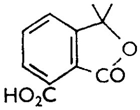
## 345. *Gamboge. Part I. The Constitutions of the Acids $C_{11}H_{10}O_4$ and $C_{12}H_{10}O_6$ derived from Gambogic Acid.*

By N. H. Dyson and W. Rigby.

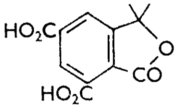
Acids derived from gambogic acid * by hydrolytic and oxidative degradation are shown to be 3,3-dimethylphthalide-7-carboxylic acid and 3,3-dimethylphthalide-5,7-dicarboxylic acid.

By acetylating the acidic portion of gamboge resin, Furrer[2a] obtained a crystalline acetate; the compound was further investigated by Lang and Katz,[2b] who esterified and then oxidised the acidic products of vigorous alkaline hydrolysis of the acetate and thereby obtained a monobasic acid $C_{11}H_{10}O_4$, m. p. 180—181° (179—180° [1,3]), and a dibasic acid $C_{12}H_{10}O_6$, m. p. 286—287° (278—280° [1,3]). The same two acids were obtained by an analogous procedure by Amorosa[1,3] from pure gambogic acid * and from that fraction of gamboge resin acids which does not give the crystalline pyridine salt. Neither acid contained methoxyl;[2] the monobasic acid contained three active hydrogen atoms.[1,3]

Besides simplifying the method of degradation leading to the acids, we have established their constitutions and synthesised them.



(I)



(II)

From their infrared spectra, it was seen that both were lactones, and their stability to oxidation made it virtually certain that they were carboxylic acid derivatives of dimethylphthalide: this was confirmed by their conversion into dimethylphthalide when they were heated with copper and quinoline. The carbonyl-stretching frequency of the

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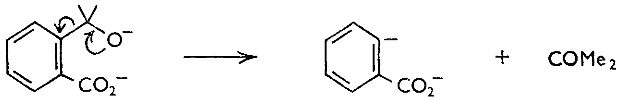
* Gambogic acid was originally isolated by Amorosa (ref. 1) who named it acido β-guttico and later revised this to acido α-guttico. After consultation with Dr. Amorosa we omit the Greek letter from the name.

[1] Amorosa, *Ann. Chim.* (*Italy*), 1955, **45**, 40.

[2] (*a*) Furrer, Dissertation, Basle, 1934 (quoted in ref. 2*b*); (*b*) Lang and Katz, *Pharm. Acta Helv.*, 1949, **24**, 387.

[3] Amorosa and Lipparini, *Ann. Chim.* (*Italy*), 1955, **45**, 40.

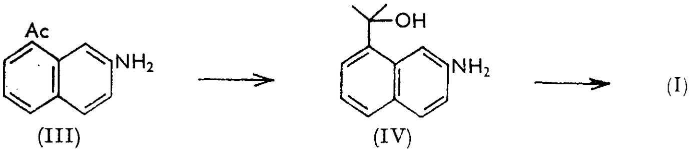
carboxyl group of the monobasic acid was rather high (1719 cm.$^{-1}$, in $CHCl_3$) and probably reflected diminished conjugation with the aromatic ring, due to the neighbouring lactone system. Fusion of the monobasic acid with potassium hydroxide gave phthalic acid and acetone, confirming the structure as (I). The expulsion of acetone from such compounds when they are fused with alkali:



will be favoured by the bulkiness of the group concerned (which is rather like t-butyl inflated by a negative charge). The reaction is related to the better known condensation of aldehydes with (reactive) aromatic nuclei, but it is not formally a strict analogue of the reverse of such a reaction.

The structure (I) had been proposed for a substance, m. p. 178·5°, prepared by Bergel and Vögele [4] by oxidation of the product of the reaction of methylmagnesium iodide with 3-methylphthalic anhydride. The element of ambiguity in their synthesis was not resolved when terephthalic acid was obtained in the alkali-fusion of the compound: the work was done long before the interconversion of the phthalic acids during alkali-fusion was cleared up.[5] Our materials of structure (I) (synthetic, and derived from gamboge) gave phthalic acid when fused with alkali in nickel vessels, and it is still not clear whether the substance prepared by Bergel and Vögele had this structure. They report that the ethyl ester of their acid melted at 146·5°; we have been unable to prepare a crystalline ethyl ester of our material, but the methyl ester (not previously obtained crystalline [2b]) melted at 40·5—42·5°.

In the synthesis of this monocarboxylic acid (I), 7-amino-1-naphthyl methyl ketone [6] (III) with methylmagnesium iodide gave the alcohol (IV) and this was oxidised by permanganate to 3,3-dimethylphthalide-7-carboxylic acid. Melting point, mixed melting point, and infrared spectrum proved its identity with the monocarboxylic acid derived from gamboge.



3,3-Dimethyl-5(?)-nitrophthalide-7-carboxylic acid, and the amine formed by its reduction, have also been prepared.

The dicarboxylic acid $C_{12}H_{10}O_6$ derived from gamboge gave 3,3-dimethylphthalide when decarboxylated; it was therefore expected to have structure (I), with an extra carboxyl group. It gave no anhydride and so was not the 6,7-dicarboxylic acid [7] (m. p. 220°; anhydride m. p. 286°); unexpectedly, the free hydroxytricarboxylic acid $C_{12}H_{12}O_7$ corresponding to this phthalide is described (though mis-named as 6-oxyisopropyl-3-methylphthalic acid) in the literature [8] (m. p. 288°)—it is presumably merely the lactone with water of crystallisation, described by Angelico (see ref. 7*b*, *c*). An acid which from its mode of formation [9] could be the 6,7-, 4,7-, or 4,5-dicarboxylic acid has m. p. 284°. The 4,7- and the 4,5-dicarboxylic acid (interconversion of which might be expected)

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[4] Bergel and Vögele, *Annalen*, 1932, **493**, 250.

[5] Kraus, Kochloefl, Beránek, Bažant, and Šorm, *Chem. and Ind.*, 1961, 1160, and references therein; Sherwood, *ibid.*, 1960, 1096, and references therein.

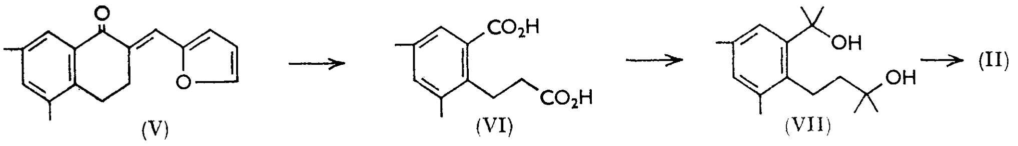
[6] Leonard and Hyson, *J. Amer. Chem. Soc.*, 1949, **71**, 1392.

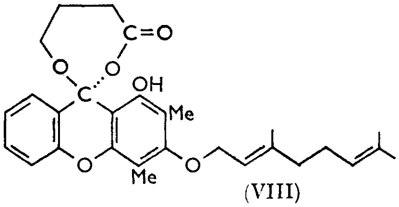
[7] (*a*) Hansen, *Ber.*, 1933, **66**, 849; (*b*) Mercer, Robertson, and Cahn, *J.*, 1935, 997; (*c*) Angelico, *Gazzetta*, 1911, **41**, II, 337; 1912, **42**, II, 540.

[8] Alder and Rickert, *Ber.*, 1937, **70**, 1364.

[9] Kariyone and Ohsumi, *J. Pharm. Soc. Japan*, 1942, **62**, 510; *Chem. Abs.*, 1951, **45**, 4709

should give a lactone-anhydride, and a 4-carboxyl group would presumably show diminished resonance with the benzene nucleus, whereas the spectrum of the acid from gamboge showed a carbonyl frequency appropriate to a simple aromatic acid. It was to be expected then that the substance would be 3,3-dimethylphthalide-5,7-dicarboxylic acid.[10]





(VIII)

3,3-Dimethylphthalide-5,7-dicarboxylic acid was synthesised by a route different from that used by Woods and Viola.[10] The furfurylidene derivative (V) of 5,7-dimethyl-1-tetralone[11] was opened by alkaline hydrogen peroxide to give β-(2-carboxy-4,6-dimethylphenyl)propionic acid (VI). The dimethyl ester of this, with methyl-lithium, gave 4-[2-(1-hydroxy-1-methylethyl)-4,6-dimethylphenyl]-2-methylbutan-2-ol (VII) which was oxidised to 3,3-dimethylphthalide-5,7-dicarboxylic acid (II), m. p. 278—280° (decomp.), by potassium permanganate. Melting point, mixed melting point, and infrared and ultraviolet spectra showed its identity with the dicarboxylic acid derived from gamboge.

Gambogic acid has been given the formulæ $C_{29}H_{34-36}O_6$[3] and $C_{33}H_{36-38}O_7$[12] and a complete structure (VIII) has been advanced.[13] The formula is now known[14] to be $C_{38}H_{44}O_8$ and so is incompatible with the $C_{29}$ structure (VIII). The degradation of gambogic acid to the acids (I) and (II) is a further indication that the formula (VIII) is untenable since there seems to be no way of reconciling this with the structures of these phthalides.

## EXPERIMENTAL

Ultraviolet spectra were determined for ethanol solutions.

*Preparation of the Acids* (I) *and* (II) *from Gamboge.*—Gamboge resin from which fat and most of the gambogic acid had been removed was usually used as the source, but purified gambogic acid gave similar results. A mixture of this resin (140 g.) and ethylene glycol (325 g.) with potassium hydroxide (325 g.) in water (325 g.) was steam-distilled for 8 hr. (bath-temp. 220°), a further 100 g. of potassium hydroxide being added after the first 1½ hr. when the reaction mixture had become homogeneous. The product was acidified with 50% sulphuric acid and steam-distilled to remove volatile acids; ether-extraction of the residue yielded a brown mass (94 g.) which was oxidised without preliminary purification.

For convenience in manipulation the oxidation was carried out in three stages. Finely powdered potassium permanganate (200 g.) was added in 10—15 portions to a stirred solution of the brown hydrolysis product (94 g.) in 0·05N-potassium hydroxide (500 ml.); the heat evolved sufficed to maintain the reaction, and complete reduction of each portion of permanganate was allowed to take place. After an excess of sulphur dioxide and sulphuric acid had

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[10] Woods and Viola, *J. Amer. Chem. Soc.*, 1956, **78**, 4380.
[11] Evans and Smith, *J.*, 1954, 798.
[12] Gupta, Rao, Vaidya, and Ramaseshan, *Chem. and Ind.*, 1962, 1469.
[13] Auterhoff, Fraudendorf, Liesenklas, and Schwandt, *Angew. Chem.* (*Internat. Edn.*), 1962, **1**, 455.
[14] Ahmad, Rigby, and Taylor, unpublished work.

been added, the crude product was extracted with ether or ethyl acetate, recovered, and dissolved in 0·05N-potassium hydroxide (400 ml.), and the oxidation was continued with a further 350 g. of permanganate, similarly added: warming was needed in the later stages. The crude product was isolated as before, and while its solution in 0·05N-potassium hydroxide (400 ml.) was stirred at 80° potassium permanganate was added, ultimately in 0·1 g. portions, until the colour persisted for 2 hr.: about 50 g. of permanganate were needed, and oxidation lasted for about 80 hr. Acidification with sulphuric acid in the presence of sulphur dioxide precipitated a white solid (A) (2·1 g.), and the filtrate from this yielded 1·0 g. of a syrup to ethyl acetate.

From the solid (A), boiling benzene (2 × 25 ml.) extracted fairly pure monocarboxylic acid, 3,3-dimethylphthalide-7-carboxylic acid (I), which was purified by recrystallisation from 80% methanol; this formed white needles (1 g.), m. p. 182—183°, $\lambda_{max.}$ 2110, 2400 (shoulder), 2880 Å ($10^{-3}\varepsilon$ 17·5, 5·0, 2·2), $\nu_{max.}$ (in $CHCl_3$) 1743, 1719, 1604 cm.$^{-1}$, the band at 1719 cm.$^{-1}$ being replaced by one at $\sim$1590 cm.$^{-1}$ in a paraffin suspension of the sodium salt (Found: C, 63·8, 63·55; H, 4·8, 4·7%; equiv., 206. Calc. for $C_{10}H_9O_2{\cdot}CO_2H$: C, 64·05; H, 4·9%; equiv., 206).

The portion of the material (A) which remained undissolved by the benzene was recrystallised from 80% methanol, yielding 3,3-dimethylphthalide-5,7-dicarboxylic acid (II) (0·38 g.), m. p. 280—282° (decomp.), $\lambda_{max.}$ 2100, 2360 (shoulder), 2970 ($10^{-3}\varepsilon$ 25·3, 13·3, 3·9), $\nu_{max.}$ (paraffin suspension) 1740, 1701 (shoulder), 1685, 1607 cm.$^{-1}$, changed to 1740, 1615, and 1579 cm.$^{-1}$ in the disodium salt [Found: C, 57·8, 57·9; H, 4·1, 4·05%; equiv., 125. Calc. for $C_{10}H_8O_2(CO_2H)_2$: C, 57·6; H, 4·05%; equiv., 125].

If the oxidation was not continued to the limit indicated, it was very difficult to obtain any crystalline product. No significantly different result was obtained when only the acidic products of the hydrolysis were submitted to the oxidation, whether or not they were esterified first.[1-3] Even the hydrolysis stage could be omitted (the monocarboxylic acid, but not the dicarboxylic acid, was then obtained) but in practice it is desirable to retain it, otherwise the amount of oxidising agent needed becomes unwieldy.

Ethereal diazomethane converted the monocarboxylic acid (I) into *methyl* 3,3-*dimethylphthalide*-7-*carboxylate*, needles, m. p. 40·5—42·5°, too soluble to be recrystallised from the usual solvents (Found: C, 65·55; H, 5·5. $C_{12}H_{12}O_4$ requires C, 65·45; H, 5·5%). Ethereal diazoethane,[15] added to a solution of the acid, gave an oil; attempts to prepare a crystalline ethyl ester [4] by interaction of the acid and methanol in the presence of hydrogen chloride, toluene-*p*-sulphonic acid, or Dowex 50 × 8 resin also failed.

Ethereal diazomethane converted the acid (II) into dimethyl 3,3-dimethylphthalide-5,7-dicarboxylate, needles (from methanol), m. p. 167·5° (lit.,[2] 164°,[10] 165—166°) (Found: C, 60·15; H, 5·0. Calc. for $C_{14}H_{14}O_6$: C, 60·45; H, 5·05%). Decarboxylation of the dicarboxylic acid (II) by the procedure used for the monocarboxylic acid (see below) gave 3,3-dimethylphthalide, m. p. and mixed m. p. 68—69°.

*Decarboxylation of the Monocarboxylic Acid* (I).—The acid (97 mg.) was boiled with quinoline (1 ml.) and copper bronze (90 mg.) for ½ hr. After filtration through charcoal, evaporation of an acid-washed benzene solution of the product yielded 3,3-dimethylphthalide (23 mg.), prisms (from cyclohexane), $\nu_{max.}$ (in $CCl_4$) 1770 cm.$^{-1}$, m. p. 67—68·5°, mixed m. p. with material prepared by Bauer's method [16] 68—69°.

*Alkali-fusion of the Monocarboxylic Acid* (I).—The acid (27 mg.) and potassium hydroxide (124 mg.) were heated in a nickel crucible to 290° and the temperature was kept at 290° for 10 min., volatile material being carried by a nitrogen stream into a solution of 2,4-dinitrophenylhydrazine in 2N-hydrochloric acid. The precipitated acetone 2,4-dinitrophenylhydrazone (3 mg. after chromatography on bentonite–kieselguhr and crystallisation from cyclohexane) had m. p. and mixed m. p. 124—125°. Acidification of the alkaline residue gave phthalic acid (15 mg.), m. p. and mixed m. p. of the sublimed anhydride 129—130°.

3,3-*Dimethyl*-5(?)-*nitrophthalide*-7-*carboxylic Acid*.—The acid (I) (0·83 g.) was heated for 4 hr. on the steam-bath with fuming sulphuric acid ($SO_3$ 20%; 4·2 g.) and fuming nitric acid (*d* 1·5; 2·25 g.). Extraction of the diluted product with ethyl acetate–ether yielded a waxy solid which, after it had been washed with cold benzene (4 ml.), cyclohexane–benzene (1 : 1, 4 ml.), and boiling benzene (4 ml.), crystallised on addition of benzene (4—5 vol.) to its solution in a minimum of ethanol; the 5(?)-*nitro-compound* formed almost white needles (0·42 g.), m. p.

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[15] Wilds and Meader, *J. Org. Chem.*, 1948, **13**, 763.

[16] Bauer, *Ber.*, 1904, **37**, 735.

230—232° (decomp.) (Found: C, 52·6; H, 3·7; N, 5·7. $C_{11}H_9NO_6$ requires C, 52·6; H, 3·6; N, 5·6%).

5(?)-*Amino*-3,3-*dimethylphthalide*-7-*carboxylic Acid*.—The nitro-compound was hydrogenated over Adams catalyst in alcohol containing hydrochloric acid. When hydrogenation was complete, pale yellow needle crystals of the free *amino-acid*, m. p. 219—220°, were deposited (Found: C, 59·15; H, 4·75; N, 6·2. $C_{11}H_{11}NO_4$ requires C, 59·7; H, 5·0; N, 6·35%).

2-(7-*Amino*-1-*naphthyl*)*propan*-2-*ol*.—7-Amino-1-naphthyl methyl ketone, m. p. 110·5—112° (lit.,[6] 109—110°), was prepared from β-naphthylamine and acetyl chloride; it had $\lambda_{max.}$ 2130, 2330, 2500 (shoulder), 3100, 3820 ($10^{-3}\varepsilon$ 23·8, 33, 27, 3·7, 5·1), $\nu_{max.}$ (in $CHCl_3$) 3320, 1670, 1633 cm.$^{-1}$ (Found: C, 77·9; H, 5·9; N, 7·55. Calc. for $C_{12}H_{11}NO$: C, 77·8; H, 6·0; N, 7·55%).

This ketone (1·85 g., 0·01 mole) in ether (250 ml.) was added during 1½ hr. to ethereal methylmagnesium iodide (0·1 mole in 100 ml.), and the mixture was boiled for a further 2 hr., the initially green suspension becoming buff. After ice–water and ammonium chloride had been added, ether-extraction yielded a gum (1·6 g.). From this, boiling carbon tetrachloride (20 ml.) extracted a brownish solid (0·86 g.), m. p. 118—124°, which was chromatographed on silica (80 g.); benzene containing 1% of ethanol eluted an impure (brown) *alcohol* (IV) which was crystallised from carbon tetrachloride, sublimed (160°/1 mm.), and finally recrystallised from benzene to give colourless plates (0·21 g.), m. p. 137·5—139°, $\lambda_{max.}$ 2090, 2160, 2390, 2850, 2950 (shoulder), 3400, ($10^{-3}\varepsilon$ 24·8, 26, 55·6, 9·3, 7·8, 3·5), $\nu_{max.}$ (in $CHCl_3$) 3380, 1636, 1387, 1370, 1185, 1159 cm.$^{-1}$ (Found: C, 77·75; H, 7·2; N, 6·95. $C_{13}H_{15}NO$ requires C, 77·6; H, 7·5; N. 6·95%).

3,3-*Dimethylphthalide*-7-*carboxylic Acid* (I).—The alcohol (IV) (0·1 g.) was shaken in 0·05N-sodium hydroxide (20 ml.) while 3·2% potassium permanganate solution was added in 1-ml. portions as each portion became reduced; 24·5 ml. were consumed. The solution was acidified with sulphuric acid, in the presence of sulphur dioxide, and the product was extracted with ethyl acetate. Recrystallisation from benzene gave colourless needles (32 mg.) of 3,3-dimethylphthalide-7-carboxylic acid (I), m. p. 180·5—182° (Found: C, 63·0; H, 4·95. Calc. for $C_{11}H_{10}O_4$: C, 64·05; H, 4·9%), mixed m. p., and the ultraviolet and infrared spectra showed its identity with the monocarboxylic acid derived from gambogic acid.

β-(2,4-Dimethylbenzoyl)propionic acid, m. p. 109—111° (lit.,[17] 114°, 111—112°) was prepared from *m*-xylene and succinic anhydride in 67% yield. Clemmensen reduction of this gave γ-(2,4-dimethylphenyl)butyric acid (28% yield), m. p. 77° (lit.,[17] 77°, 74°), which was cyclised by polyphosphoric acid[11] to give, in 56% yield, 5,7-dimethyl-1-tetralone, m. p. 48·5—49·5° (lit.,[11] 49—50°), b. p. 100—104°/0·5 mm., $\lambda_{max.}$ 2130, 2560, 2950, 3050 Å ($10^{-3}\varepsilon$ 34·2, 15, 2·5, 2·6), $\nu_{max.}$ (in $CHCl_3$) 3545, 1680, 1620 cm.$^{-1}$.

2-*Furfurylidene*-5,7-*dimethyl*-1-*tetralone* (V).—A mixture of 5,7-dimethyl-1-tetralone (5·9 g.), 5% methanolic potassium hydroxide (60 ml.), and redistilled furfuraldehyde (7 g.) was kept for ½ hr. under nitrogen; the product crystallised. Recrystallisation from methanol gave the *derivative* (V) (7·8 g.) as pale yellow needles, m. p. 116·5—117°, $\lambda_{max.}$ 2420, 2540 (shoulder), 2840, 3540 Å ($10^{-3}\varepsilon$ 8·8, 8·3, 7·9, 24·6), $\nu_{max.}$ (in $CHCl_3$) 1667, 1600 cm.$^{-1}$ (Found: C, 81·5; H, 6·4. $C_{17}H_{16}O_2$ requires C, 80·9; H, 6·4%).

β-(2-*Carboxy*-4,6-*dimethylphenyl*)*propionic Acid* (VI).—The finely powdered furfurylidene compound (V) (7·81 g.) was added in 10 portions during 10 min. to a rapidly stirred suspension of sodium peroxide, which had been made by dissolving sodium (78 g.) in methanol (3800 ml.) and adding 130-volume hydrogen peroxide (460 ml.). Stirring was continued until a sample became homogeneous, then it was diluted with water (9 pts.). The mixture was concentrated (bath at 50°) to 750 ml. and then diluted with water (1 l.), and neutral material was removed in ether. The solution was acidified with hydrochloric acid and extracted thoroughly with ether; the extract was washed with aqueous ferrous sulphate, then water and evaporated, giving a brownish-white solid which was crystallised from 66% aqueous methanol and then from water; this yielded almost colourless needles (1·63 g.) of β-(2-*carboxy*-4,6-*dimethylphenyl*)-*propionic acid* (VI), m. p. 190—191°, $\lambda_{max.}$ 2430 (shoulder), 2850 Å ($10^{-3}\varepsilon$ 3·2, 0·78), $\nu_{max.}$ (in paraffin suspension) 1700 (shoulder), 1687 cm.$^{-1}$ (Found: C, 64·7;' H, 6·3%; equiv., 115. $C_{12}H_{14}O_4$ requires C, 64·85; H, 6·35%; equiv., 111).

4-[2-(1-*Hydroxy*-1-*methylethyl*)-4,6-*dimethylphenyl*]-2-*methylbutan*-2-*ol* (VII).—Diazomethane was distilled into an ethereal solution of the acid (VI), the solution was evaporated to

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[17] Tucker, Whalley, and Forrest, *J.*, 1949, 3194.

remove the excess of diazomethane, and 1·01 g. (4·04 mmoles) of the residue, dissolved in ether (50 ml.), were added during 10 min. to methyl-lithium (38 mmoles) in ether (80 ml.). The mixture was boiled for 2½ hr. and poured into iced ammonium chloride solution, and the product was extracted with ether. Evaporation of the dried ($K_2CO_3$) extract gave an oil which crystallised when a filtered (kieselguhr) solution in light petroleum (b. p. 60—80°; 15 ml.) was concentrated. Recrystallisation from 30% methanol gave the *glycol* (VII) (0·77 g.) as needles, m. p. 83—85°, re-solidifying, and melting again at 102—103°, $\lambda_{max.}$ 2160 (shoulder), 2700 Å ($10^{-3}\varepsilon$ 8·6, 0·5), $\nu_{max.}$ (in $CCl_4$) 3380, 1378, 1368, 1157 cm.$^{-1}$ (Found: C, 74·2, 73·95; H, 10·35, 10·35. $C_{16}H_{26}O_2,0{\cdot}5H_2O$ requires C, 74·1; H, 10·5%). Sublimation at 160°/0·3 mm. yielded a glass which crystallised in the presence of a drop of light petroleum (b. p. 60—80°), no doubt because atmospheric moisture was introduced as the solvent evaporated, since the product was again the hemihydrate (Found: C, 74·25; H, 10·25%).

3,3-*Dimethylphthalide*-5,7-*dicarboxylic Acid* (II).—Powdered potassium permanganate was added to a stirred suspension of the glycol (VII) (0·375 g.) in 0·3N-potassium hydroxide (150 ml.) at 90°, until a 0·1-g. portion gave a colour which persisted for 6 hr.; this required 41 hr. and required 2·35 g. of permanganate. Working up in the usual way gave 3,3-dimethylphthalide-5,7-dicarboxylic acid (II) (53 mg.), m. p. 278—280° (decomp.) (lit.,[10] 273—275°) (Found: C, 57·35; H, 4·0. Calc. for $C_{12}H_{10}O_6$: C, 57·6; H, 4·0%). It was identical (mixed m. p., infrared and ultraviolet spectra) with the dicarboxylic acid $C_{12}H_{10}O_6$ from gambogic acid.

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Department of Organic Chemistry,
The University, Leeds.

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