Syntheses in the Naphthalene Series. Part V. Action of Sulphuric Acid on Substituted Ethyl γ-Phenylacetoacetates.*

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Five new α-substituted ethyl γ-phenylacetoacetates have been prepared, hydrolysed, and converted into pyrazolones and *iso*oxazoles. In sulphuric acid they gave 1 : 3-dihydroxynaphthalene derivatives and lactones.

IT has been shown (Soliman *et al.*, *J.*, 1944, 53, 55, 56; 1951, 93) that α-substituted ethyl γ-phenylacetoacetates exhibit keto-enol tautomerism (except the α-diphenylmethyl derivative), and are converted by sulphuric acid into 1 : 3-dihydroxynaphthalenes, most of which are oxidised in alcoholic potassium hydroxide by air to 3-hydroxy-1 : 4-naphthaquinones. With the object of synthesising hydroxynaphthaquinones which might have antihæmorrhagic or antimalarial activity, five further esters have now been examined.

p-Nitrobenzyl chloride and ethyl sodio-γ-phenylacetoacetate in benzene gave ethyl α-*p*-nitrobenzyl-γ-phenylacetoacetate (I; R = *p*-NO_2·C_6H_4·CH_2), together with a small amount of ethyl αα-di-*p*-nitrobenzyl-γ-phenylacetoacetate which was the major product when the reaction was carried out in ethanol. The disubstituted ester resisted acid-catalysed hydrolysis and other attempted reactions, but ethyl α-*p*-nitrobenzyl-γ-phenylacetoacetate was readily hydrolysed to 4-*p*-nitrophenyl-1-phenylbutan-2-one and converted into an *iso*oxazole and a pyrazolone.

Unlike ethyl α-benzyl-γ-phenylacetoacetate (I; R = CH_2Ph) which was cyclised to 1-hydroxy-2 : 3-benzofluorene, ethyl α-*p*-nitrobenzyl-γ-phenylacetoacetate was converted into 1 : 3-dihydroxy-2-*p*-nitrobenzylnaphthalene (II) by sulphuric acid, the nitro-group retarding further cyclisation just as it did cyclisation of ethyl γ-*p*-nitrophenylacetoacetate (*loc. cit.*).

1 : 3-Dihydroxy-2-*p*-nitrobenzylnaphthalene was characterised as diacetate and by oxidation in methanol by air to 2-hydroxy-3-*p*-nitrobenzyl-1 : 4-naphthaquinone (III) (Fieser, Leffler, and their co-workers, *J. Amer. Chem. Soc.*,19 48, **70**, 3174). This oxidation can be interpreted on the basis of the hydroperoxide mechanism proposed for the oxidation of tetralin to α-tetralone (Frank, *Chem. Reviews*, 1950, **46**, 162), dependent on the presence of a methylene group adjacent to a double bond (cf. II).

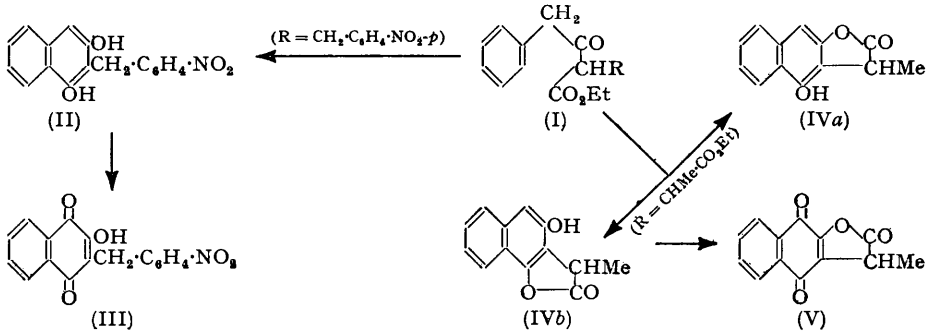
Ethyl α-*p*-methoxybenzyl-γ-phenylacetoacetate (I; R = *p*-MeO·C_6H_4·CH_2) was similarly prepared and converted into 4-*p*-methoxyphenyl-1-phenylbutan-2-one and an *iso*oxazole. However, it did not give a crystalline naphthalene derivative in sulphuric acid; the presence of the methoxyl group seems to have enhanced sulphonation which rendered the intermediary cyclisation product water-soluble.

Whereas ethyl α-bromo*iso*butyrate has failed to condense with ethyl sodio-γ-phenylacetoacetate in the normal way, ethyl α-methyl-α'-phenylacetylsuccinate (I; R = CHMe·CO_2Et) was readily formed by the action of ethyl α-bromopropionate: it was hydrolysed to α-methyl-γ-oxo-δ-phenylvaleric acid. This ester was cyclised by sulphuric acid to a crystalline product $C_{13}H_{10}O_3$ which formed a monoacetate and accordingly was the γ-lactone (IV *a* or *b*) which arose from such an intermediate as α-(1 : 3-dihydroxynaphthyl)propionic acid. Like the γ-lactone formed from ethyl phenylacetylsuccinate (I; R = CH_2·CO_2Et), this homologue was quantitatively oxidised to a quinone in presence of alcoholic potassium hydroxide, but the quinone (V) isolated on acidification was the lactone in which the methyl group contributes to the stability of the lactonic ring.

In an attempt to establish the structure of the product (V) by an alternative synthesis, the course of the Liebermann reaction for the synthesis of 3-hydroxy-1 : 4-naphthaquinon-2-ylacetic acid (Liebermann, *Ber.*, 1899, **32**, 260; 1900, **33**, 566) has been studied. Though 2 : 3-dibromonaphthaquinone failed to yield the desired compounds with diethyl sodiomethylmalonate and diethyl sodiophenylmalonate in alcohol, diethyl α-(3-bromo-1 : 4-naphthaquinon-2-yl)-α-methylmalonate was readily prepared in ether. Similarly, diethyl

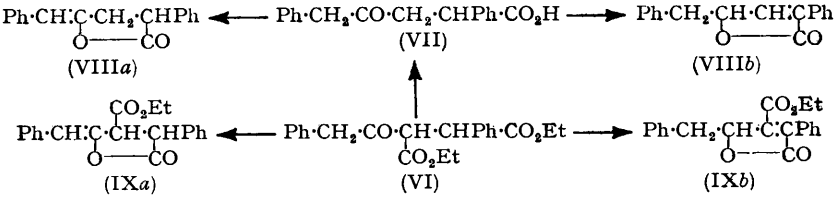
* Part IV, *J.*, 1951, 93.

3-bromo-1 : 4-naphthaquinon-2-ylmalonate, tetraethyl 1 : 4-napththaquinone-2 : 3-dimalonate, and ethyl α-(3-bromo-1 : 4-naphthaquinon-2-yl)acetoacetate were prepared in satisfactory yields unobtainable otherwise (cf. Liebermann, *loc. cit.*); the last two esters were accompanied by diethyl 2-oxo-1′ : 4′-naphthaquinono(2′ : 3′-4 : 5)*cyclo*pentene-1 : 3-dicarboxylate and 1 : 3-diethoxycarbonyl-2-methylbenz[*f*]indene-4 : 9-quinone (Liebermann, *loc. cit.*; Suryanarayana and Tilak, *Proc. Indian Acad. Sci.*, 1953, **38**, *A*, 534). Before the latter publication, the high ethoxyl value of the benzindene-4 : 9-quinone convinced us that Liebermann's formula was inadequate.



Contrary to expectation, hydrolysis of diethyl α-(3-bromo-1 : 4-naphthaquinon-2-yl)-α-methylmalonate did not lead to α-(3-hydroxy-1 : 4-naphthaquinon-2-yl)propionic acid or to the quinone (V).

Ethyl α-phenyl-α′-phenylacetylsuccinate (VI), prepared by the action of ethyl α-bromophenylacetate on ethyl sodio-γ-phenylacetoacetate, is exclusively ketonic; it was hydrolysed to γ-oxo-αδ-diphenylvaleric acid (VII) which was identified as the methyl ester (Spiegel, *Ber.*, 1881, **14**, 1686) and the semicarbazone (Asano and Kameda, *Ber.*, 1935, **68**, 1565). This acid (dihydrocorniculatic acid) was converted by Spiegel (*Annalen*, 1883, **219**, 25) into the lactone (VIII*a*) and by Thiele and Straus (*ibid.*, 1901, **319**, 211) into the lactone (VIII*b*). Like ethyl α-diphenylmethyl-γ-phenylacetoacetate, the ester (VI)



with sulphuric acid gave only traces of a naphthalene derivative, but at 0° and at room temperature it afforded two isomeric lactones, $C_{20}H_{18}O_4$, m. p. 180° and 75°, probably (IX*a* and *b* or *vice versa*).

Experimental

Light petroleum used had b. p. 40—60°.

Ethyl α-p-*Nitrobenzyl-γ-phenylacetoacetate.*—*p*-Nitrobenzyl chloride (14 g., 1 mol.) was added to a suspension of ethyl sodio-γ-phenylacetoacetate (18·9 g., 1 mol.) in benzene, and after 4 hours' heating the solution was washed, dried, and distilled. The oily residue (25 g.) which solidified on cooling yielded 15 g. of the ester, m. p. 62°, on treatment with cold methanol. When digested with hot methanol, it was freed from ethyl αα-di-*p*-nitrobenzyl-γ-phenylacetoacetate (1 g.), m. p. 158°, which remained undissolved. The *mono*-p-*nitrobenzyl* compound crystallised from benzene–light petroleum in needles, m. p. 65° (Found: C, 66·8; H, 5·7; N, 4·2; OEt, 14·0. $C_{19}H_{19}O_5N$ requires C, 66·8; H, 5·6; N, 4·1; OEt, 13·2%). Its alcoholic solution gave a reddish colour with ferric chloride and a yellow colour with sodium hydroxide.

3-*Benzyl*-5-*hydroxy*-4-p-*nitrobenzyl*isoo*xazole* was obtained when an alcoholic solution of this product (0·5 g.) was heated for 6 hr. with hydroxylamine hydrochloride (0·5 g.) and sodium

acetate (0·5 g.). It crystallised from benzene in needles, m. p. 125°, which gave a green colour with ferric chloride and a yellow colour with sodium hydroxide (Found: C, 66·0; H, 4·7; N, 8·8. $C_{17}H_{14}O_4N_2$ requires C, 65·8; H, 4·6; N, 9·0%).

3-Benzyl-4-p-nitrobenzyl-1-phenyl-5-pyrazolone was prepared when an alcoholic solution of the ester was heated with phenylhydrazine hydrochloride and sodium acetate for 2 hr. It crystallised from methanol in needles, m. p. 160° (Found: C, 72·1; H, 5·1; N, 10·2. $C_{23}H_{19}O_3N_3$ requires C, 71·7; H, 5·0; N, 10·9%).

4-p-Nitrophenyl-1-phenylbutan-2-one.—Ethyl α-*p*-nitrobenzyl-γ-phenylacetoacetate (0·5 g.) was hydrolysed for 10 hr. with a boiling mixture (25 ml.) of acetic acid (90 ml.), sulphuric acid (3 ml.), and water (7 ml.). The ketone crystallised from benzene–light petroleum in needles, m. p. 70°, which gave a faint reddish colour with sodium hydroxide (Found: C, 71·3; H, 5·6; N, 5·2. $C_{16}H_{15}O_3N$ requires C, 71·3; H, 5·6; N, 5·2%). Its *oxime* crystallised from benzene–light petroleum in needles, m. p. 95° (Found: C, 67·6; H, 5·5; N, 9·9. $C_{16}H_{16}O_3N_2$ requires C, 67·6; H, 5·7; N, 9·9%).

1 : 3-Dihydroxy-2-p-nitrobenzylnaphthalene.—Ethyl α-*p*-nitrobenzyl-γ-phenylacetoacetate (4 g.) was stirred into ice-cold concentrated sulphuric acid (12 ml.), and after being kept at room temperature for 2 days the solution was poured on ice. The sticky product was extracted with ether, and the ethereal solution shaken with 5% aqueous ammonia. The ammoniacal solution gave on acidification and extraction with ether 0·4 g. of *2-hydroxy-3-p-nitrobenzyl-1 : 4-naphthaquinone*. The neutral ethereal solution yielded 3 g. of the diol which crystallised from benzene–methanol in yellowish needles, m. p. 162° (Found: C, 69·3; H, 4·5; N, 4·8. $C_{17}H_{13}O_4N$ requires C, 69·1; H, 4·4; N, 4·7%). Its *diacetate*, prepared by acetic anhydride and sodium acetate, crystallised from benzene in prisms, m. p. 201° (Found: C, 66·4; H, 4·4; N, 3·7. $C_{21}H_{17}O_6N$ requires C, 66·5; H, 4·5; N, 3·7%).

3-Hydroxy-2-p-nitrobenzyl-1 : 4-naphthaquinone was obtained almost quantitatively when a methanolic solution of the preceding diol was exposed to air for several days. It crystallised from acetone in yellow needles, m. p. 236° (Found: C, 65·9; H, 3·7; N, 4·5. Calc. for $C_{17}H_{11}O_5N$: C, 66·0; H, 3·6; N, 4·5%). It was also prepared by heating 4-nitrophenylacetyl peroxide (1 g.), m. p. 90° (decomp.), with 2-hydroxy-1 : 4-naphthaquinone (0·5 g.) in acetic acid for 3 hr.

Ethyl αα-Di-p-nitrobenzyl-γ-phenylacetoacetate.—*p*-Nitrobenzyl chloride (17·2 g.) and ethyl sodio-γ-phenylacetoacetate [formed by addition of the ester (20·6 g.) to an alcoholic solution (80 ml.) of sodium (2·3 g.)] were heated for 3 hr. and, on cooling, the ester (13 g.) crystallised. It recrystallised from benzene in prisms, m. p. 160° (Found: C, 65·5; H, 5·1; N, 5·8; OEt, 9·6. $C_{26}H_{24}O_7N_2$ requires C, 65·5; H, 5·1; N, 5·9; OEt, 9·5%). It gave a negative test with ferric chloride and was recovered unchanged after being heated with hydroxylamine or acetic–sulphuric acid–water. The mother-liquor from the main reaction yielded on concentration and extraction with ether an oil which deposited 3 g. of ethyl α-*p*-nitrobenzyl-γ-phenylacetoacetate.

Ethyl α-p-*Methoxybenzyl-γ-phenylacetoacetate.*—*p*-Methoxybenzyl chloride (10·5 g.) (Ofner, *Helv. Chim. Acta*, 1935, **18**, 951) was added to ethyl sodio-γ-phenylacetoacetate (11 g.) in benzene, and after 6 hours' heating the solution was washed, dried, and distilled. The residual *ester* was fractionally distilled and the fraction (8 g.), b. p. 250—260°/3 mm., was redistilled at 258—260°/3 mm. It gave a reddish-violet colour with ferric chloride (Found: C, 73·8; H, 6·8; OMe, 9·6; OEt, 13·9. $C_{20}H_{22}O_4$ requires C, 73·6; H, 6·8; OMe, 9·5; OEt, 13·8%).

3-Benzyl-5-hydroxy-4-p-methoxybenzylisooxazole was prepared from this ester by hydroxylamine in hot alcohol (3 hr.); it crystallised from benzene–light petroleum in needles, m. p. 130°, which gave a yellowish-green colour with ferric chloride (Found: C, 73·4; H, 5·8; N, 4·4; OMe, 11·2. $C_{18}H_{17}O_3N$ requires C, 73·2; H, 5·8; N, 4·7; OMe, 10·5%).

4-p-Methoxyphenyl-1-phenylbutan-2-one was prepared by refluxing the ester (1 g.) with 25% aqueous potassium hydroxide (20 ml.) for 4 hr. It was recovered by extraction with ether as an oil which solidified at 25° and gave a *semicarbazone* which crystallised from benzene–light petroleum in needles, m. p. 160° (Found: C, 69·5; H, 6·8; N, 13·2. $C_{18}H_{21}O_2N_3$ requires C, 69·4; H, 6·8; N, 13·5%).

Action of sulphuric acid. A solution of ethyl α-*p*-methoxybenzyl-γ-phenylacetoacetate (2 g.) in cold concentrated sulphuric acid (8 ml.) was kept at room temperature for 24 hr., and when poured on ice gave a clear solution. This was neutralised with barium carbonate, and after evaporation of the filtrate, a reddish-violet barium salt was obtained. It gave a faint reddish colour with ferric chloride and a positive test for sulphonic group.

*3 : 4-Dibenzyl-5-hydroxy*isooxazole.—This *compound* was prepared by heating an alcoholic

solution of ethyl α-benzyl-γ-phenylacetoacetate with hydroxylamine for 4 hr. It crystallised from benzene–light petroleum in prisms, m. p. 102° (Found: C, 76·4; H, 5·6; N, 5·3. $C_{17}H_{15}O_2N$ requires C, 77·0; H, 5·7; N, 5·3%).

1-*Methoxy*-2 : 3-*benzofluorenone*.—A solution of 1-methoxy-2 : 3-benzofluorene (0·5 g.) in glacial acetic acid (15 ml.) was treated with a solution of chromic oxide (0·5 g.) in 5 ml. of acetic acid and 1 ml. of water at room temperature for 3 hr., then diluted with water, and extracted with ether. The ethereal solution was shaken with sodium hydrogen carbonate. The *ketone* recovered from the solvent crystallised from dioxan in yellow plates, m. p. 334° (Found: C, 83·0; H, 4·4. $C_{18}H_{12}O_2$ requires C, 83·1; H, 4·6%).

Ethyl α-Methyl-α'-phenylacetylsuccinate.—This *ester* was prepared by heating ethyl sodio-γ-phenylacetoacetate (20 g.) and ethyl α-bromopropionate (15·9 g.) in absolute alcohol for 6 hr. The product was distilled at 3 mm. and the fraction (12 g.), b. p. 185—190°/3 mm., was redistilled at 188—190°/3 mm. It was a pale yellowish oil which gave a reddish-violet colour with ferric chloride (Found: C, 66·5; H, 7·1; OEt, 27·8. $C_{17}H_{22}O_5$ requires C, 66·6; H, 7·2; 2OEt, 29·4%).

α-Methyl-γ-oxo-δ-phenylvaleric Acid.—The foregoing ester (3 g.) was hydrolysed by boiling 20% aqueous potassium hydroxide (25 ml.) for 5 hr. The solution was acidified and extracted with ether, and the acid extracted with sodium hydrogen carbonate. On acidification of the latter solution and extraction with ether, the *acid* was obtained as an oil which did not solidify on cooling [Found: Equiv. (by titration), 209·0. $C_{12}H_{14}O_3$ requires Equiv., 206·1]. Its *semicarbazone* crystallised from benzene–methanol in needles, m. p. 140° (Found: C, 59·6; H, 6·4; N, 15·8. $C_{13}H_{17}O_3N_3$ requires C, 59·3; H, 6·5; N, 16·0%).

α-(1 : 3-*Dihydroxynaphthyl*)*propionic* 1- *or* 3-*Lactone* (IV*a* or *b*).—Ethyl α-methyl-α'-phenylacetylsuccinate (12 g.) was stirred into ice-cold concentrated sulphuric acid (30 ml.) and kept at 40° for 7 hr. and at room temperature for 24 hr., then poured on ice. The sticky product was extracted with ether, and the oily residue (4·6 g.) recovered from the ethereal solution deposited glistening plates on cooling. After removal of the oily impurities by washing with benzene, the *lactone* (1·6 g.) crystallised from benzene–methanol in prisms, m. p. 203° (Found: C, 72·6; H, 4·7. $C_{13}H_{10}O_3$ requires C, 72·9; H, 4·7%). It gave a red colour with sodium hydroxide and a negative test with ferric chloride. Its *acetate* crystallised from methanol in prisms, m. p. 108° (Found: C, 70·4; H, 4·8. $C_{15}H_{12}O_4$ requires C, 70·3; H, 4·7%).

α-(3-*Hydroxy*-1 : 4-*naphthaquinon*-4-*yl*)*propionic Lactone* (V).—The lactone (IV*a* or *b*) (0·5 g.) in 5% alcoholic potassium hydroxide (15 ml.) was exposed to air for 3 days. On acidification of the red potassium salt, *the quinone*, m. p. 186°, was obtained. It crystallised from methanol in golden-yellow needles, m. p. 192° (Found: C, 68·2; H, 3·5. $C_{13}H_8O_4$ requires C, 68·4; H, 3·5%).

Condensations with 2 : 3-*Dibromonaphthaquinone*.—This quinone (Kohen and Schwarz, *Monatsh.*, 1926, **46**, 347) failed to condense with diethyl sodiomethylmalonate or diethyl sodiophenylmalonate in alcohol, but in both cases 2-bromo-3-ethoxy- and 2-bromo-3-hydroxy-1 : 4-naphthaquinone were found alongside the reactants.

α-(3-*Bromo*-1 : 4-*naphthaquinon*-2-*yl*)-α-*methylmalonate*.—2 : 3-Dibromonaphthaquinone (2 g., 1 mol.) was added to diethyl sodiomethylmalonate (2 mols.) formed by the action of sodium (0·3 g.) on the ester (2·2 g.) in dry ether. The violet mixture was kept at room temperature for 24 hr. with frequent shaking, and was then mixed with water, and the two layers were separated. The residue recovered from the ethereal solution yielded 1·5 g. of the *ester* after being washed with cold light petroleum. It crystallised from light petroleum (b. p. 60—80°) in yellow prisms, m. p. 143° (Found: C, 53·2; H, 4·1; Br, 19·3. $C_{18}H_{17}O_6Br$ requires C, 52·8; H, 4·2; Br, 19·6%). This ester dissolved completely when kept in 10% aqueous potassium hydroxide for 24 hr. The red solution gave on acidification a brownish solid, m. p. 145—150° (decomp.), which decomposed during attempted purification.

Tetraethyl 1 : 4-*Naphthaquinone*-2 : 3-*dimalonate*.—This product was prepared in 40% yield when 2 : 3-dibromonaphthaquinone (1 mol.) and diethyl sodiomalonate (2 mols.) in ether were shaken for about 12 hr. and then refluxed for 2 hr. It crystallised from light petroleum in yellow prisms, m. p. 92° (Found: C, 60·5; H, 5·5. Calc. for $C_{24}H_{26}O_{10}$: C, 60·7; H, 5·5%).

Ethyl α-(3-*Bromo*-1 : 4-*naphthaquinon*-2-*yl*)*acetoacetate*.—This *ester* was prepared in 70% yield and crystallised from light petroleum in yellow prisms, m. p. 97° (Found: C, 52·3; H, 3·6; Br, 21·6; OEt, 12·5. $C_{16}H_{13}O_5Br$ requires C, 52·6; H, 3·5; Br, 21·9; OEt, 12·4%). 1 : 3-Diethoxycarbonyl-2-methylbenz[*f*]indene-4 : 9-quinone was isolated from the alkaline fraction of the reaction and crystallised from ethanol in garnet-red needles, m. p. 155° (Found: C, 67·4; H, 5·1; OEt, 25·5. Calc. for $C_{20}H_{18}O_6$: C, 67·8; H, 5·1; 2OEt, 25·4%).

Ethyl α-Phenyl-α-phenylacetylsuccinate.—Ethyl α-bromophenylacetate (19·4 g.) (Truit and Jeans, *J. Amer. Chem. Soc.*, 1948, **70**, 4214) was refluxed with ethyl sodio-γ-phenylacetoacetate (18·2 g.) in absolute alcohol for 4 hr. After separation of sodium bromide and distillation of alcohol, the residue (26 g.) yielded 12·7 g. of the solid *succinate* on treatment with methanol. It crystallised from methanol in needles, m. p. 96° (Found: C, 72·1; H, 6·6; OEt, 24·4. $C_{22}H_{24}O_5$ requires C, 71·7; H, 6·6; 2OEt, 24·5%).

γ-Oxo-αδ-diphenylvaleric acid was obtained by hydrolysis of this ester with alcoholic potassium hydroxide and crystallised from light petroleum in prismatic needles, m. p. 134° (Found: C, 76·3; H, 6·0. Calc. for $C_{17}H_{16}O_3$: C, 76·1; H, 6·0%). Its methyl ester, prepared by diazomethane, crystallised from methanol in prisms, m. p. 68°, and its semicarbazone, m. p. 178°, similarly (Found: C, 66·3; H, 5·8; N, 13·0. Calc. for $C_{18}H_{19}O_3N_3$: C, 66·4; H, 5·9; N, 12·9%).

The Lactones (IX).—Ethyl α-phenyl-α′-phenylacetylsuccinate (3 g.) was stirred into 6 ml. of ice-cold concentrated sulphuric acid, and the solution was kept at 0° for 2 days, then poured on ice, and the sticky product was extracted with ether. The ethereal solution was shaken with hydrogen carbonate and 2% aqueous sodium hydroxide (excess). The neutral ethereal solution yielded 1·4 g. of a viscous oil which on treatment with cold methanol deposited a *lactone* that crystallised from methanol in prisms, m. p. 180° (red colour with Legal reagent) [Found: C, 74·9; H, 5·6; OEt, 13·3%; *M*(Rast), 370. $C_{20}H_{18}O_4$ requires C, 74·5; H, 5·6; OEt, 14·0%; *M*, 322·1.

In another similar experiment, the sulphuric acid solution of the ester was kept at room temperature for 2 days and then worked up as before. The neutral ethereal solution yielded 1·4 g. of a viscous oil from which a *lactone* was obtained on treatment with cold methanol. This crystallised from methanol in yellowish rhombic crystals, m. p. 75°, which gave a positive Legal test [Found: C, 74·7; H, 5·6; OEt, 13·7%; *M*(Rast), 317]. The sodium hydrogen carbonate and sodium hydroxide extracts of the two experiments gave traces of acidic substances on acidification.

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