20. *Syntheses in the Naphthalene Series. Part IV.* 3-*Hydroxy*-1 : 4-*naphthaquinone*-2-*acetic Acid and its Homologues.*

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Ethyl phenylacetylsuccinate and ethyl α-phenylacetylglutarate, prepared by substitution of ethyl γ-phenylacetoacetate, were converted into a γ- and a δ-lactone, respectively, by the action of sulphuric acid at 40°. The two lactones were oxidised to 3-hydroxy-1 : 4-naphthaquinone-2-acetic and -2-β-propionic acid.

In previous communications (*J.*, 1944, 53, 55, 56), the utility of ethyl γ-phenylacetoacetate as a synthetic reagent was illustrated by the preparation of 2-alkyl-1 : 3-dihydroxynaphthalenes, 1-hydroxy-2 : 3-benzfluorene, and 4-hydroxy-2-methyl-5 : 6-benzocoumaran. Furthermore, a new synthesis of 2-alkyl-3-hydroxy-1 : 4-naphthaquinones was described, and the object of this paper is to record the results of a brief survey of the applicability of this synthesis to the acidic members of the series.

Ethyl phenylacetylsuccinate (ethyl β-carbethoxy-γ-keto-δ-phenylvalerate) (I; R = $CH_2 \cdot CO_2Et$) and ethyl α-phenylacetylglutarate (ethyl 4-carbethoxy-5-keto-6-phenylhexanoate) (I; R = $CH_2 \cdot CH_2 \cdot CO_2Et$) were prepared by the action of ethyl bromoacetate and ethyl β-iodopropionate, respectively, on ethyl sodio-γ-phenylacetoacetate in absolute alcohol. The two esters were shown to be α-substituted by hydrolysis; the former yielded β-phenylacetylpropionic acid (Fittig and Stern, *Annalen*, 1892, **268**, 89; Russwurm, Stobbe, and Schulz, *ibid.*, 1899, **308**, 179; Lukês, *Coll. Trav. Chim. Tchecosl.*, 1932, **4**, 181; *Chem. Zentr.*, 1932, I, 3062), and the latter ester yielded γ-phenylacetylbutyric acid, characterised by the formation of a semicarbazone.

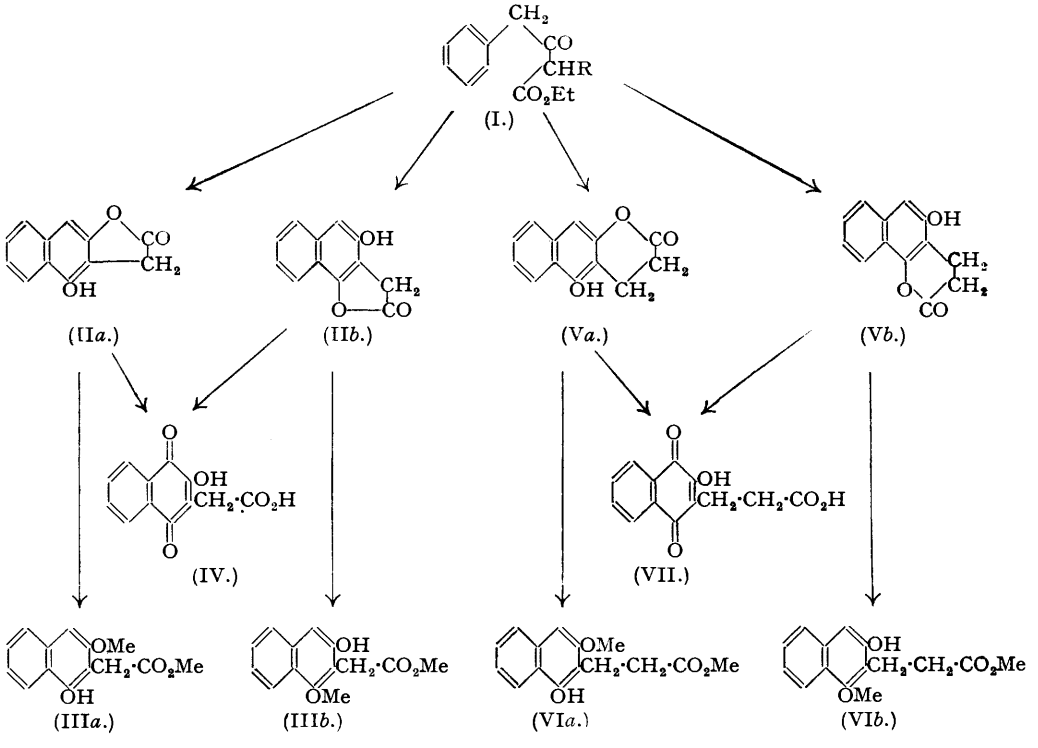
Whereas cyclisation of ethyl phenylacetylmalonate (I; R = CO_2Et) by cold sulphuric acid (cf. Metzner, *Annalen*, 1897, **298**, 383; Soliman and West, *J.*, 1944, 53) yielded 2-carbethoxy-1 : 3-dihydroxynaphthalene, cyclisation of its next two higher homologues at 40° proceeded to a secondary stage of ring closure. Ethyl phenylacetylsuccinate gave a product $C_{12}H_8O_3$ which formed a monoacetate, and yielded a methyl methoxy-ester $C_{14}H_{14}O_4$ on treatment with hydrogen chloride in methanol. Formation of this ester (III*a* or *b*) by methanolysis

indicated that this cyclisation product is a γ-lactone (II*a* or *b*) which arose by dehydration of such an intermediate as 1 : 3-dihydroxynaphthalene-2-acetic acid, and would be analogous to the conversion of 3-hydroxynaphthalene-2-acetic acid into 5 : 6-benzocoumaran-2-one by the action of heat or phosphoric oxide (Stoermer, *Annalen*, 1900, **313**, 91; Eistert and Krizkalla, *J. pr. Chem.*, 1935, **143**, 50; Eistert, *Ber.*, 1936, **69**, 1074). This conclusion is supported by the fact that the lactone was quantitatively oxidised in presence of alcoholic potassium hydroxide (cf. Soliman and Latif, *J.*, 1944, 55) to 3-hydroxy-1 : 4-naphthaquinone-2-acetic acid (IV), previously synthesised by lengthy methods (Liebermann, *Ber.*, 1900, **33**, 566; Bamberger and Praetorius, *Monatsh.*, 1911, **22**, 587; Newman, Crowder, and Anderson, *J. Biol. Chem.*, 1934, **105**, 279).

Similarly, ethyl α-phenylacetylglutarate yielded on cyclisation under identical conditions a crystalline product $C_{13}H_{10}O_3$ which formed a monoacetate and a methyl methoxy-ester $C_{15}H_{16}O_4$ (VI*a* or *b*) and was thus shown to be a δ-lactone (V*a* or *b*). Furthermore, this lactone was also quantitatively oxidised to 3-hydroxy-1 : 4-naphthaquinone-2-β-propionic acid (VII), recently prepared by peroxide alkylation of 2-hydroxy-1 : 4-naphthaquinone (Fieser *et al.*, *J. Amer. Chem. Soc.*, 1948, **70**, 3206).

However, 2-carbethoxy-3-hydroxy-1 : 4-naphthaquinone, prepared by oxidation of 2-carbethoxy-1 : 3-dihydroxynaphthalene in presence of alcoholic potassium hydroxide (Soliman and Latif, *loc. cit.*), was found to possess the same properties as the product obtained by Fieser *et al.* (*loc. cit.*) by oxidation of 4-amino-2-carbethoxy-1 : 3-dihydroxynaphthalene with dichromate.

Owing to the difficulties encountered in isolating and purifying the above-mentioned lactones, they have not been fully characterised but attempts are in progress to differentiate between the alternative formulæ illustrated.



In an attempt to study the action of sulphuric acid on other derivatives of ethyl γ-phenylacetoacetate, ethyl α-diphenylmethyl-γ-phenylacetoacetate (I; R = $CHPh_2$) was prepared in the usual manner and shown to be α-substituted by hydrolysis to ββ-diphenylpropionic acid (Henderson, *J.*, 1891, **59**, 731) and benzyl 2 : 2-diphenylethyl ketone. However, by the action of sulphuric acid at room temperature or at 40° it gave a resinous product which could not be converted into a crystalline derivative.

Experimental.

(M. p.s are not corrected; microanalyses were done by Drs. Weiler and Strauss, Oxford.)

Ethyl Phenylacetylsuccinate (*Ethyl β-Carbethoxy-γ-keto-δ-phenylvalerate*).—This was prepared by the action of ethyl bromoacetate (1 mol., 16·6 g.) on ethyl sodio-γ-phenylacetoacetate (from ester, 20·6 g., and sodium, 2·3 g., in absolute alcohol). The reaction was complete after 4 hours' heating; alcohol was then distilled off, and the ester extracted with ether and distilled. The fraction (20 g.), b. p. 182—184°/3 mm., gave a violet-red colour with ferric chloride (Found: C, 65·8; H, 7·1. $C_{16}H_{20}O_5$ requires C, 65·9; H, 6·9%). Hydrolysis of the *ester* (3·5 g.) by heating it with 10% aqueous potassium hydroxide solution (40 ml.) yielded β-phenylacetylpropionic acid (2·2 g.), which crystallised from chloroform–light petroleum (b. p. 40—60°) in needles, m. p. 55° [Found: C, 68·6; H, 6·3%; *M* (by titration), 191·6. Calc. for $C_{11}H_{12}O_3$: C, 68·8; H, 6·3%; *M*, 192·1]. Its semicarbazone crystallised from dilute alcohol in needles, m. p. 183° (Found: C, 58·2; H, 6·1; N, 16·5. Calc. for $C_{12}H_{15}O_3N_3$: C, 57·8; H, 6·0; N, 16·85%).

Ethyl α-Phenylacetylglutarate (*Ethyl 4-Carbethoxy-5-keto-6-phenylhexanoate*).—Prepared by the action of ethyl β-iodopropionate (1 mol., 22·2 g.) on the sodio-derivative (1 mol.) of ethyl γ-phenylacetoacetate (20·6 g.) in absolute alcohol, this *ester*, when fractionated (22 g.), had b. p. 200—204/6 mm., and gave a violet-red colour with ferric chloride (Found: C, 66·9; H, 7·0. $C_{17}H_{22}O_5$ requires C, 66·6; H, 7·2%).

γ-Phenylacetylbutyric Acid.—Hydrolysis (5 hours' heating) of the foregoing ester (3 g.) with 10% aqueous potassium hydroxide solution (30 ml.) and acidification precipitated the *acid* (2 g.), which crystallised from hot water in needles, m. p. 58° [Found: C, 70·1; H, 6·7%; *M* (by titration), 207·2. $C_{12}H_{14}O_3$ requires C, 69·9; H, 6·8%; *M*, 206·1]. Its *semicarbazone* crystallised from dilute alcohol in needles, m. p. 173° (Found: C, 59·5; H, 6·5; N, 15·5. $C_{13}H_{17}O_3N_3$ requires C, 59·3; H, 6·5; N, 15·6%).

Ethyl α-Diphenylmethyl-γ-phenylacetoacetate.—Diphenylmethyl bromide (1 mol., 12·4 g.) was heated with solid ethyl sodio-γ-phenylacetoacetate (1 mol., 11·5 g.) in benzene for 4 hours. The oily residue left after distillation of benzene solidified on cooling and yielded a crystalline solid (12 g.) on treatment with cold methanol. The solid gave a negative ferric chloride test, whereas the methanolic liquor gave a violet-red colour. The solid *ester* crystallised from alcohol in prisms, m. p. 112°, which dissolved readily in concentrated sulphuric acid, giving a red solution having a green fluorescence (Found: C, 80·6; H, 6·5; OEt, 11·8. $C_{25}H_{24}O_3$ requires C, 80·6; H, 6·5; OEt, 12·1%).

Benzyl 2 : 2-Diphenylethyl Ketone.—The foregoing ester (3 g.) was refluxed with 5% alcoholic potassium hydroxide solution (30 ml.) for 3 hours. The residue left after distillation of alcohol was mixed with water and extracted with ether. After distillation of ether, the oily residue solidified on cooling and the *ketone* crystallised from light petroleum (b. p. 40—60°) in fine needles, m. p. 72° (Found: C, 88·1; H, 6·8. $C_{22}H_{20}O$ requires C, 88·0; H, 6·7%). Its *oxime* crystallised from light petroleum in needles, m. p. 124° (Found: C, 83·9; H, 6·7; N, 4·3. $C_{22}H_{21}ON$ requires C, 83·8; H, 6·7; N, 4·4%). The alkaline solution left after extraction of the ketone was evaporated to dryness, and the residue digested with alcohol. The residue left after evaporation of the alcoholic extract yielded on acidification ββ-diphenylpropionic acid, which crystallised from dilute alcohol in needles, m. p. and mixed m. p. 154° (cf. Henderson, *loc. cit.*).

The γ-Lactone (II*a*, or *b*).—Ice-cold concentrated sulphuric acid (40 ml.) was gradually added to ethyl phenylacetylsuccinate (15 g.), and the solution kept at 40° for 4 hours and at room temperature for 24 hours and then poured on ice. The brownish, sticky mass which separated was extracted with ether, and the ethereal solution dried. The viscous residue (8 g.) which was recovered from the ethereal solution was treated with benzene and thus separated into a pinkish crystalline solid (3 g.) and a brownish mother-liquor. The solid *lactone*, m. p. 165—170°, was freed from a water-soluble impurity by washing it with hot water. It crystallised from dilute methanol in plates, m. p. 218° (decomp.) (Found: C, 72·4; H, 4·2. $C_{12}H_8O_3$ requires C, 72·0; H, 4·0%), which gave a red colour with aqueous potassium hydroxide solution. Its *monoacetate* was prepared by heating the lactone (0·5 g.) with acetic anhydride (5 ml.) and fused sodium acetate (0·5 g.) for 2 hours on the steam-bath, and crystallised from methanol in needles, m. p. 155° (Found: C, 69·0; H, 4·0. $C_{14}H_{10}O_4$ requires C, 69·2; H, 4·1%).

Methanolysis. A solution of the lactone (0·5 g.) in 10 ml. of methanol was cooled in ice and then saturated with hydrogen chloride; after 3 hours at room temperature, the *methyl* ester (IV*a* or *b*) was precipitated by dilution with water. It crystallised from dilute methanol and recrystallised from light petroleum (b. p. 40—60°) in needles, m. p. 120° (Found: C, 68·4; H, 5·7; OMe, 23·8. $C_{14}H_{14}O_4$ requires C, 68·3; H, 5·8; 2OMe, 25·2%). Its *monoacetate* crystallised from light petroleum (b. p. 40—60°) in needles, m. p. 83° (Found: C, 66·5; H, 5·6. $C_{16}H_{16}O_5$ requires C, 66·7; H, 5·6%).

3-Hydroxy-1 : 4-naphthaquinone-2-acetic Acid.—When a solution of the above-mentioned lactone (0·5 g.) in 5 ml. of alcohol was mixed with 15 ml. of 5% alcoholic potassium hydroxide solution, and the mixture exposed to air for 2 days, the red potassium salt separated; it was dissolved in water, and the solution acidified, and the resulting yellow quinone (0·5 g.) crystallised from water in golden-yellow plates, m. p. 208° (decomp.) (Found: C, 62·0; H, 3·5. Calc. for $C_{12}H_8O_5$: C, 62·0; H, 3·5%). Its methyl ester was prepared by the action of hydrogen chloride on a methanolic solution of the quinone, and crystallised from dilute methanol in lemon-yellow needles, m. p. 145° (Found: C, 63·0; H, 4·0; OMe, 11·8. Calc. for $C_{13}H_{10}O_5$: C, 63·3; H, 4·1; OMe, 12·6%). Decarboxylation of the acid with copper–barium chromite catalyst (Adkins, Connor, and Folkers, *J. Amer. Chem. Soc.*, 1932, **54**, 1138) in diphenyl ether yielded 3-hydroxy-2-methyl-1 : 4-naphthaquinone (Soliman and Latif, *loc. cit.*), m. p. and mixed m. p. 174°. More quinone was obtained by oxidation of the brownish residue recovered from the benzene mother-liquor left after isolation of the lactone. The crude quinone (1·8 g.), m. p.

170—180°, was digested with warm ether and the insoluble residue, m. p. 200°, was further purified by crystallisation from water.

δ-*Lactone* (V*a* or *b*).—Ethyl α-phenylacetylglutarate (12 g.) was dissolved in 35 ml. of ice-cold concentrated sulphuric acid, and the solution kept at 40° for 4 hours and at room temperature for 24 hours, then poured on ice; the brownish sticky product was extracted with ether and the residue (6·5 g.) recovered from the ethereal solution yielded a crystalline *lactone* (3·5 g.) on treatment with benzene. It crystallised from benzene in glistening plates, m. p. 175°, which lost their lustre on dehydration over phosphoric oxide (Found: C, 73·0; H, 4·7. $C_{13}H_{10}O_3$ requires C, 72·9; H, 4·7%). Its *monoacetate* crystallised from methanol in long needles, m. p. 147° (Found: C, 70·4; H, 4·8. $C_{15}H_{12}O_4$ requires C, 70·3; H, 4·7%).

Methanolysis. An ice-cold solution of the lactone (0·5 g.) in 10 ml. of methanol was saturated with hydrogen chloride, and after 3 hours at room temperature the *methyl methoxy*-ester was precipitated by dilution with water. It crystallised from light petroleum (b. p. 40—60°) in needles, m. p. 103° (Found: C, 69·3; H, 6·1; OMe, 23·3. $C_{15}H_{16}O_4$ requires C, 69·2; H, 6·1; 2OMe, 23·8%).

2-*Hydroxy*-1 : 4-*naphthaquinone*-2-β-*propionic Acid.*—Prepared by oxidation of a solution of the δ-lactone (0·5 g.) in 5% alcoholic potassium hydroxide (15 ml.) by 2 days' exposure to air, the quinone crystallised from water in needles, m. p. 195° (Found: C, 63·6; H, 4·0. Calc. for $C_{13}H_{10}O_5$: C, 63·4; H, 4·1%). Its methyl ester, prepared by the action of hydrogen chloride and methanol, crystallised from alcohol in yellow needles, m. p. 138° (Found: C, 64·4; H, 4·7. Calc. for $C_{14}H_{12}O_5$: C, 64·4; H, 4·6%). More of the quinone was obtained as for the lower homologue. The crude quinone (1·7 g.) was digested with hot benzene, and the insoluble fraction was further purified by crystallisation.

2-*Carbethoxy*-3-*hydroxy*-1 : 4-*naphthaquinone.*—Oxidation of a solution of 2-carbethoxy-1 : 3-dihydroxynaphthalene (1 g.) in 20 ml. of 3% alcoholic potassium hydroxide by 2 days' exposure to air afforded an orange-yellow potassium salt; on acidification this gave the quinone (0·7 g.), which crystallised from ethyl acetate (slow evaporation) in prisms, and recrystallised from light petroleum (b. p. 40—60°) in orange plates, m. p. 110° (Found: C, 63·1; H, 4·2; OEt, 17·8. Calc. for $C_{13}H_{10}O_5$: C, 63·4; H, 4·1; OEt, 18·3%).

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