817. *Some Derivatives of 2 : 3-Dihydroxynaphthalene.*

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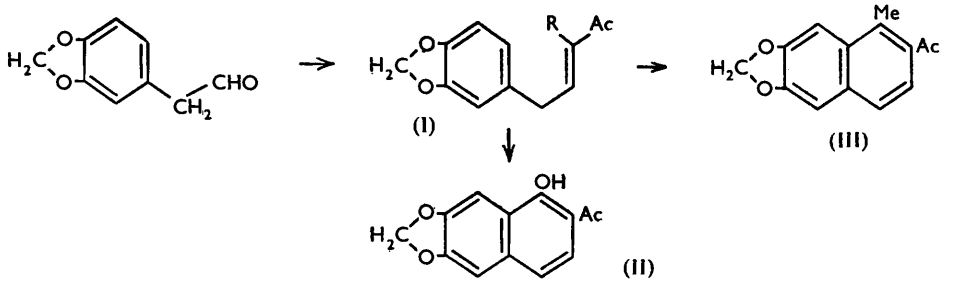
2-Acetyl-6 : 7-dimethoxy-1-methylnaphthalene, 2-acetyl-1-methyl-6 : 7-methylenedioxynaphthalene, and some related compounds have been synthesised.

2-Acetyl-6 : 7-dihydroxy-1-methylnaphthalene was required for a projected synthesis. This compound has not yet been prepared, although derivatives have now been made by several methods.

1-Methylnaphthalene-2-carboxylic acid has been prepared by cyclisation and dehydrogenation of ethyl β-phenethylacetoacetate [1] and in the first instance an attempt was made to extend this method to the preparation of the dimethoxy-compound. 3 : 4-Dimethoxyphenethyl alcohol, prepared by Fulton and Robinson [2] by Bouveault–Blanc reduction of ethyl homoveratrate, was obtained in higher yield by the reduction of this ester with lithium aluminium hydride, and, better, by interaction of 3 : 4-dimethoxyphenyl-lithium and ethylene oxide. The lithium derivative was prepared by the interaction of 4-bromoveratrole and butyl-lithium, and the essential condition [3] for the interchange was that reaction should be carried out below −50° : at higher temperatures 3 : 4 : 3′ : 4′-tetramethoxydiphenyl was obtained, at −10° in >80% yield. The alcohol was converted by thionyl chloride into 3 : 4-dimethoxyphenethyl chloride, which however with ethyl sodioacetoacetate gave only a low-boiling liquid, probably 3 : 4-dimethoxystyrene.

An alternative route to the required keto-ester appeared to be condensation of homoveratraldehyde with ethyl acetoacetate, followed by hydrogenation : alternatively, cyclisation of the condensation product before hydrogenation might lead directly to a naphthalene derivative. It was found more convenient to use homopiperonaldehyde, which Erdtman and Robinson have prepared [4] by lead tetra-acetate oxidation of safrole glycol, itself made by permanganate oxidation of safrole. We found it easier experimentally to use performic acid for the hydroxylation of safrole. Homopiperonaldehyde condensed readily with ethyl acetoacetate in the presence of pyridine, but the product (I; R = CO_2Et), on distillation in a high vacuum, lost ethanol and gave a substance which is considered to be 2-acetyl-1-hydroxy-6 : 7-methylenedioxynaphthalene (II) : it is insoluble in alkali but gives a green ferric chloride colour.



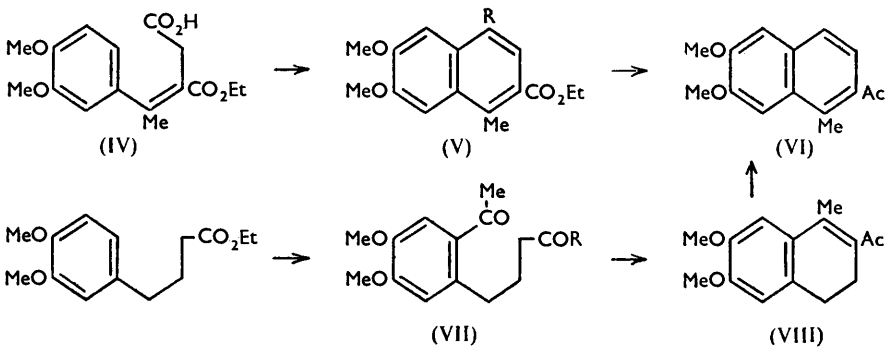
To avoid this cyclisation, the symmetrical product (I; R = Ac) from homopiperonaldehyde and acetylacetone was prepared. This proved to be stable on distillation, but was rather resistant to cyclisation, being unattacked by formic acid, or by toluene-*p*-sulphonic acid or iodine in boiling benzene, and was decomposed by sulphuric acid or by

[1] Auwers and Möller, *J. prakt. Chem.*, 1925, **109**, 148.
[2] Fulton and Robinson, *J.*, 1933, 1463.
[3] Calvin, Heidelberger, Reid, Talbert, and Yankwich, "Isotopic Carbon," John Wiley and Sons, New York, 1949, p. 183.
[4] Erdtman and Robinson, *J.*, 1933, 1530.

bases. However, on treatment with hydrogen chloride in chloroform a substance, m. p. 134°, was obtained which had lost one molecule of water, no longer gave a ferric chloride colour, and was stable to alkali. The structure, 2-acetyl-1-methyl-6 : 7-methylenedioxynaphthalene (III), is proposed for this compound.

In view of the known difficulty of removing methylenedioxy-groups this work was now repeated with methyleugenol in place of safrole. Homoveratraldehyde condensed readily with ethyl acetoacetate and with acetylacetone, but in contrast to the behaviour of the methylenedioxy-compounds, neither of the products could be cyclised.

Attention was next turned to the Stobbe reaction between acetoveratrone and diethyl succinate. The half-ester (IV) was obtained in high yield in the presence of sodium hydride. The crude product, when refluxed with acetic anhydride and sodium acetate, gave a moderate yield of a crystalline product. In view of the known high reactivity of veratrole derivatives in positions 4 and 5, this product is taken to be ethyl 4-acetoxy-6 : 7-dimethoxy-1-methylnaphthalene-2-carboxylate (V; R = OAc). Treatment with sodium



ethoxide gave the free phenol. In order to remove the phenolic hydroxyl group, this compound was converted into the toluene-*p*-sulphonate, which was refluxed with Raney nickel in ethanol (cf. Kenner and Murray [5]), but gave only a small yield of substance giving analytical figures for the expected ethyl 6 : 7-dimethoxy-1-methylnapthalene-2-carboxylate (V; R = H), the major part of the ester being hydrolysed back to the phenol.

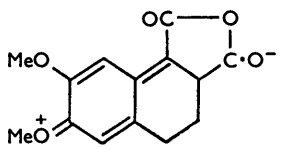
The ethyl ester (V) was converted into the acid chloride, which with dimethylcadmium gave 2-acetyl-6 : 7-dimethoxy-1-methylnaphthalene (VI), identical with a specimen prepared more conveniently from 3-(2-acetyl-4 : 5-dimethoxyphenyl)propyl methyl ketone (VII; R = Me). For the preparation of this ketone, ethyl γ-3 : 4-dimethoxyphenylbutyrate was acetylated by the Friedel–Crafts method, the product being isolated as the acid (VII; R = OH) in 60% yield (an attempt was made to cyclise the ethyl ester of this compound, but it was unchanged by sodium ethoxide in ethanol). The derived acid chloride (VII; R = Cl) with dimethylcadmium formed the methyl ketone (VII; R = Me) which was cyclised by sodium ethoxide to 2-acetyl-3 : 4-dihydro-6 : 7-dimethoxy-1-methylnaphthalene (VIII) in 60% overall yield from the acid.

The intermediate diketone (VII; R = Me) could be isolated if desired, although this was inadvisable as it was rather soluble; it could then be cyclised with sodium ethoxide or with acid in quantitative yield. The dihydronaphthalene was dehydrogenated by sulphur or palladium to the required naphthalene derivative (VI). Unfortunately the methoxy-groups in this compound have only been removed under conditions which lead to extensive decomposition.

6 : 7-Dimethoxynaphthalene-1 : 2-dicarboxylic acid has also been prepared. Ethyl γ-3 : 4-dimethoxyphenylbutyrate was condensed with diethyl oxalate, and the product cyclised with sulphuric acid in phosphoric acid, yielding the dihydronaphthalene which was

[5] Kenner and Murray, *J.*, 1949, S 178.

dehydrogenated with sulphur. 3 : 4-Dihydro-6 : 7-dimethoxynaphthalene-1 : 2-dicarboxylic acid, formed by hydrolysis of the ester, crystallised in yellow needles which readily formed the anhydride. This change was most striking, as the anhydride, previously prepared by Fieser and Hershberg [6] and by Bruckner,[7] has an intense red colour. In the fully aromatic series the anhydride [7] was again more deeply coloured than the ester, but not nearly so intensely. The colour of the anhydride is probably concerned with the formation of the extended quinonoid system (IX), in which it might be expected that the more strongly electron-attracting anhydride substituent would give rise to a more intense colour than the ester. This cannot, however, be the whole answer, otherwise the ketone (VIII) would be yet more strongly coloured, which is not so. Cross-conjugation due to the second carbonyl group may also assist, but this is again not more than a part of the answer. It seems probable that the inclusion of the carbonyl group in a ring may be a major contributing factor. The lower intensity of colour in the fully aromatic compounds can be explained since in these compounds formation of the quinonoid structure involves loss of the resonance energy of a naphthalene nucleus, instead of that of only one benzene ring.



(IX)

Experimental

3 : 4-*Dimethoxyphenethyl Alcohol.*—(*a*) To a solution of lithium aluminium hydride (8 g.) in ether (250 ml.) was added ethyl homoveratrate (31 g.) in ether (50 ml.) with striring. The whole was then refluxed for 0·5 hr. and excess of hydride destroyed by the addition of methanol in ether. The ethereal solution was washed with dilute acid and water and evaporated and the residue distilled (b. p. 178°/16 mm.). The distillate, 3 : 4-dimethoxyphenethyl alcohol, formed colourless prisms (18 g. 72%), m. p. 42—43°, from ether–light petroleum (Found : C, 66·2; H, 7·6. Calc. for $C_{10}H_{14}O_3$: C, 65·9; H, 7·7%). Fulton and Robinson [2] give m. p. 48°.

(*b*) To a solution of butyl-lithium prepared from lithium (5 g.) and *n*-butyl bromide (45 g.) in ether (400 ml.) was added at −60°, with stirring, 4-bromoveratrole (70 g.) in ether (200 ml.). The thick suspension obtained was allowed to warm to about −40° and ethylene oxide (40 g.) added slowly, the temperature being kept below about −10°. Then the mixture was stirred for 1 hr. at 0°, and washed with hydrochloric acid and with water, and the product distilled. After crystallisation from ether–light petroleum the alcohol (42 g., 73%) was obtained with m. p. 43°.

3 : 4 : 3′ : 4′-*Tetramethoxydiphenyl.*—To a solution of butyl-lithium from lithium (3·5 g.) and butyl bromide (34 g.) in ether (200 ml.) was added at 0° 4-bromoveratrole (50 g.) in ether (100 ml.). Ethylene oxide (20 g.) was then added, and the solution kept at 0° for 1 hr., washed with hydrochloric acid and with water, and evaporated. The residue, crystallised from ethanol, gave 3 : 4 : 3′ : 4′-tetramethoxydiphenyl (21 g.), m. p. 133—134° (Found : C, 70·3; H, 6·5. Calc. for $C_{16}H_{18}O_4$: C, 70·1; H, 6·6%).

Safrole Glycol.—Safrole (158 g.) was stirred with 90% formic acid (450 ml.) and 30% hydrogen peroxide (140 ml.) at <25°. After 24 hr. the solution was heated to 40° and stirred until per-acid was no longer detectable (about 3 hr.). The acid was then evaporated in a vacuum on the steam-bath, and the residue hydrolysed for a few minutes with an excess of warm 20% aqueous potassium hydroxide. The solution was then continuously extracted for 12 hr. with ether, the ether evaporated, and the residue distilled. After safrole (44 g.) had been removed at 125°/15 mm. the pressure was reduced and safrole glycol distilled at 176°/0·15 mm. Crystallisation from benzene gave 69 g. (35%) of glycol, m. p. 69°.

Homopiperonaldehyde.—Safrole glycol (45 g.) in benzene (76 ml.) was added to lead tetra-acetate (103 g.) in benzene (455 ml.). After 2 hr. (occasional shaking), the solution was filtered from precipitated lead diacetate, washed with sodium hydrogen carbonate solution and with water, and evaporated. Homopiperonaldehyde (31 g., 82%) distilled at 147/0·8 mm. (n_D^{20} 1·5521).

2-*Acetyl*-6 : 7-*methylenedioxy*-1-*naphthol* (II).—Homopiperonaldehyde (31 g.), ethyl acetoacetate (72 ml.), pyridine (72 ml.), and piperidine (1 ml.) were heated on the steam-bath for 4 hr. The volatile matter was removed at 14 mm., and the residue distilled in a high vacuum. 2-*Acetyl*-6 : 7-*methylenedioxy*-1-*naphthol* was collected at 160/0·5 mm. and crystallised from

[6] Fieser and Hershberg, *J. Amer. Chem. Soc.*, 1936, **58**, 2314.
[7] Bruckner *Ber.*, 1942, **75**, 2034.

ethanol in yellow prisms (14·1 g., 37%), m. p. 165—167° (Found : C, 68·0; H, 4·3. $C_{13}H_{10}O_4$ requires C, 67·8; H, 4·3%). It gave an intense green colour with ferric chloride in ethanol.

3-Homopiperonylideneacetylacetone (I; R = Ac).—Homopiperonaldehyde (44 g.), acetylacetone (80 g.), pyridine (50 ml.), and piperidine (1 ml.) were heated on the steam-bath for 6 hr. The volatile material was removed under reduced pressure on the steam-bath, and the residue crystallised from ethanol. The *product* formed colourless prisms (40·7 g., 63%), m. p. 105—106°, b. p. 180°/0·1 mm. One further crystallisation from ethanol gave a specimen, m. p. 108° (Found : C, 68·0; H, 6·05. $C_{14}H_{14}O_4$ requires C, 68·3; H, 5·7%). The substance gave a very intense but transient pure blue colour with ferric chloride in ethanol.

2-Acetyl-1-methyl-6 : 7-methylenedioxynaphthalene (III).—A solution of homopiperonylideneacetylacetone (100 mg.) in chloroform (10 ml.) was saturated at room temperature with hydrogen chloride. After 14 days it was washed with water and evaporated. *2-Acetyl-1-methyl-6 : 7-methylenedioxynaphthalene* (41 mg.), crystallised from ethanol as prisms, m. p. 134—135° (Found : C, 73·5; H, 5·3. $C_{14}H_{12}O_3$ requires C, 73·7; H, 5·3%), giving no colour with ferric chloride. Reaction for a shorter time sometimes gave mixtures with homopiperonylideneacetylacetone which were difficult to purify : however, warming the mixture for a few minutes with a drop of piperidine converted the diketone into a very soluble unidentified substance which was then readily removed by crystallisation.

Homoveratraldehyde.—This was prepared precisely as described for homopiperonaldehyde. The yield in the oxidation of methyleugenol to the glycol, b. p. 170/0·15 mm., was 48%; lead tetra-acetate oxidation then gave 78% of homoveratraldehyde, b. p. 130/0·3 mm., n_D^{20} 1·5469.

Ethyl 4-Acetoxy-6 : 7-dimethoxy-1-methyl-2-naphthoate (V; R = OAc).—To sodium hydride (18 g.), stirred in dry benzene (125 ml.) under nitrogen, 4-acetylveratrole (68·0 g.) and diethyl succinate (197 g.) were added slowly. The reaction soon started and continued with spontaneous refluxing for 2 hr. The mixture was then acidified with acetic acid, and benzene and water were added. Extraction of the benzene layer with sodium carbonate and acidification gave an oily acid (80·6 g.). This (15 g.) was refluxed for 5 hr. with sodium acetate (5 g.) and acetic anhydride (30 ml.), and the solution was diluted with water (500 ml.) and left overnight. The brown semisolid precipitate was filtered off and extracted with light petroleum (b. p. 60—80°) (Soxhlet). Removal of the solvent gave the yellow *ester*, which gave colourless needles (6 g.), m. p. 127°, from ethanol (Found : C, 64·7; H, 5·8. $C_{18}H_{20}O_6$ requires C, 65·0; H, 6·0%).

Ethyl 4-Hydroxy-6 : 7-dimethoxy-1-methyl-2-naphthoate (V; R = OH).—The above acetate (15 g.) was refluxed in ethanol (150 ml.) containing sodium (0·5 g.) for 4 hr., the solution was acidified with dilute hydrochloric acid, and the precipitate recrystallised from ethanol. The *phenol* (12·9 g., 96%) formed colourless needles, m. p. 205° (Found : C, 66·1; H, 6·1. $C_{16}H_{18}O_5$ requires C, 66·2; H, 6·2%). The *toluene*-p-*sulphonate* had m. p. 131° (Found : C, 62·1; H, 5·5. $C_{23}H_{24}O_7S$ requires C, 62·1; H, 5·4%).

Ethyl 6 : 7-Dimethoxy-1-methyl-2-naphthoate (V; R = H).—The above toluenesulphonate (7·0 g.) and Raney nickel (35 g.) in ethanol (400 ml.) were refluxed for 3 hr. The solution was filtered and concentrated to small volume; crystals separated and on crystallisation from benzene gave the phenol (1·3 g.), m. p. and mixed m. p. 206°. Extraction of the residue from the mother-liquor with hot light petroleum (b. p. 60—80°), cooling (crystals; 3·2 g.; m. p. 85—97°), sublimation at 120°/0·03 mm., and recrystallisation from light petroleum gave *ethyl 6 : 7-dimethoxy-1-methyl-2-naphthoate* as colourless plates (1·1 g.), m. p. 108—109° (Found : C, 70·3; H, 6·6. $C_{16}H_{18}O_4$ requires C, 70·1; H, 6·6%).

2-Acetyl-6 : 7-dimethoxy-1-methylnaphthalene (VI).—*Method A.* The preceding naphthoate (200 mg.) was hydrolysed with sodium hydroxide to the *acid* (163 mg., 91%), m. p. 276° (Found : C, 68·1; H, 5·9. $C_{14}H_{14}O_4$ requires C, 68·3; H, 5·7%), which (57·2 mg.) with phosphorus pentachloride (60 mg.) in hot toluene (10 ml.) on the steam-bath for 0·5 hr. gave the solid acid chloride. This was refluxed with dimethylcadmium [from magnesium (100 mg.), methyl bromide (400 mg.), and cadmium chloride (500 mg.)] in benzene (10 ml.) for 0·5 hr. Dilute sulphuric acid and ether were added and the organic layer was worked up in the usual way. *2-Acetyl-6 : 7-dimethoxy-1-methylnaphthalene* formed plates (33 mg.), m. p. 161°, from ethanol (Found : C, 73·1; H, 6·3. $C_{15}H_{16}O_3$ requires C, 73·7; H, 6·6%).

γ-(2-Acetyl-4 : 5-dimethoxyphenyl)butyric Acid.—Ethyl γ-3 : 4-dimethoxyphenylbutyrate (32·5 g.) in methylene chloride (40 ml.) was added to aluminium chloride (12 g.) in nitrobenzene (40 ml.) containing acetyl chloride (6 ml.) and kept overnight. The solution was added to ice and hydrochloric acid, the organic layer washed with aqueous sodium hydroxide and water and evaporated, and the residue distilled. The distillate (32 g.), b. p. 188/0·5 mm., was hydrolysed with aqueous sodium hydroxide to the *acid* (20 g., 58%), m. p. 88—89° (from toluene)

(Found : C, 62·7; H, 6·5. $C_{14}H_{18}O_5$ requires C, 63·2; H, 6·8%). The *semicarbazone* of the ethyl ester had m. p. 167—168° (from ethanol) (Found : C, 58·3; H, 7·0; N, 12·4. $C_{17}H_{25}O_5N_3$ requires C, 58·2; H, 7·1; N, 12·0%).

5-(2-*Acetyl*-4 : 5-*dimethoxyphenyl*)*pentan*-2-*one* (VII; R = Me).—γ-(2-Acetyl-4 : 5-dimethoxyphenyl)butyric acid (27 g.) was kept overnight in toluene (175 ml.) with phosphorus pentachloride (22 g.). The toluene was then evaporated on the steam-bath at 15 mm. and the residue added in benzene (30 ml.) to a solution of dimethylcadmium [from magnesium (4·9 g.), excess of methyl bromide, and cadmium chloride (19·6 g.) in ether (100 ml.)] in benzene (120 ml.). After the initial vigorous reaction the solution was refluxed for 1 hr., then poured on ice and dilute hydrochloric acid, and the organic layer worked up in the usual way. From the alkaline washings was obtained recovered acid (2·2 g.). The neutral product (24·5 g.), crystallised from light petroleum (b. p. 80—100°), gave 5-(2-*acetyl*-4 : 5-*dimethoxyphenyl*)*pentan*-2-*one* (8 g.) as yellow prisms, m. p. 88° (Found : C, 68·4; H, 7·55. $C_{15}H_{20}O_4$ requires C, 68·2; H, 7·6%).

2-*Acetyl*-3 : 4-*dihydro*-6 : 7-*dimethoxy*-1-*methylnaphthalene* (VIII).—The foregoing pentanone (5 g.) was heated in ethanol (20 ml.) containing sodium (0·4 g.) for 1 hr. Next morning 2-*acetyl*-3 : 4-*dihydro*-6 : 7-*dimethoxy*-1-*methylnaphthalene* (4·2 g.) was filtered off and recrystallised from ethanol as yellow plates, m. p. 109° (Found : C, 73·4; H, 7·4. $C_{15}H_{18}O_3$ requires C, 73·2; H, 7·3%).

In a similar way the mother-liquors from the preparation of the diketone were cyclised, to yield a total of 15·5 g. of pure cyclised ketone from the 27 g. of acid.

2-*Acetyl*-6 : 7-*dimethoxy*-1-*methylnaphthalene*.—*Method B.* (*a*) The dihydro-ketone (1·0 g.) and sulphur (0·121 g.) were heated at 230° for 15 min. and then at 250° for 15 min. The product, crystallised from benzene and then ethanol, yielded 2-acetyl-6 : 7-dimethoxy-1-methylnaphthalene (0·7 g.) as reddish-brown crystals, m. p. 162° alone or mixed with the previous sample (Found : C, 73·8; H, 6·6%), but could not be obtained colourless.

(*b*) The dihydro-ketone (5 g.) and 10% palladised charcoal (0·2 g.) were refluxed for 5 hr. in toluene (50 ml.). The product crystallised as colourless plates, m. p. 161° (2·3 g.).

Diethyl 3 : 4-*Dihydro*-6 : 7-*dimethoxynaphthalene*-1 : 2-*dicarboxylate*.—Ethanol (16 ml.) was added to powdered potassium (10·4 g.) under ether (150 ml.) and the mixture kept overnight. Ethyl oxalate (53 ml.) was then added, and after ½ hr. ethyl γ-3 : 4-dimethoxyphenylbutyrate (67 g.). The mixture was refluxed for 2 hr., then cooled in ice and decomposed with ice–water. The aqueous layer was acidified with sulphuric acid and the liberated red oil extracted with ether. After the removal of volatile matter on the steam-bath, the residue was stirred at 0° into syrupy phosphoric acid (220 ml.) and concentrated sulphuric acid (46 ml.) and the deep red solution kept for 1 hr. at room temperature, then poured into ice water (3 l.). An oil which separated rapidly crystallised. Recrystallisation from acetone gave *diethyl* 3 : 4-*dihydro*-6 : 7-*dimethoxynaphthalene*-1 : 2-*dicarboxylate* (38 g., 42%) as bright yellow tablets, m. p. 104—105° (Found : C, 64·5; H, 6·8. $C_{18}H_{22}O_6$ requires C, 64·7; H, 6·6%).

Hydrolysis of the diethyl ester with potassium hydroxide gave the dicarboxylic acid as pale yellow needles which reddened and then melted at 187—188° as it was converted into the anhydride. The anhydride, which was more conveniently prepared by heating the acid with acetic anhydride, crystallised from benzene as scarlet needles, m. p. 188° (Found : C, 64·3; H, 4·8. Calc. for $C_{14}H_{12}O_5$: C, 64·6; H, 4·6%). On boiling with aqueous alkali, the acid was recovered.

Diethyl 6 : 7-*Dimethoxynaphthalene*-1 : 2-*dicarboxylate*.—The 3 : 4-dihydro-ester (2·6 g.) and sulphur (0·32 g.) were heated to 235° for 20 min. and then at 250° for 30 min. The product was sublimed at 300° in a vacuum and crystallised from light petroleum (b. p. 60—80°). *Diethyl* 6 : 7-*dimethoxynaphthalene*-1 : 2-*dicarboxylate* formed pale yellow prisms (1·1 g.), m. p. 91—92° (Found : C, 64·9; H, 6·1. $C_{18}H_{20}O_6$ requires C, 65·06; H, 6·0%).

The acid, produced by hydrolysis with potassium hydroxide, formed nearly colourless needles (from water), which became yellow and melted at 233°. The anhydride, prepared with acetic anhydride, formed yellow prisms, m. p. 233°, from benzene (Found : C, 65·3; H, 4·3. Calc. for $C_{14}H_{10}O_5$: C, 65·1; H, 3·9%).

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