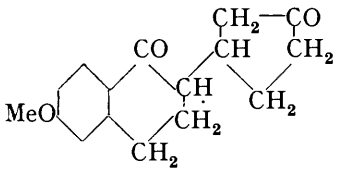
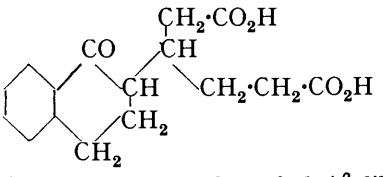
380. *Experiments on the Synthesis of Substances related to the Sterols. Part XXVI.*

By Robert Robinson and J. M. C. Thompson.

(1) The diketone (I) is an objective as an intermediate in an oestrone synthesis.

(I.) 

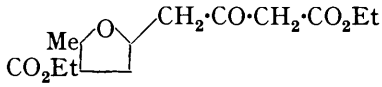
 (II.)

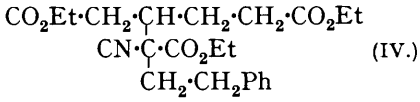
Starting with β-phenylethyl bromide, ethyl cyanoacetate and methyl Δ^{β}-dihydromuconate, the acid (II) has been obtained, but the overall yield was not encouraging.

(2) The Friedel–Crafts succinoylation of methyl γ-(6-methoxy-3 : 7-dihydro-1-naphthyl)butyrate was previously carried out in carbon disulphide solution and gave the 5-succinoyl derivative (Robinson and Walker, this vol., p. 183). It is now found that, in nitrobenzene solution, a small quantity of an isomeric acid (the 2- or 4-succinoyl derivative) is produced, but the main product is the same as that previously obtained. When a chlorine atom was introduced in the 5-position, no succinoylation could be effected and this attractive route was therefore blocked.

Some substances derived from 1-chloro-2-methoxynaphthalene are described.

(1) In the series of reactions mentioned below it was originally intended to use ethyl α-furylacetoacetate instead of ethyl cyanoacetate or ethyl malonate with the idea of subsequently oxidising the furyl nucleus to carboxyl. Furylacetic acid is, however, not readily accessible (cf. Runde, Scott, and Johnson, *J. Amer. Chem. Soc.*, 1930, **52**, 1284; Reichstein, *Ber.*, 1930, **63**, 749; Erlenmeyer and Stadlin, *Annalen*, 1904, **337**, 283), and for this reason we made a ketonic ester (III) from methronic acid which might have served just as well. In view of our later experiences it seemed hopeless to persevere with this idea. The scheme

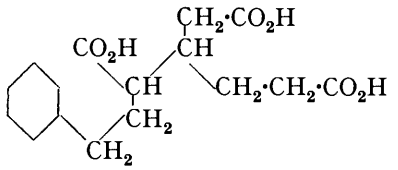
(III.) 

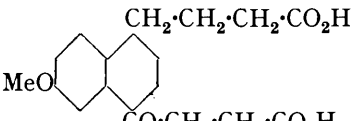
 (IV.)

of synthesis was therefore tested in a simpler case.

Farmer (J., 1923, **123**, 3324) has shown that esters of Δ^{β}-dihydromuconic acid are in equilibrium with those of Δ^{α}-dihydromuconic acid in the presence of basic catalysts and that in Michael additions the βγ-unsaturated ester may be employed instead of the αβ-isomeride.

Methyl Δ^{β}-dihydromuconate and ethyl cyanoacetate gave an adduct, which was hydrolysed with formation of β-carboxymethyladipic acid. Phenylethylation, followed by hydrolysis, or hydrolysis of the adduct (IV) of methyl Δ^{β}-dihydromuconate and *ethyl α-cyano-γ-phenylbutyrate*, afforded (V). The cyclisation of (V) to the keto-dibasic *acid* (II) was effected by means of sulphuric acid.

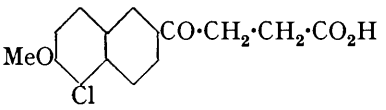
(V.) 

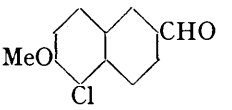
 (VI.)

(2) Although 2-methoxynaphthalene is acylated in Friedel–Crafts reactions in carbon disulphide in the 2-position, Haworth and Sheldrick (J., 1934, 864; cf. Short, Stromberg, and Wiles, J., 1936, 319) showed that the 6-position is attacked in a nitrobenzene medium.

The succinoylation of methyl γ-(6-methoxy-3 : 4-dihydro-1-naphthyl)butyrate (*loc. cit.*) in carbon disulphide solution was found to be accompanied by disproportionation and acids $C_{19}H_{20}O_6$ and $C_{19}H_{24}O_6$ were isolated. The former was recognised as the 5-succinoyl

derivative of γ-(6-methoxy-1-naphthyl)butyric acid. When nitrobenzene was used, this substance was still the main product, but an isomeride was also obtained, probably (VI). Hindrance in the 2-position is indicated by the fact that γ-(5-chloro-6-methoxy-1-naphthyl)-butyric ester could not be succinoylated (*o*- and *peri*-hindrance), whereas 1-chloro-2-methoxynaphthalene afforded β-(5-*chloro*-6-*methoxy*-2-*naphthoyl*)*propionic acid* (VII) in good yield.

(VII.) 



(VIII.)

Oxidation of (VII) with alkaline hypochlorite gave about equal amounts (39% yield each) of the *aldehyde* (VIII) and the corresponding *acid*. 1- and 4-*Keto*-8-*chloro*-7-*methoxy*-1 : 2 : 3 : 4-*tetrahydrophenanthrenes* have been prepared.

Experimental.

Ethyl α-Cyano-γ-phenylbutyrate.—The mono-phenylethylation of ethyl cyanoacetate is even more difficult than that of ethyl malonate (cf. Cohen, Marshall, and Woodman, J., 1915, **107**, 895) and the formation of a considerable proportion of disubstituted ester could not be avoided.

The condensation was carried out under the usual conditions with ethyl cyanoacetate (68 g.; 2 mols.), sodium (6·9 g.), alcohol (160 c.c.), and β-phenylethyl bromide (55 g.; 1 mol.); the mixture was refluxed for 4 hours. There were obtained 39 g., b. p. 170—173°/10 mm., $n_D^{16°}$ 1·5008; redistilled, b. p. 182—183°/17 mm., *n* unaltered (Found : C, 71·5; H, 7·1. $C_{13}H_{15}O_2N$ requires C, 71·9; H, 6·9%). The corresponding *acid*, obtained after hydrolysis of the ester with 20% aqueous sodium hydroxide for 2 hours at 0°, crystallised from benzene–light petroleum (b. p. 60—80°) in rhombic plates, m. p. 74·5° (Found : N, 7·4. $C_{11}H_{11}O_2N$ requires N, 7·4%).

5-Carboxy-4-carboxymethyl-7-phenylheptoic Acid (V).—Methyl and ethyl Δ^{β}-dihydromuconates were obtained by Farmer's method (J., 1923, **123**, 2541) in 50—54% yield calculated on the mucic acid employed. It was found that the crude chlorinated ester intermediates could be reduced directly without fractionation.

(A) Ethyl cyanophenylbutyrate (26 g.) and then methyl Δ^{β}-dihydromuconate (21·5 g.) in ether (100 c.c.) were successively added to a solution of potassium ethoxide (4·8 g. of potassium) in alcohol (35 c.c.). The mixture was refluxed for 10 minutes and kept for 2 days. The product, isolated by means of ether, was a very viscous, pale yellow oil, b. p. 215—230°/0·5 mm. (almost all at 220—225°) (22 g. or 46%); $n_D^{16°}$ 1·5100. When ethyl Δ^{β}-dihydromuconate was used, the product had b. p. 225—230°/0·4 mm. The analyses gave unsatisfactory results for carbon but the anticipated value for nitrogen.

(B) Ethyl cyanoacetate (26 g.) and methyl Δ^{β}-dihydromuconate (20 g.) were successively added to a solution of sodium ethoxide (3·5 g. of sodium) in alcohol (80 c.c.). The mixture was refluxed for 2 hours and kept for 2 days. On working up in the usual fashion, 26 g. (79%), b. p. 178—180°/0·3 mm., were obtained. On hydrolysis with boiling hydrochloric acid, β-carboxymethyladipic acid, m. p. 123°, was obtained (cf. Farmer, *loc. cit.*). This adduct (25 g.) was added to a suspension of powdered potassium (3 g.) in toluene (300 c.c.), and the mixture refluxed until a clear solution was obtained. After the addition of β-phenylethyl bromide (20 g.) the refluxing was continued for 16 hours; a further quantity of the bromide (5 g.) was then introduced, and the mixture refluxed for 12 hours more. The solution was washed with aqueous sodium carbonate and with water, dried, and distilled. After toluene, there were obtained 10 g., b. p. 160—210°/0·4 mm. (mainly 175—180°), consisting of unchanged ester, and 12·5 g., b. p. 210—225°/0·4 mm., apparently identical with the ester obtained as in (A) above (IV).

The ester from (A) or (B) (20 g.) was hydrolysed by boiling for 8 hours with an excess of 20% aqueous alcoholic potassium hydroxide, followed by isolation of the acid product and boiling of this with concentrated hydrochloric acid for 8 hours. The oil, isolated in the known manner, did not crystallise and was esterified by means of diazomethane. The resulting methyl ester had b. p. 200—205°/0·7 mm. (8 g.) and on hydrolysis with 20% aqueous potassium hydroxide gave a syrupy acid, which crystallised on long contact with ethyl acetate–light petroleum (b. p. 40—60°). The tricarboxylic *acid* crystallised from ether–light petroleum (b. p. 40—60°) and then from water as a sandy crystalline powder, m. p. 139—140° (Found : C, 62·4; H, 6·5. $C_{14}H_{20}O_6$ requires C, 62·3; H, 6·5%).

β-(1-*Keto*-1 : 2 : 3 : 4-*tetrahydro*-2-*naphthyl*)*adipic Acid* (II).—The above tricarboxylic acid was dissolved in 20 times its weight of sulphuric acid at 0°, and the solution kept for 40 minutes at 0°. After the addition of ice, the product was isolated and crystallised from ethyl acetate–light

petroleum (b. p. 40—60°) and then from water. Several recrystallisations were necessary in order to remove the unchanged material, but the pure *acid* was eventually obtained in rhombohedra, m. p. 158—159° (Found: C, 66·6; H, 6·2. $C_{16}H_{18}O_6$ requires C, 66·2; H, 6·2%). The keto-group in this substance is inert and no semicarbazone could be obtained as was the case with the somewhat similarly constituted 1-keto-2-(*trans*-2′-carbomethoxy*cyclo*pentyl)-1 : 2 : 3 : 4-tetrahydronaphthalene (Rapson and Robinson, J., 1935, 1533).

Ethyl 4-*Carbethoxy*-5-*methylfuran*-2-*acetoacetate* (III).—Monoethyl methronate (Trephilieff, *Ber.*, 1906, **39**, 1860) (10·5 g.), by the thionyl chloride–ether–pyridine method, gave the acid chloride, b. p. 124—127°/0·5 mm. (4·8 g.). This substance (11·5 g.) was condensed with ethyl sodioacetoacetate (6·5 g. of the ester), and the product hydrolysed according to the general method of Claisen (*Annalen*, 1896, **291**, 67). The keto-ester (5·2 g.) had b. p. 150—157°/14 mm.; it redistilled as a pale yellow, limpid oil, b. p. 153—156°/14 mm. (3·1 g.) (Found: C, 60·1; H, 6·7. $C_{14}H_{18}O_6$ requires C, 59·6; H, 6·4%). It gave a ferric reaction in alcoholic solution and rapidly darkened in the air.

Condensation of Methyl γ-(6-*Methoxy*-1-*naphthyl*)*butyrate with* β-*Carbomethoxypropionyl Chloride in the Presence of Aluminium Chloride in Nitrobenzene Solution.*—Methyl methoxynaphthylbutyrate (6·1 g.) and carbomethoxypropionyl chloride (5·2 g.) were gradually and alternately added to a well-stirred solution of aluminium chloride (7·5 g.) in nitrobenzene (65 c.c.) below 0°. After 36 hours at room temperature the product was isolated (and methylated) exactly as described by Robinson and Walker (*loc. cit.*) except that longer steam-distillation was necessary in order to remove the nitrobenzene. The solid was extracted twice with boiling light petroleum (b. p. 40—60°), very little passing into solution, and once with hot water. After drying, it was dissolved in ethyl acetate (100 c.c.), filtered from a few flocks, mixed with benzene (100 c.c.), and kept in the ice-box. The crystals (2·6 g.) consisted of almost pure γ-(6-methoxy-5-succinoyl-1-naphthyl)butyric acid and gave a good yield of 1-keto-7-hydroxy-1 : 2 : 3 : 4-tetrahydrophenanthrene (dinitrophenylhydrazone of the methyl ether, m. p. 304°) on boiling with concentrated hydriodic acid. After recrystallisation the acid had m. p. 157°, alone or mixed with the specimen previously obtained.

The mother-liquor was mixed with light petroleum (1·5 vols., b. p. 40—60°) and kept below 0° for a few days; it deposited a greenish-grey crystalline crust, which was treated with boiling acetone (10 c.c.) and again chilled. The solid crystallised from aqueous acetic acid in colourless prismatic needles, m. p. 201—202° (Found in material dried at 100°: C, 65·7, 66·1; H, 6·4, 6·0. $C_{19}H_{20}O_6$ requires C, 66·3; H, 5·8%). The acid is ketonic (yellow dinitrophenylhydrazone, soluble in aqueous sodium carbonate) and saturated to permanganate. On demethylation with hydriodic acid, a β-naphthol derivative (red azo-compound) was produced and, on methylation, the original acid, m. p. 200—201°, was regenerated. Hence this substance is doubtless γ-(6-*methoxy*-2- or 4-*succinoyl*-1-*naphthyl*)*butyric acid.* As there was no evidence of the formation of a neutral ketone on strong heating with acetic anhydride and distillation to incipient decomposition, the succinoyl group is perhaps to be located in position 4 (VI) with the greater probability.

γ-(5-*Chloro*-6-*methoxy*-1-*naphthyl*)*butyric Acid.*—This acid is the main product of the action of phosphorus pentachloride on methoxynaphthylbutyric acid, but cyclisation also occurs and it is better to chlorinate the methyl ester. On hydrolysis of the product (below) the *acid* is obtained and this separates from alcohol or acetic acid in colourless leaflets, m. p. 189—190° (Found: C, 64·3; H, 5·6. $C_{15}H_{15}O_3Cl$ requires C, 64·6; H, 5·4%).

The *methyl* ester was obtained by heating a mixture of methyl γ-(6-methoxy-1-naphthyl)-butyrate (6·25 g.) and phosphorus pentachloride (5·3 g.) for 10 minutes on the steam-bath. After decomposition with water, the product was collected, washed, and crystallised from methyl alcohol. The glistening, colourless plates (6·2 g.) had m. p. 76·5° (Found: C, 65·8; H, 5·7; Cl, 12·3. $C_{16}H_{17}O_3Cl$ requires C, 65·7; H, 5·8; Cl, 12·1%). When an attempt was made to condense this ester with β-carbomethoxypropionyl chloride under the conditions prescribed above for the chlorine-free ester, no succinoylation occurred and the above chloro-acid was recovered as the sole product.

8-*Chloro*-1-*keto*-7-*methoxy*-1 : 2 : 3 : 4-*tetrahydrophenanthrene.*—A mixture of γ-(5-chloro-6-methoxy-1-naphthyl)butyric acid (0·6 g.), sulphuric acid (6 c.c.), and water (2 c.c.) was heated for 30 minutes at 100°, then diluted with water, and the precipitate collected. The material was triturated with hot dilute aqueous sodium hydroxide, collected, washed with water, and crystallised (0·48 g.) from acetic acid. The *ketone* crystallised from ethyl acetate (charcoal) in colourless, prismatic needles, m. p. 219—220° (Found: C, 68·8; H, 5·0. $C_{15}H_{13}O_2Cl$ requires C, 69·1; H, 5·0%).

β-(5-*Chloro*-6-*methoxy*-2-*naphthoyl*)*propionic Acid* (VII).—1-Chloro-2-methoxynaphthalene

(14·4 g.) and β-carbomethoxypropionyl chloride (12·4 g.) were added gradually and alternately during 15 minutes to a solution of aluminium chloride (20 g.) in nitrobenzene (60 c.c.), cooled in a freezing mixture and well shaken. After 36 hours at room temperature, ice was added, and the nitrobenzene distilled in steam. On cooling, the residue solidified; it was collected, hydrolysed by means of hot 10% aqueous sodium hydroxide, and the *acid* isolated as usual. It crystallised from ethyl alcohol (charcoal) in colourless, glistening plates, m. p. 199—200° (yield, 17 g. or 78%) (Found: C, 61·2; H, 4·5; Cl, 12·3. $C_{15}H_{13}O_4Cl$ requires C, 61·5; H, 4·4; Cl, 12·1%).

The *methyl* ester, prepared by refluxing the acid with 15% methyl-alcoholic hydrogen chloride, crystallised from methyl alcohol in plates, m. p. 156° (Found: C, 62·4; H, 4·8. $C_{16}H_{15}O_4Cl$ requires C, 62·6; H, 4·9%).

β-(6-*Hydroxy*-2-*naphthoyl*)*propionic Acid*.—A mixture of chloromethoxynaphthoylpropionic acid (1 g.), hydriodic acid (8 g., *d* 1·7), acetic acid (29 c.c.), and water (1 c.c.) was refluxed for 18 hours, then cooled, diluted with water, and free iodine removed by passage of sulphur dioxide. The solid was collected, washed with water, and crystallised from aqueous alcohol, being obtained in prismatic needles, m. p. 235° (decomp.) (Found: C, 68·8; H, 5·0. $C_{14}H_{12}O_4$ requires C, 68·9; H, 4·9%). The yellow solution in aqueous sodium carbonate exhibited an intense green fluorescence. The bright scarlet *p*-nitrobenzeneazo-derivative dissolved in sulphuric acid to an eosin-red solution.

5-*Chloro*-6-*methoxy*-2-*naphthoic Acid*.—A solution of chloromethoxynaphthoylpropionic acid (3 g.) in an alkaline hypochlorite solution (300 c.c., 0·5N-sodium hydroxide; 0·25M-sodium hypochlorite) was heated for 20 minutes on the steam-bath and then boiled for 20 minutes. A solid (see below) separated during this period and the liquid was filtered hot and then acidified by the passage of sulphur dioxide. The precipitated *acid* (0·95 g.) crystallised from alcohol in slender needles, m. p. 305° (Found: C, 60·7; H, 3·8. $C_{12}H_9O_3Cl$ requires C, 60·9; H, 3·9%). Demethylation and dechlorination by means of boiling hydriodic acid in acetic acid solution afforded 6-hydroxy-2-naphthoic acid, m. p. 240° (Butler and Royle, J., 1923, **123**, 1654), which exhibited the distinctive purple fluorescence in alkaline solution.

5-*Chloro*-6-*methoxy*-2-*naphthaldehyde* (VIII).—The solid (0·88 g.), obtained in the course of the experiment last described, crystallised from alcohol in colourless prisms, m. p. 141° (Found: C, 65·2; H, 4·2; Cl, 16·0. $C_{12}H_9O_2Cl$ requires C, 65·3; H, 4·1; Cl, 16·1%). On oxidation with alkaline potassium permanganate it gave 5-chloro-6-methoxy-2-naphthoic acid, m. p. and mixed m. p. 305°. The 2 : 4-*dinitrophenylhydrazone* was very sparingly soluble in most organic solvents; it crystallised from toluene in red prisms, m. p. 315° (decomp.) (Found: N, 13·9. $C_{18}H_{13}O_5N_4Cl$ requires N, 14·0%).

β-(5-*Chloro*-6-*methoxy*-2-*naphthyl*)*acrylic Acid*.—A mixture of chloromethoxynaphthaldehyde (0·8 g.), malonic acid (0·8 g.), a drop of piperidine, and pyridine (5 c.c.) was heated on the steam-bath for 3 hours. The *acid* then precipitated by dilute hydrochloric acid was collected, washed, and dried. It was sparingly soluble in most organic solvents and crystallised from much acetic acid in prisms, m. p. 310° (Found: C, 63·9; H, 4·3; Cl, 13·2. $C_{14}H_{11}O_3Cl$ requires C, 64·0; H, 4·2; Cl, 13·5%).

γ-(5-*Chloro*-6-*methoxy*-2-*naphthyl*)*butyric Acid*.—A mixture of chloromethoxynaphthoylpropionic acid (4 g.), toluene (20 c.c.), amalgamated zinc filings (20 g.), hydrochloric acid (16 c.c.), and water (20 c.c.) was refluxed for 12 hours with further additions of hydrochloric acid (2 c.c.) every 2 hours. The product was isolated by extraction with ethyl acetate and washing of the concentrated solution with aqueous sodium carbonate. The alkaline solutions were acidified, and the precipitate collected and crystallised from aqueous alcohol, being obtained in colourless plates (1·9 g.), m. p. 137—138° (Found: C, 64·2; H, 5·4. $C_{15}H_{15}O_3Cl$ requires C, 64·6; H, 5·4%).

8-*Chloro*-4-*keto*-7-*methoxy*-1 : 2 : 3 : 4-*tetrahydrophenanthrene*.—A mixture of chloromethoxynaphthylbutyric acid (0·4 g.), sulphuric acid (3 c.c.), and water (1 c.c.) was heated at 100° for 30 minutes. The neutral product, freed from acid by washing in ethereal solution with dilute aqueous sodium hydroxide, crystallised from methyl alcohol in colourless prisms (0·275 g.), m. p. 169—170° (Found: C, 69·3; H, 5·2. $C_{15}H_{13}O_2Cl$ requires C, 69·1; H, 5·0%). The ketonic properties were qualitatively observed by the ready formation of a sparingly soluble, yellow benzylidene derivative and an orange-red dinitrophenylhydrazone.

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