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718. *Synthesis of Lapachenole.*

By R. Livingstone and R. B. Watson.

The synthesis by two independent routes is described of 4′-methoxy-6 : 6-dimethylnaphtho(1′ : 2′-2 : 3)pyran (I) which is identical with lapachenole [1] isolated from the heartwood of " Brazilian white peroba " (*Paratecoma alba*).

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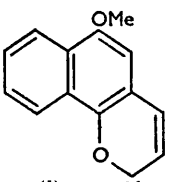
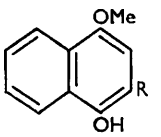
The first method for the synthesis of 4′-methoxy-6 : 6-dimethylnaphtho(1′ : 2′-2 : 3)pyran (I) was based on the formation of the coumarin system from 1-hydroxy-4-methoxy-2-naphthaldehyde (II; R = CHO). Friedlander's method [2] for the preparation of the aldehyde (II; R = CHO) could not be repeated and the sodium–amalgam reduction of 1-hydroxy-4-methoxy-2-naphthoic acid (II; R = CO_2H) was therefore considered. Weil [3] obtained a 60% yield of salicylaldehyde from salicylic acid in the presence of boric acid and a primary amine; this method also gave good yields with 1-hydroxy-2-naphthoic acid and 2 : 3-, 2 : 5-, and 2 : 4-hydroxytoluic acids but failed with 1-naphthoic acid, 3-acetoxy-2-naphthoic acid, and quinol- and pyrogallol-carboxylic acids.

The acid (II; R = CO_2H) was eventually prepared by Homeyer and Wallingford's method [4] from 1 : 4-dihydroxy-2-naphthoic acid. Reduction of the acid (II; R = CO_2H) by 2½% sodium amalgam gave only a 3% yield of the aldehyde (II; R = CHO). Preparation from 4-methoxy-1-naphthol by Reimer–Tiemann reaction as developed by Rubenstein,[5] and from methyl 1-hydroxy-4-methoxy-2-naphthoate (IIIc) by the McFadyen–Stevens method [6] both gave a 2% yield of the desired aldehyde.

Methyl 1-hydroxy-4-methoxy-2-naphthoate was therefore reduced to 2-hydroxymethyl-4-methoxy-1-naphthol (II; R = CH_2·OH) by means of lithium aluminium hydride, in 45% yield when Nystrom and Brown's [7] method was followed. Direct reduction of the acid (II; R = CO_2H) with lithium aluminium hydride gave alcohol (II; R = CH_2·OH) in 35% yield.



(I)



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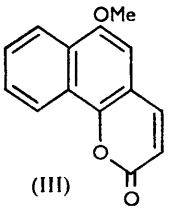

(III)

This was then oxidised by the Oppenauer method, *p*-benzoquinone being used as hydrogen acceptor, in 52% yield, and the aldehyde (II; R = CHO) was then converted into 6-methoxy-7 : 8-benzocoumarin (III) by Perkin's method. Attempts to prepare the benzocoumarin (III) from 4-methoxy-1-naphthol, malic acid, and concentrated sulphuric acid failed to give any identifiable product. 4-Methoxy-1-naphthol was prepared in 88% yield by the decarboxylation of 1-hydroxy-4-methoxy-2-naphthoic acid.

Reaction of 6-methoxy-7 : 8-benzocoumarin (III) with excess of methylmagnesium iodide gave 4′-methoxy-6 : 6-dimethylnaphtho(1′ : 2′-2 : 3)pyran as a gum; decomposition of its picrate by chromatography gave a product identical with lapachenole (I). The identity of the product was also confirmed by treatment with formic acid, giving lapachenole dimer.[1]

In the second synthesis, 6-methoxy-2 : 2-dimethyl-7 : 8-benzochroman-4-one (IV) was obtained by an extension of the method for the preparation of substituted chromanones.[8]

[1] Livingstone and Whiting, *J.*, 1955, 3631.
[2] Friedlander, *Ber.*, 1908, **41**, 1035.
[3] Weil, *ibid.*, p. 4147; 1921, **54**, 3217; 1922, **55**, 224, 2664.
[4] Homeyer and Wallingford, *J. Amer. Chem. Soc.*, 1942, **64**, 798.
[5] Rubenstein, *J.*, 1925, **127**, 1998.
[6] McFadyen and Stevens, *J.*, 1936, 584.
[7] Nystrom and Brown, *J. Amer. Chem. Soc.*, 1947, **69**, 2548.
[8] Cavill, Dean, McGookin, Marshall, and Robertson, *J.*, 1954, 4573.

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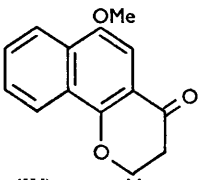
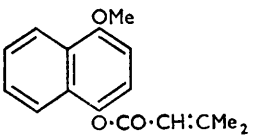
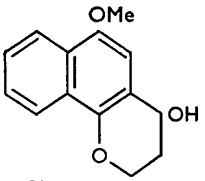
Esterification of 4-methoxy-1-naphthol with ββ-dimethylacryloyl chloride [9,10] by Fries rearrangement of the product (V) in the absence of solvent, followed by acidic isomerisation and ring closure, gave the benzochromanone (IV). Reduction by lithium aluminium



(IV)



(V)



(VI)

hydride readily gave the corresponding chromanol (VI). The removal of water by Klages's method [10] or with acetic anhydride was unsuccessful but on treatment with syrupy phosphoric acid lapachenole dimer was obtained.

Pyrolysis of the acetate of (VI) gave lapachenole.

Experimental

1-Hydroxy-4-methoxy-2-naphthoic Acid (II; R = CO_2H) *and Methyl 1-Hydroxy-4-methoxy-2-naphthoate.*—1 : 4-Dihydroxy-2-naphthoic acid [4] (20 g.) in methanol (280 g.) was cooled in ice and saturated with dry hydrogen chloride. The solution was refluxed for 3 hr., cooled, and resaturated with hydrogen chloride. After 18 hr. at room temperature, the mixture was added to water and the solid filtered off, washed, and dried.

An ethereal solution of the product was extracted with dilute sodium hydrogen carbonate solution; acidification of the extract and recrystallisation from aqueous ethanol gave 1-hydroxy-4-methoxy-2-naphthoic acid (6·1 g.), m. p. 194—196° (decomp.) [Homeyer and Wallingford [4] give m. p. 196—198° (decomp.)].

Evaporation of solvent from the ethereal fraction gave methyl 1-hydroxy-4-methoxy-2-naphthoate (10·9 g.), forming pale cream needles, m. p. 136—138° after recrystallisation (Homeyer and Wallingford [4] give m. p. 137—138°).

4-Methoxy-1-naphthol.—1-Hydroxy-4-methoxy-2-naphthoic acid (6·2 g.) was heated at 210—215° for 30 min., the loss agreeing with that expected for loss of carbon dioxide. The product was extracted with ether and the ethereal solution extracted with sodium hydroxide solution containing a little sodium dithionite. Acidification of the extract with ice–dilute hydrochloric acid and recrystallisation of the product from light petroleum (b. p. 80—100°) gave 4-methoxy-1-naphthol as needles (4·1 g.), m. p. and mixed m. p. 124—125°.

2-Hydroxymethyl-4-methoxy-1-naphthol (II; R = CH_2·OH).—(1) A suspension of lithium aluminium hydride (0·9 g.) in dry ether (230 c.c.) was boiled in a flask equipped with a Soxhlet extractor containing methyl 1-hydroxy-4-methoxy-2-naphthoate (4 g.) in the thimble. After 2½ hr. the mixture was cooled and water added, followed by ice–10% sulphuric acid. The ethereal layer was washed with water and dried. Removal of solvent and recrystallisation of the residue from chloroform–light petroleum (b. p. 80—100°) gave needles (1·6 g.), m. p. 95—97° of the *alcohol* (Found: C, 71·3; H, 5·85. $C_{12}H_{12}O_3$ requires C, 70·6; H, 5·9%).

(2) 1-Hydroxy-4-methoxy-2-naphthoic acid (4·3 g.) was reduced in the same way. After the decomposition of the complex, the ethereal layer was separated and extracted with sodium hydrogen carbonate solution. This aqueous solution when acidified gave 1-hydroxy-4-methoxy-2-naphthoic acid (1·35 g.). The ethereal solution was washed with water and dried. Evaporation of solvent and crystallisation of the product from chloroform–light petroleum (b. p. 80—100°) gave 2-hydroxymethyl-4-methoxy-1-naphthol (1·4 g.), m. p. 95—97°.

1-Hydroxy-4-methoxy-2-naphthaldehyde (II; R = CHO).—A solution of aluminium *tert.*-butoxide (1·2 g.) in dry benzene (30 c.c.) was added to one of 2-hydroxymethyl-4-methoxy-1-naphthol (2·7 g.) and *p*-benzoquinone (4 g.) in dry benzene (30 c.c.). The solution was refluxed for 1 hr. and the excess of benzene and *p*-benzoquinone then removed by steam distillation. The flask was cooled, concentrated sulphuric acid (2 c.c.) added, and the reaction mixture then steam-distilled for a further 6—8 hr. The yellow solid in the distillate was recrystallised from

[9] Bridge, Heys, and Robertson, *J.*, 1937, 283.
[10] Klages, *Ber.*, 1904, **37**, 3987.

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petroleum (b. p. 60—80°), giving 1-hydroxy-4-methoxy-2-naphthaldehyde (5·2 g., 52%) as yellow needles, m. p. 99—100° (Friedlander [2] gives m. p. 100°).

6-Methoxy-7 : 8-benzocoumarin (III). 1-Hydroxy-4-methoxy-2-naphthaldehyde (6 g.), acetic anhydride (6·5 c.c.), fused potassium acetate (3 g.), and iodine (0·05 g.) were heated at 120—125° for 2 hr., and then at 165—170° for 5 hr. The mixture was poured into warm water and set aside overnight. The solid was filtered off, washed with 2% sodium hydroxide solution (50 c.c.) and then water, dried, and crystallised from acetic acid by addition of water. *6-Methoxy-7 : 8-benzocoumarin* (3·8 g., 56%) formed fine yellowish-white needles, m. p. 132—134° (Found : C, 74·4; H, 4·7. $C_{14}H_{10}O_3$ requires C, 74·3; H, 4·4%); its solution in concentrated sulphuric acid was yellowish-green with a slight greenish-blue fluorescence.

4′-Methoxy-6 : 6-dimethylnaphtho(1′ : 2′-2 : 3)pyran.—6-Methoxy-7 : 8-benzocoumarin (3·7 g.) in dry benzene (100 c.c.) was added slowly (1 hour) to a stirred Grignard solution prepared from methyl iodide (9·7 g.), magnesium (1·8 g.), and ether (80 c.c.). The reddish solution was refluxed for 1 hr. and then set aside overnight. Decomposition by 22% ammonium chloride solution (75 c.c.) and extraction with ether gave a red ethereal solution, which was washed with water and dried ($CaCl_2$). Removal of solvent and distillation of the residue gave an oil (0·7 g.), b. p. 130—150°/20 mm.

Steam-distillation of the product (0·48 g.) gave a volatile fraction (0·23 g.), which again did not solidify. Addition of a saturated methanolic solution of picric acid and crystallisation from methanol gave dark-violet needles (0·15 g.), m. p. 145—147° undepressed on admixture with an authentic specimen of lapachonole picrate. The picrate was dissolved in ether and decomposed by chromatography to give a gum, which on crystallisation from light petroleum (b. p. 40—60°) formed needles (0·03 g.), m. p. 57—59° undepressed on admixture with natural lapachenole [1] (Found : C, 80·2; H, 6·55. $C_{16}H_{16}O_2$ requires C, 80·0; H, 6·65%).

Lapachenole Dimer.—A mixture of the crude distillation product (0·2 g.) and formic acid (6 c.c.; s.g. 1·2) was heated on a steam-bath for 1 hr. The mixture was cooled and the precipitate separated by filtration, washed with sodium hydrogen carbonate solution and water, and dried. Crystallisation from ethyl acetate afforded needles (0·1 g.), m. p. 255—256° undepressed on admixture with authentic lapachenole dimer.[1]

4-Methoxy-1-naphthyl ββ-Dimethylacrylate (V).—4-Methoxynaphthol (IV) (7 g.), ββ-dimethylacryloyl chloride [10] (8 g.; b. p. 47°/11 mm.), magnesium (0·6 g.), and benzene (60 c.c.) were refluxed for 1 hr. Distillation of the oily *product* gave a fraction (6·55 g.), b. p. 214—215°/4 mm., crystallising in yellowish squat prisms, m. p. 64—65° (Found : C, 74·9; H, 6·4. $C_{16}H_{16}O_3$ requires C, 75·0; H, 6·3%).

6-Methoxy-2 : 2-dimethyl-7 : 8-benzochroman-4-one (IV).—4-Methoxy-1-naphthyl ββ-dimethylacrylate (6·5 g.) and anhydrous aluminium chloride (8 g.) were heated at 140—150° for 3 hr. Addition of hydrochloric acid (1 : 1; 40 c.c.), isolation with ether–chloroform (4 : 1), and removal of the solvent gave a gum (5·5 g.).

This was extracted with dry methanol (200 c.c.); after filtration the methanolic solution was saturated with dry hydrogen chloride, warmed on a steam-bath for 3 hr., cooled, resaturated with dry hydrogen chloride, and set aside overnight. Water (70 c.c.) was added and the alcohol removed by distillation. The cooled residue was saturated with ammonium sulphate, and the oil dissolved in ether.

Evaporation of solvent gave a gum (4·4 g.), which was boiled with ethanol (130 c.c.) and hydrochloric acid (3%; 100 c.c.) for 24 hr., and then set aside at room temperature for 36 hr. After distillation of ethanol (130 c.c.), the residue was diluted with saturated ammonium sulphate solution. The mixture was extracted with ether (3 × 150 c.c.), and the ethereal solution washed with sodium hydroxide solution, and water. Evaporation of the dried ($CaCl_2$) extract gave a brownish-yellow solid (1·8 g.) which was chromatographed on alumina from benzene solution. Removal of solvent and crystallisation from aqueous ethanol afforded *6-methoxy-2 : 2-dimethyl-7 : 8-benzochroman-4-one* as cream needles (1·2 g.), m. p. 120·5—121·5° (Found : C, 74·9; H, 6·2. $C_{16}H_{16}O_3$ requires C, 75·0; H, 6·3%).

6-Methoxy-2 : 2-dimethyl-7 : 8-benzochroman-4-ol (VI).—6-Methoxy-2 : 2-dimethyl-7 : 8-benzochroman-4-one (1 g.) in ether (25 c.c.) was slowly added to an excess of lithium aluminium hydride in ether. The solution was refluxed for 1 hr. and set aside at room temperature for a further 1 hr. After decomposition, the ethereal layer was separated and the aqueous layer extracted with ether after being saturated with ammonium sulphate. The combined ethereal solutions were washed with sodium hydrogen carbonate solution and water. Evaporation of solvent and crystallisation from aqueous ethanol gave fine needles, m. p. 107·5—109° (Found : C, 74·1; H, 6·8. $C_{16}H_{18}O_3$ requires C, 74·4; H, 7·0%).

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Lapachenole (I).—Acetic anhydride (1 c.c.) was slowly added to a well-cooled solution of 6-*methoxy*-2 : 2-*dimethyl*-7 : 8-*benzochroman*-4-*ol* (0·35 g.) in pyridine (5 c.c.). After 2 hours at room temperature the solution was poured into ice–hydrochloric acid. The product was isolated with ether and the ethereal solution repeatedly washed with dilute hydrochloric acid. Removal of solvent yielded a gum (0·35 g.) which was heated at 180—190° for 1 hr. at 13—14 mm. in a wide tube fitted with a cooled finger and connected with a cooled trap. An ethereal solution of the distillate and residue was washed with sodium hydrogen carbonate solution and with water. Evaporation of the dried extract gave a brown gum (0·2 g.); addition of a saturated methanolic solution of picric acid and crystallisation from methanol gave dark-violet needles (0·25 g.), m. p. 148—149° undepressed on admixture with authentic lapachenole picrate. The picrate in ether was decomposed by chromatography; the product (0·13 g.) after crystallisation from light petroleum (b. p. 40—60°) had m. p. 57—59°, undepressed on admixture with authentic lapachenole.

Lapachenole Dimer.—6-Methoxy-2 : 2-dimethyl-7 : 8-benzochroman-4-ol (0·05 g.) was heated with syrupy phosphoric acid (5 c.c.) at 180° for ¾ hr. The mixture was poured into water and the product extracted with ether. Removal of solvent from the cleaned and dried extract gave a gum (0·01 g.), which was triturated with methanol. Recrystallisation of the product from ethyl acetate gave needles (0·004 g.), m. p. 245—254° undepressed on admixture with authentic lapachenole dimer.

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