of 4-hydroxynaphthoic acid directly from α -naphthol and carbon tetrachloride, sodium hydroxide, and the alcohol, in the presence of copper powder.

An indirect route to the alkyl 4-hydroxynaphthoates was therefore indicated. 4-Benzyloxynaphthaldehyde was oxidised to 4-benzyloxynaphthoic acid which, in turn, was esterified; hydrogenation of the benzyloxy-ester gave the required alkyl 4-hydroxynaphthoate.

The first step was best carried out by Pearl's procedure; oxidation with potassium permanganate in aqueous acetone was also investigated but this method invariably gave mixtures of the benzyloxynaphthoic acid and α -naphthol (presumably the latter arises from oxidation of the benzyl ether to the benzoyl ester, which is followed by hydrolysis to

the free hydroxynaphthoic acid and then decarboxylation). Esterification of sodium 4-benzyloxynaphthoate with the appropriate *n*-alkyl bromide or iodide required several days' reflux, and the reaction was only partly completed. Reduction of an alcoholic solution of the alkyl benzyloxynaphthoate with hydrogen and Raney nickel gave an almost quantitative yield of the alkyl 4-hydroxynaphthoate. These esters have a green alcoholic ferric reaction, less intense than that of 4-hydroxynaphthaldehyde.

Whilst the reduction of the esters proceeded smoothly, it has not proved possible to reduce the 4-benzyloxynaphthoic acid by the action of hydrogen with Raney nickel, or palladium-charcoal, in alcohol, ethyl acetate, or acetic acid. Thus the parent acid, which gave a red alcoholic ferric reaction and a chocolate precipitate in more concentrated solution (cf. Heller, *loc. cit.*), has so far only been obtained by direct oxidation of 4-hydroxynaphthaldehyde.

The biological activity of these compounds will be reported elsewhere.

EXPERIMENTAL

4-Hydroxynaphthaldehyde.—The aldehyde was prepared by the method of Gattermann and von Horlacher (*Ber.*, 1899, 32, 285), as modified by Adams and Levine (*J. Amer. Chem. Soc.*, 1923, 45, 2373), from α -naphthol with zinc cyanide and hydrogen chloride in dry ether. It was obtained as clusters of needles, m. p. 178—179°, from aqueous alcohol. Adams and Levine record m. p. 178°. The aldehyde gave a green alcoholic ferric reaction and was characterised by the formation of an *oxime*, which crystallised as needles, m. p. 140° (decomp.), from aqueous ethanol (Found: C, 70.7; H, 4.7; N, 7.7. $C_{11}H_9O_2N$ requires C, 70.6; H, 4.8; N, 7.5%). The *O*-acetyl derivative crystallised as long needles, m. p. 99°, from aqueous ethanol (Found: C, 72.7; H, 4.7. Calc. for $C_{13}H_{10}O_3$: C, 72.9; H, 4.7%). Kann *et al.* (*J. Amer. Chem. Soc.*, 1917, 39, 1247) give m. p. 110°.

4-Hydroxynaphthoic Acid.—Silver oxide, prepared from silver nitrate (4.2 g.) and sodium hydroxide (1.0 g.), was suspended in water (25 ml.) and then treated with sodium hydroxide (5 g.). With continuous stirring 4-hydroxynaphthaldehyde (4.4 g.) was added and the temperature of the mixture was increased from 40° to 88—90° and kept there for 90 minutes. The silver was filtered off and washed with water (100 ml.), and the cooled filtrates were acidified with sulphur dioxide and then ether extracted. 4-Hydroxynaphthoic acid was separated from unchanged aldehyde by a sodium hydrogen carbonate extraction. Acidification of the extract with sulphur dioxide followed by ether extraction gave a yellow-reddish solution, which after evaporation at room temperature gave clusters of yellow needles in a red tar. 4-Hydroxynaphthoic acid (1.1 g.) was obtained as small buff needles, m. p. 180° (decomp.), from ethyl acetate-light petroleum (Found: C, 69.7; H, 4.3. Calc. for $C_{11}H_8O_3$: C, 70.2; H, 4.3%). Heller (*Ber.*, 1912, 45, 675) gives m. p. 183—184°. 4-Hydroxynaphthaldehyde (2.3 g.) was recovered. The 4-hydroxynaphthoic acid was characterised as the *O*-acetyl derivative, crystallising as long needles, m. p. 179—180°, from aqueous ethanol (Found: C, 67.6; H, 4.3. Calc. for $C_{13}H_{10}O_4$: C, 67.8; H, 4.4%). Heller (*loc. cit.*) gives m. p. 178—179°. The acid gave a red alcoholic ferric reaction, and a chocolate precipitate in more concentrated solution.

4-Benzyloxynaphthaldehyde.—Sodium ethoxide [from sodium (3 g.) and ethanol (100 ml.)], 4-hydroxynaphthaldehyde (20 g.), and benzyl chloride (14.6 g.) were refluxed for 7 hours. The initial green colour slowly changed to brown during 5 hours. Filtration of the sodium chloride was followed by evaporation of the alcohol under reduced pressure and ether extraction. The washed and dried extract on vacuum distillation gave two fractions, benzyl ethyl ether (4.3 g.), b. p. 42°/3 mm., 185°/760 mm., and a yellow oil, b. p. 200—208°/0.3 mm. Trituration of the latter with light petroleum gave *4-benzyloxynaphthaldehyde* (9.4 g.) which crystallised as rectangular plates, m. p. 75°, from light petroleum (Found: C, 82.1; H, 5.4. $C_{18}H_{14}O_2$ requires C, 82.4; H, 5.4%). The aldehyde was characterised by the formation of an *oxime*, obtained as needles, m. p. 104°, from aqueous ethanol (Found: C, 77.8; H, 5.3; N, 5.2. $C_{18}H_{15}O_2N$ requires C, 78.0; H, 5.4; N, 5.0%).

4-Benzyloxynaphthoic Acid.—(a) Potassium permanganate (0.19 g.) in water (20 ml.) was added during 5 minutes to a boiling solution of 4-benzyloxynaphthaldehyde (0.65 g.) in acetone (50 ml.) and water (30 ml.). After 30 minutes' refluxing the hot solution was filtered and cooled; α -naphthol (0.35 g.), m. p. and mixed m. p. 90°, separated. Filtration and acidification with dilute hydrochloric acid gave crude 4-benzyloxynaphthoic acid (0.05 g.), m. p. 186°.

4-Benzyloxynaphthoic acid crystallised as plates, m. p. 194° [mixed m. p. with product (b) 194°], from ethyl acetate.

(b) Sodium hydroxide (2 g.) was added to silver oxide (1.2 g.) in water (10 ml.). At 55°, 4-benzyloxynaphthaldehyde (1.0 g.) was added, and the temperature of the mixture was increased to and kept at 80—90° for 30 minutes. The silver was filtered off and washed with water (50 ml.), and the combined filtrates were acidified with dilute hydrochloric acid. An ether extraction gave the crude acid (0.88 g.), m. p. 190°, which, when crystallised from ethyl acetate, formed long rectangular plates, m. p. 191—192° (Found: C, 77.6; H, 5.1. $C_{18}H_{14}O_3$ requires C, 77.7; H, 5.1%).

Methyl 4-Benzyloxynaphthoate.—Sodium (0.6 g.) was dissolved in absolute ethanol (100 ml.), and 4-benzyloxynaphthoic acid (2.8 g.) was added with shaking. Methyl iodide (4 g.) was added to the boiling mixture in three portions during 8 hours. After another 8 hours' refluxing the solution was filtered from sodium iodide, and the bulk of the solvent was removed under reduced pressure. The crude ester was extracted with ether, washed with 10% sodium hydroxide solution and then water, and dried. Evaporation of the ethereal solution gave a brown oil (2.1 g.) which solidified on cooling. A vacuum sublimation of the solid at 120—140°/4 × 10⁻³ mm. gave a sublimate, m. p. 61—62°. *Methyl 4-benzyloxynaphthoate* (1.42 g.) crystallised as rectangular plates, m. p. 59—60°, from light petroleum (Found: C, 77.9; H, 5.6. $C_{19}H_{16}O_3$ requires C, 78.0; H, 5.5%). 4-Benzyloxynaphthoic acid (0.4 g.) was recovered.

The following 4-benzyloxynaphthoates were similarly prepared (yields, given in parentheses, are from 2.8 g. of the acid and refer to the pure products; recovery refers to the quantity of unreacted acid recovered): *ethyl* (1.2 g.; recovery, 0.9 g.), needles, m. p. 63—64° (Found: C, 78.2; H, 5.7. $C_{20}H_{18}O_3$ requires C, 78.3; H, 5.9%); *n-propyl* (1.3 g.; recovery, 0.9 g.), prisms, m. p. 67—68° (Found: C, 78.5; H, 6.2. $C_{21}H_{20}O_3$ requires C, 78.7; H, 6.3%); prepared in *n*-propanol; *n-butyl* (0.65 g.; recovery, 0.5 g.), needles, m. p. 51° (Found: C, 79.0; H, 6.6. $C_{22}H_{22}O_3$ requires C, 79.0; H, 6.6%); and *n-amyl* (1.0 g.; recovery, 1.2 g.), b. p. 242—246°/0.8 mm. (Found: C, 79.2; H, 7.0. $C_{23}H_{24}O_3$ requires C, 79.3; H, 6.9%).

Methyl 4-Hydroxynaphthoate.—Methyl 4-benzyloxynaphthoate (0.5 g.) in ethanol (30 ml.) was hydrogenated at room temperature and pressure, in the presence of Raney nickel. Hydrogen (55 ml.) was absorbed during 10 minutes, then, after filtration, the ethanol was removed under reduced pressure and the product crystallised from aqueous ethanol. Methyl 4-hydroxynaphthoate (0.3 g.) was isolated as plates, m. p. 167°, from petroleum-ethyl acetate (Found: C, 71.4; H, 5.1. Calc. for $C_{12}H_{10}O_3$: C, 71.3; H, 5.0%). Montmollin and Spieler (U.S.P. 1,474,928) give m. p. 178°. The ester gave a pale green alcoholic ferric reaction.

The following 4-hydroxynaphthoates were similarly prepared: *ethyl* (0.70 g.; from 1.1 g. of the 4-benzyloxy-compound), small plates, m. p. 136° (Found: C, 72.0; H, 5.6. Calc. for $C_{13}H_{12}O_3$: C, 72.2; H, 5.6%) (Montmollin and Spieler, *loc. cit.*, give m. p. 134°); *n-propyl* (0.62 g.; from 1.0 g.), plates, m. p. 110° (Found: C, 73.0; H, 6.0. $C_{14}H_{14}O_3$ requires C, 73.0; H, 6.1%); *n-butyl* (0.35 g.; from 0.65 g.), plates, m. p. 114° (Found: C, 73.7; H, 6.5. $C_{15}H_{16}O_3$ requires C, 73.7; H, 6.6%); *n-amyl* (0.35 g.; from 0.9 g.), plates, m. p. 100° (Found: C, 74.3; H, 7.0. $C_{16}H_{18}O_3$ requires C, 74.4; H, 7.0%). The last named gave a pale green reaction with alcoholic ferric chloride.

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