A Synthesis of Methyl Homologues of Naphthols and Dihydroxynaphthalenes.

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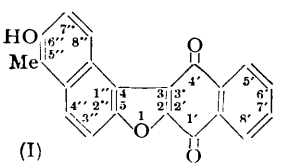
A three-step method for the synthesis of methyl homologues of α- and β-naphthol and of dihydroxynaphthalenes consists of formylation of the corresponding methyl ether, reduction of the naphthaldehyde formed, and subsequent demethylation. Application of this method to α- and β-naphthol and to 2 : 6- and 2 : 7-dihydroxynaphthalene is reported.

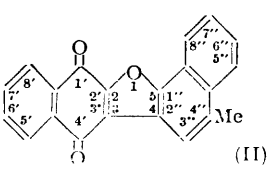
Few convenient methods are known for introducing a methyl group into a β-naphthol. The methods due to Fries and Huebner [*Ber.*, 1906, **39**, 439; cf. Robinson and Weygand (*J.*, 1941, 386), Cornforth and Robinson (*J.*, 1942, 682), and Barclay, Burawoy, and Thompson (*J.*, 1944, 400)] cannot be extended to α-naphthols or dihydroxynaphthalenes and sometimes involve tedious separations. It has now been found that methyl groups can be readily introduced into α- or β-naphthol, or into dihydroxynaphthalenes, by formylation of the corresponding methyl ethers, Wolff–Kishner reduction (Huang-Minlon's technique, *J. Amer. Chem. Soc.*, 1946, **68**, 2487) of the aldehyde, and demethylation with pyridine hydrochloride. This gives excellent overall yields of 1-methyl-2- and 4-methyl-1-naphthol and 1-methyl-2 : 6- and 1-methyl-2 : 7-dihydroxynaphthalene. The reaction sequence can be repeated, and from the last three substances were easily obtained 2 : 4-dimethyl-1-naphthol and 2 : 6-dihydroxy-1 : 5- and 2 : 7-dihydroxy-1 : 8-dimethylnaphthalene respectively.

Formylation of alkyl ethers of β-napthol is known to take place at position 1 (cf. Wood and Bost, *ibid.*, 1937, **59**, 1721; Buu-Hoï, Hoán, and Khenissi, *J.*, 1951, 2307), and this was now proved to hold for ethers of 2 : 6- and 2 : 7-dihydroxynaphthalene by identity of the aldehydes obtained with the methylation products of 2 : 6- and 2 : 7-dihydroxy-1-naphthaldehyde (Gattermann, *Annalen*, 1907, **357**, 313, 341; Morgan and Vining, *J.*, 1921, **119**, 177). Orientation of the formylation products of 1-methoxy- and 1-methoxy-4-methylnaphthalene was established by formation therefrom of the 4-methyl-1-naphthol (Lesser, *Annalen*, 1914, **402**, 1; Elbs and Christ, *J. prakt. Chem.*, 1923, **106**, 17) and 2 : 4-dimethyl-1-naphthol (Cornforth and Robinson, *loc. cit.*). In the formylation of 2 : 6-dimethoxynaphthalene, a small amount of 1 : 5-diformyl derivative was obtained, and this underwent Wolff–Kishner reduction to 2 : 6-dimethoxy-1 : 5-dimethylnaphthalene.

The dihydroxynaphthalenes prepared showed pronounced antioxidant properties, and are being tested for protective effects against lethal radiations (cf. Lacassagne, Duplan, and Buu-Hoï, *J. Nat. Cancer Inst.*, 1955, **15**, 915). With 2 : 3-dichloro-1 : 4-naphtha-



(I)



(II)

quinone (cf. Buu-Hoï, *J.*, 1952, 489) 1-methyl-2 : 6-dihydroxynaphthalene readily gave the quinone (I); the isomeric 1-methyl-2 : 7-dihydroxynaphthalene failed to react, probably on account of steric hindrance. 4-Methyl-1-naphthol gave, as was expected, the quinone (II) (cf. Buu-Hoï and Demerseman, *J.*, 1952, 4699).

In biological tests kindly performed by Dr. Chester Stock (Sloan-Kettering Institute for Cancer Research, New York), 4-methoxy-1-naphthaldehyde thiosemicarbazone inhibited growth of sarcoma 180 in mice, at a daily dose of 250 mg./kg. In tests for tuberculostatic properties *in vitro* (performed by Prof. Welsch, University of Liège), this substance was active against *Mycobacterium tuberculosis*, var. *hominis* (strain H37 Rv), only at a

concentration of $1 : 10^{-4}$, unlike anisaldehyde thiosemicarbazone, which is active at a concentration of $1 : 10^{-6}$.

Experimental

Preparation of 4-Methoxy-1-naphthaldehyde.—To a mixture of 1-methoxynaphthalene (90 g.) and dimethylformamide (47 g., or the equivalent amount of *N*-methylformanilide), phosphorus oxychloride (105 g.) was added portionwise, and the mixture heated for 3 hr. on a water-bath and then shaken with concentrated sodium acetate. The aldehyde was taken up in benzene, and the benzene solution washed with hydrochloric acid (6N), then with water, and dried (Na_2SO_4). The residue from evaporation of the solvent gave on fractionation *in vacuo* 4-methoxy-1-naphthaldehyde (86 g.), b. p. 205—206°/16 mm. Von Auwers and Frühling (*Annalen*, 1921, **422**, 198) gave b. p. 204—205°/15 mm. The *thiosemicarbazone* formed yellowish needles, m. p. 258°, from *n*-propanol (Found : C, 59·9; H, 5·1. $C_{13}H_{13}ON_3S$ requires C, 60·2; H, 5·0%); the *4-oxo-*Δ^2*-thiazolin-2-ylhydrazone*, prepared from the foregoing compound with chloroacetic acid (cf. Buu-Hoï *et al.*, *J.*, 1952, 4590; 1954, 1975), formed pale yellow needles, m. p. 278°, from acetic acid (Found : C, 60·0; H, 4·5. $C_{15}H_{13}O_2N_3S$ requires C, 60·2; H, 4·3%); the iso*nicotinoylhydrazone* formed yellowish prisms, m. p. 246°, from toluene (Found : C, 70·5; H, 4·9. $C_{18}H_{15}O_2N_3$ requires C, 70·8; H, 4·9%).

Preparation of 4-Methyl-1-naphthol.—A mixture of 4-methoxy-1-naphthaldehyde (83 g.), 95% hydrazine hydrate (40 g.), and diethylene glycol (500 c.c.) was heated at 100° for 5 min.; after cooling, potassium hydroxide (30 g.) was added, and the mixture was boiled until evolution of nitrogen ceased (45 min.). After addition of water, the product was taken up in benzene, and the benzene solution washed with dilute hydrochloric acid, then with water, and dried (Na_2SO_4), the solvent evaporated, and the residue fractionated *in vacuo*. 1-Methoxy-4-methylnaphthalene (69·5 g.) was a pale yellow oil, b. p. 154—155°/15 mm.; Kon and Ruzicka (*J.*, 1936, 187) gave b. p. 121°/0·8 mm. A mixture of this ether (34 g.) and pyridine hydrochloride (105 g.) was refluxed for 30 min. Water was added on cooling, and the product was taken up in chloroform and fractionated in a vacuum, giving 4-methyl-1-naphthol (20 g.), b. p. 165—167°/13 mm., which crystallised as silky, colourless needles, m. p. 85°, from ligroin; Lesser (*loc. cit.*) gave m. p. 84—85°. The picrate formed bright red needles, m. p. 179°, from ethanol.

4''-Methyldinaphtho(2′ : 3′-2 : 3)(1'' : 2''-5 : 4)*furan*-1′ : 4′-*quinone* (II).—A solution of 4-methyl-1-naphthol (1 g.) and 2 : 3-dichloro-1 : 4-naphthaquinone (1·4 g.) in dry pyridine (15 c.c.) was refluxed for 10 min.; after cooling, ethanol was added, and the precipitated *quinone* recrystallised from nitrobenzene, giving orange needles, m. p. 275°, and giving with sulphuric acid the dark blue halochromy characteristic of brazanquinones derived from α-naphthols (Found : C, 80·5; H, 4·0. $C_{21}H_{12}O_2$ requires C, 80·8; H, 3·8%).

Preparation of 1-Methyl-2-naphthol.—2-Methoxy-1-naphthaldehyde was obtained in 90% yield as for the isomer, and was characterised by its *thiosemicarbazone*, shiny yellow leaflets, m. p. 166° (from ethanol) (Found : C, 60·1; H, 5·2%), and its iso*nicotinoylhydrazone*, pale yellow leaflets, m. p. 209° (from ethanol) (Found : C, 70·6; H, 5·1%). Reduction gave 2-methoxy-1-methylnaphthalene (80% yield), m. p. 41°; Fries and Huebner (*loc. cit.*) gave m. p. 41—42°. Demethylation by pyridine hydrochloride afforded 1-methyl-2-naphthol (90% yield), m. p. 110—111° (lit., m. p. 111°).

1-Methoxy-4-methyl-2-naphthaldehyde.—A mixture of 1-methoxy-4-methylnaphthalene (69 g.), dimethylformamide (38 g., or the equivalent amount of *N*-methylformanilide), and phosphorus oxychloride (70 g.) was treated in the usual way, to yield 18 g. of *1-methoxy-4-methyl-2-naphthaldehyde*, b. p. 185—186°/12 mm., crystallising as shiny, colourless prisms, m. p. 90°, from ethanol (Found : C, 78·0; H, 6·2. $C_{13}H_{12}O_2$ requires C, 78·0; H, 6·0%), giving a bright red solution in sulphuric acid. The *thiosemicarbazone* formed pale yellow needles, m. p. 266° (decomp. above 240° on prolonged heating), from acetic acid (Found : C, 61·9; H, 5·8. $C_{14}H_{15}ON_3S$ requires C, 61·5; H, 5·5%), and the *4-oxo-*Δ^2*-thiazolin-2-ylhydrazone* formed silky yellow needles, m. p. 299—300°, from acetic acid (Found : C, 61·0; H, 5·1. $C_{16}H_{15}O_2N_3S$ requires C, 61·3; H, 4·8%).

1-Methoxy-2 : 4-dimethylnaphthalene.—The foregoing aldehyde (10 g.) gave, on reduction with hydrazine hydrate (5 g.) and potassium hydroxide (5 g.) in diethylene glycol (150 c.c.), *1-methoxy-2 : 4-dimethylnaphthalene* (6 g.), b. p. 150—151°/12 mm., n_D^{23} 1·6055 (Found : C, 83·8; H, 7·5. $C_{13}H_{14}O$ requires C, 83·9; H, 7·5%). Demethylation as above gave a 92% yield of 2 : 4-dimethyl-1-naphthol, m. p. 82—83° (from ligroin) [picrate (from ethanol), m. p. 144°]. Cornforth *et al.* (*loc. cit.*) gave m. p. 84—85° for the naphthol, and m. p. 143—144° for the picrate.

2 : 7-*Dimethoxy*-1-*naphthaldehyde*.—A mixture of 2 : 7-dimethoxynaphthalene (53 g.) (cf. Ullmann, *Annalen*, 1903, **327**, 104; Fischer and Kern, *J. prakt. Chem.*, 1916, **94**, 34), dimethylformamide (27·5 g.), phosphorus oxychloride (49 g.), and dry toluene (50 c.c.) was heated for 9 hr. on a water-bath, then for a further 30 min. with concentrated sodium acetate (when *N*-methylformanilide was used, heating was not necessary for hydrolysis of the imine). The product was taken up in benzene and treated in the usual way. 2 : 7-*Dimethoxy*-1-*naphthaldehyde* (50 g.), b. p. 230—231°/20 mm., crystallised as prisms, m. p. 98°, from ethanol (Found : C, 72·2; H, 5·5. $C_{13}H_{12}O_3$ requires C, 72·2; H, 5·6%). The same product was obtained by methylation of 2 : 7-dihydroxy-1-naphthaldehyde (Morgan and Vining, *loc. cit.*) with methyl iodide and potassium hydroxide in ethanol. The *thiosemicarbazone* formed yellowish needles, m. p. 183°, from acetic acid (Found : C, 58·0; H, 5·0. $C_{14}H_{15}O_2N_3S$ requires C, 58·1; H, 5·2%); the 4-*oxo*-Δ^2-*thiazolin*-2-*ylhydrazone* formed yellowish needles, m. p. 266°, from acetic acid (Found : C, 58·1; H, 4·3. $C_{16}H_{15}O_3N_3S$ requires C, 58·4; H, 4·6%).

2 : 7-*Dimethoxy*-1-*methylnaphthalene*.—Reduction of the foregoing aldehyde (37 g.) with hydrazine hydrate (16 g.) and potassium hydroxide (16 g.) in diethylene glycol (300 c.c.) yielded 2 : 7-*dimethoxy*-1-*methylnaphthalene* (31 g.), b. p. 178—179°/12 mm., needles, m. p. 58° (from ethanol) (Found : C, 77·0; H, 7·0. $C_{13}H_{14}O_2$ requires C, 77·2; H, 6·9%); the picrate formed red needles, m. p. 106°, from ethanol.

2 : 7-*Dihydroxy*-1-*methylnaphthalene*.—Demethylation of the foregoing methyl ether (3 g.) (15 minutes' boiling with 20 g. of pyridine hydrochloride) afforded 2 : 7-*dihydroxy*-1-*methylnaphthalene* (2·4 g.), colourless needles, m. p. 150° (from toluene) (Found : C, 75·6; H, 5·8. $C_{11}H_{10}O_2$ requires C, 75·9; H, 5·7%); the picrate formed brown-red needles, m. p. 169°, from methanol. This naphthol gave yellow solutions in aqueous sodium hydroxide, and did not react with 2 : 3-dichloro-1 : 4-naphthaquinone in pyridine; it readily autoxidised in solution.

2 : 7-*Dimethoxy*-8-*methyl*-1-*naphthaldehyde*.—A mixture of 2 : 7-dimethoxy-1-methylnaphthalene (27·5 g.), dimethylformamide (12·5 g.), phosphorus oxychloride (23·5 g.), and toluene (25 c.c.) was treated as for the lower homologue, to yield 26 g. of 2 : 7-*dimethoxy*-8-*methyl*-1-*naphthaldehyde*, b. p. 232—233°/14 mm., pale yellow needles, m. p. 96° (from ethanol) (Found : C, 72·9; H, 6·1. $C_{14}H_{14}O_3$ requires C, 73·0; H, 6·1%).

2 : 7-*Dimethoxy*-1 : 8-*dimethylnaphthalene*.—Obtained by reducing the foregoing aldehyde (20 g.) with hydrazine hydrate (10 g.) and potassium hydroxide (10 g.) in diethylene glycol, this *ether* (14 g.), b. p. 199—200°/16 mm., formed colourless needles, m. p. 101°, from ethanol (Found : C, 77·7; H, 7·6. $C_{14}H_{16}O_2$ requires C, 77·8; H, 7·4%), and gave a picrate crystallising as brown-red needles, m. p. 118°, from ethanol.

2 : 7-*Dihydroxy*-1 : 8-*dimethylnaphthalene*.—Obtained from the foregoing methyl ether (5 g.) and pyridine hydrochloride (30 g.), 2 : 7-*dihydroxy*-1 : 8-*dimethylnaphthalene* (3·9 g.) formed colourless needles, m. p. 151—152°, from toluene, giving in aqueous sodium hydroxide a yellow solution (Found : C, 76·3; H, 6·5. $C_{12}H_{12}O_2$ requires C, 76·6; H, 6·4%).

Formylation of 2 : 6-*Dimethoxynaphthalene*.—A mixture of 2 : 6-dimethoxynaphthalene (34·5 g.) (cf. Willstätter and Parnas, *Ber.*, 1907, **40**, 1406), dimethylformamide (17·5 g.), phosphorus oxychloride (32 g.), and toluene (25 c.c.), treated in the usual way, yielded : (*a*) a benzene-soluble portion, which gave on vacuum-distillation 2 : 6-*dimethoxy*-1-*naphthaldehyde* (32 g.), b. p. 223—225°/15 mm., yellowish prisms, m. p. 90° (from ethanol) (Found : C, 72·0; H, 5·6%) [*thiosemicarbazone*, greenish-yellow prisms, m. p. 215° (decomp. above 195° on prolonged heating), from ethanol (Found : C, 58·4; H, 5·3%); 4-*oxo*-Δ^2-*thiazolin*-2-*ylhydrazone*, yellow needles, m. p. 274°, from acetic acid (Found : C, 58·5; H, 4·5%); identical with the dimethylation product of 1-formyl-2 : 6-dihydroxynaphthalene with methyl iodide and potassium hydroxide in ethanol]; and (*b*) a benzene-insoluble portion (2 g.), consisting of 1 : 5-*diformyl*-2 : 6-*dimethoxynaphthalene*, bright yellow, sublimable needles, m. p. 273° (from acetic acid), giving a red halochromy in sulphuric acid (Found : C, 68·9; H, 5·0. $C_{14}H_{12}O_4$ requires C, 68·9; H, 4·9%).

2 : 6-*Dimethoxy*-1-*methylnaphthalene*.—Prepared from 1-formyl-2 : 6-dimethoxynaphthalene (27 g.), hydrazine hydrate (12 g.), and potassium hydroxide (12 g.) in diethylene glycol, this *ether* (22·1 g.), b. p. 185°/15 mm., formed colourless needles, m. p. 109°, from ethanol (Found : C, 77·1; H, 7·0%), giving a brown-red picrate (from benzene), m. p. 123°.

2 : 6-*Dihydroxy*-1-*methylnaphthalene*.—Prepared from the foregoing ether (3 g.) and pyridine hydrochloride (20 g.), this *compound* (2·1 g.) crystallised as sublimable needles, m. p. 206°, from toluene (Found : C, 76·3; H, 6·3%), which gave yellow solutions in aqueous sodium hydroxide. 6″-*Hydroxy*-5″-*methyldinaphtho*(2′ : 3′-2 : 3)(1″ : 2″-4 : 5)*furan*-1′ : 4′-*quinone*, prepared from this compound (1 g.), 2 : 3-dichloro-1 : 4-naphthaquinone, and pyridine (12 c.c.), formed brown-red

prisms, m. p. 233—234° (decomp.) (from nitrobenzene), giving with sulphuric acid the deep turquoise colour characteristic of brasanquinones derived from β-naphthols (Found : C, 76·6; H, 3·7. $C_{21}H_{12}O_4$ requires C, 76·8; H, 3·7%).

2 : 6-*Dimethoxy*-5-*methyl*-1-*naphthaldehyde*.—Prepared from 2 : 6-dimethoxy-1-methylnaphthalene (16 g.), dimethylformamide (7·5 g.), and phosphorus oxychloride (14 g.) in toluene (10 c.c.), this *aldehyde* (13·8 g.), b. p. 236—237°/15 mm., formed yellow prisms, m. p. 165°, from ethanol (Found : C, 73·1; H, 6·3%), giving a deep red colour with sulphuric acid; the *thiosemicarbazone* formed yellow leaflets, m. p. 240—241° (decomp. above 230° on prolonged heating), from acetic acid (Found : C, 59·0; H, 5·7. $C_{15}H_{17}O_2N_3S$ requires C, 59·4; H, 5·6%).

2 : 6-*Dimethoxy*-1 : 5-*dimethylnaphthalene*.—This compound (7·5 g.), obtained from the foregoing aldehyde (9·5 g.), hydrazine hydrate (4 g.), and potassium hydroxide (4 g.) in diethylene glycol (200 c.c.), crystallised as leaflets, m. p. 183°, b. p. 199—200°/17 mm., from ethanol (Found : C, 77·7; H, 7·4%), and gave a dark brown picrate, m. p. 133°, from benzene. The same substance was obtained on reduction of 1 : 5-diformyl-2 : 6-dimethoxynaphthalene.

2 : 6-*Dihydroxy*-1 : 5-*dimethylnaphthalene*.—This *substance* crystallised as sublimable needles. m. p. 298°, from acetic acid, becoming violet on exposure to the air and light (Found : C, 76·3; H, 6·2%), and soluble in aqueous alkalis; it autoxidised in solution much less readily than its 2 : 7-dihydroxy-isomer.

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