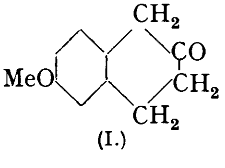
378. *Experiments on the Synthesis of Substances related to the Sterols. Part XXIV. Some Derivatives of β-Tetralone.*

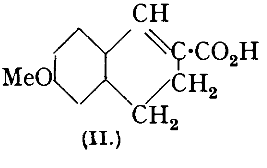
By G. P. Crowley and Robert Robinson.

β-Tetralone and 6-*methoxy*-β-*tetralone* (I) have been obtained by the Curtius degradation of dihydro-2-naphthoic acid and its 6-*methoxy*-derivative (II). The latter is available after cyclisation of the formylation product (III) of ethyl γ-*m*-methoxyphenylbutyrate.

The sodio-derivative of (I) condenses with 4-diethylaminobutan-2-one methiodide



(I.)



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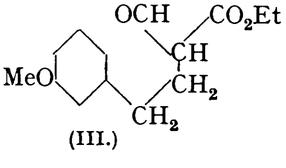
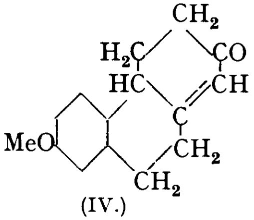


(III.)

with formation of (IV), characterised as a 2 : 4-*dinitrophenylhydrazone*. An *acid* (V) corresponding to (II) in the phenanthrene series has been prepared, but has not yet been converted into the ketomethoxytetrahydrophenanthrene; work along these lines is in progress. The ethoxalyl derivative of ethyl γ-*m*-methoxyphenylbutyrate has also been prepared and dehydrated with formation of a methoxydihydronaphthalene-dicarboxylic acid (VI) (cf. Fieser and Hershberg, 1935).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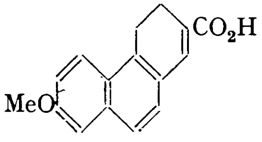
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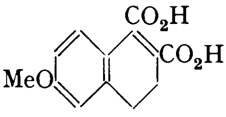
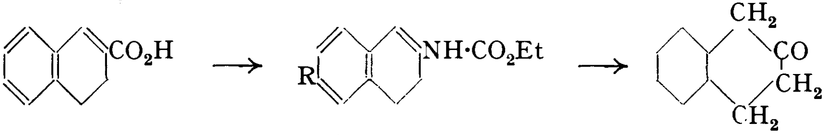

(VI.)

In several sections of this investigation we have studied various 1-keto- and 3-keto-derivatives of hydrophenanthrene, but there is no doubt that 2-keto-7-methoxy-1 : 2 : 3 : 4-tetrahydrophenanthrene, if accessible, would also be a valuable intermediate in the synthesis of equilenin; similarly, the related methoxyoctahydrophenanthrone offers a plausible route to oestrone. Unfortunately it is not easy to devise a satisfactory synthesis of these substances.

The experiments now placed on record may serve as models for their synthesis, but even so the desirable β-hydrophenanthrones could only be obtained by making laborious many-staged preparations.

3 : 4-Dihydro-β-naphthoic acid (VII) (Derick and Kamm, *J. Amer. Chem. Soc.*, 1916, **38**, 400) has been converted by way of its ethyl ester into a hydrazide, and the azide therefrom on boiling with alcohol and hydrolysis of the resulting urethane (VIII, R = H) affords β-tetralone (IX), the process being more expeditious and giving better overall yields than that of Bamberger and Voss (*Ber.*, 1894, **27**, 1547) in which dihydronaphthalene chlorohydrin is employed.


(VII.) (VIII.) (IX.)

In the 6-methoxy-series a similar method has been used, the cyclisation of the ester of (II) being best accomplished by the use of a mixture of sulphuric and phosphoric acids in order to avoid the sulphonation which occurs if sulphuric acid is used alone.

Ethyl α-ethoxalyl-γ-*m*-methoxyphenylbutyrate was cyclised by a method similar to that used by Auwers and Müller (*J. pr. Chem.*, 1925, **217**, 124) and by Fieser and Hershberg (*J. Amer. Chem. Soc.*, 1935, **57**, 1851) in analogous cases and a number of derivatives of 6-*methoxy*-3 : 4-*dihydronaphthalene*-1 : 2-*dicarboxylic acid* (VI) have been prepared.

The *imide* was submitted to the action of sodium hypochlorite in methyl-alcoholic solution (Weerman), but no ketonic product could be isolated.

EXPERIMENTAL.

β-*Tetralone*.—A mixture of ethyl 3 : 4-dihydro-β-naphthoate (13·6 g.), hydrazine hydrate (5 g.), and alcohol (3 c.c.) was refluxed (oil-bath at 120°) for 6 hours. The *hydrazide* separated on cooling and, after washing with cold alcohol, was crystallised from alcohol. The colourless prisms had m. p. 141° (Found : N, 15·0. $C_{11}H_{12}ON_2$ requires N, 14·9%).

A solution of sodium nitrite (3·8 g.) in water (10 c.c.) was gradually added to one of the hydrazide (9 g.) in hydrochloric acid (300 c.c. of 0·33N) at 0°. The azide separated and was collected and dried over potassium hydroxide in a vacuum (8·5 g.). The whole product was refluxed with alcohol (20 c.c.) for 3 hours, the alcohol evaporated, and the residue stirred with sulphuric acid (200 c.c. of 0·33N) for 3 hours at 100°. The tetralone formed was isolated by means of ether and distilled, b. p. 140°/18 mm. (3·9 g.); ethyl carbamate was obtained as a by-product. The phenylhydrazone formed yellow plates, m. p. 108°.

6-*Methoxy*-3 : 4-*dihydro*-β-*naphthoic Acid* (II).—Ethyl γ-*m*-methoxyphenylbutyrate, a colourless oil, b. p. 170—1°/20 mm., was obtained in 90% yield by refluxing the acid with an excess of alcoholic sulphuric acid (2·5%). A solution of this ester (141 g.) and *iso*amyl formate (88·4 g.) in ether (100 c.c.) was slowly added to a suspension of alcohol-free sodium ethoxide (43·6 g.) in ether at 0°. After 2 hours the mixture was allowed to reach room temperature and after 2 days it was decomposed with ice. The separated aqueous layer was washed with ether (from the combined ethereal solutions, 50—60 g. of unchanged ester were recovered) and acidified with dilute sulphuric acid, the product isolated by means of ether, and traces of *iso*amyl formate removed by exposure to a vacuum and heating in the steam-bath. The residual oil (60 g.), consisting of mixed ethyl and *iso*amyl α-formyl-γ-*m*-methoxyphenylbutyrates, could not be crystallised. It gave a reddish-blue ferric reaction in alcoholic solution.

The formyl derivative (60 g.) was added with stirring to a mixture of phosphoric acid (200 c.c., *d* 1·75) and sulphuric acid (50 c.c.) at − 10°. After 2 hours the red solution was poured on ice, the product taken up in ether, and the extract washed with aqueous sodium carbonate, dried, and distilled, b. p. 162—170°/0·3 mm. (55 g.).

The cyclisation was also effected by heating the formyl derivative (10 g.) at 230—240°/30 mm. until the ferric reaction was negative. The yield of distilled mixed condensed esters was inferior (4·5 g.).

The distilled condensate (5 g.) was refluxed for 1½ hours with aqueous sodium hydroxide (20 c.c. of 20%) and at this stage the formation of some *iso*amyl alcohol, resulting from alkyl transposition in the esters, was noted. The cold, diluted solution was acidified; the solid (3 g.) obtained crystallised from alcohol in prisms, m. p. 176°, that readily sublimed (Found: C, 71·0; H, 6·1. $C_{12}H_{12}O_3$ requires C, 70·6; H, 5·9%).

The *ethyl* ester (2·2 g., b. p. 148°/0·5 mm.) was isolated after a mixture of the acid (2·5 g.), alcohol (40 c.c.), and sulphuric acid (1·3 c.c.) had been refluxed for 6 hours (Found: C, 72·4; H, 6·8. $C_{14}H_{16}O_3$ requires C, 72·4; H, 6·8%).

For the preparation of the *hydrazide* it was unnecessary to obtain the pure ethyl ester. A mixture of the distilled condensate mixture (55 g.), hydrazine hydrate (20 g.), and alcohol (10 c.c.) was refluxed (bath at 115°) for 7 hours. The hydrazide (37 g.) separated on cooling (1 g. more from the filtrate and washings) and after washing with alcohol and drying could be used for the next stage. The substance crystallised from alcohol in colourless plates, m. p. 145° (Found: N, 12·9. $C_{12}H_{14}O_2N_2$ requires N, 12·8%).

6-*Methoxy*-3 : 4-*dihydro*-β-*naphthylurethane* (VIII, R = MeO).—A solution of sodium nitrite (20 g.) in water (50 c.c.) was added to one of the above hydrazide (37·5 g.) in hydrochloric acid (1000 c.c. of 0·5N) at − 2°. After ½ hour the pale yellow prisms of the azide were collected, washed, and dried (39 g.). This product, mixed with alcohol (300 c.c.), was heated to 70° and when the vigorous evolution of nitrogen ceased, the solution was refluxed for 1½ hours and then concentrated to half its volume. On cooling, the *urethane* separated in colourless prisms (36 g.), m. p. 116° after recrystallisation from alcohol (Found: N, 5·7. $C_{14}H_{17}O_3N$ requires N, 5·6%).

Phthalo-6′-*methoxy*-3′ : 4′-*dihydro*-β-*naphthylimide*.—A mixture of methoxydihydronaphthylurethane (2 g.) and phthalic anhydride (1·6 g.) was heated at 220° until evolution of gas ceased. After cooling to about 100°, the product was triturated with aqueous potassium hydrogen carbonate, and the solid collected and washed with warm methyl alcohol. The *derivative* (2 g.) crystallised from alcohol in straw-coloured needles, m. p. 195° (Found: C, 74·5; H, 4·8. $C_{19}H_{15}O_3N$ requires C, 74·7; H, 4·9%).

6-*Methoxy*-β-*tetralone* (I).—A suspension of methoxydihydronaphthylurethane (36 g.) in sulphuric acid (1000 c.c. of 0·6N) was gradually heated to 100° with stirring. After 3 hours the product was isolated by means of ether and distilled. The fraction, b. p. 80—90°/11 mm., crystallised from light petroleum in colourless plates, m. p. 49° (Found: C, 40·4; H, 7·9. Calc. for $C_3H_7O_2N$: C, 40·4; H, 7·8%), and was then identified as ethyl carbamate. The fraction, b. p. 164°/11 mm. (20 g.), solidified on cooling; it crystallised from light petroleum (b. p. 40—60°) in colourless needles, m. p. 36° (Found: C, 74·7; H, 6·8. $C_{11}H_{12}O_2$ requires C, 75·0; H, 6·8%). The *ketone* forms a crystalline sodium bisulphite adduct. The 2 : 4-*dinitrophenylhydrazone* crystallised from alcohol in orange prisms, m. p. 132° (Found: N, 15·5. $C_{17}H_{16}O_5N_4$ requires N, 15·7%).

2 : 4-*Dinitrophenylhydrazone of* 2-*Keto*-7-*methoxy*-2 : 3 : 4 : 9 : 10 : 12-*hexahydrophenanthrene* (IV for the ketone).—A mixture of 6-methoxy-β-tetralone (10 g.), ether (50 c.c.), and powdered sodamide (2·25 g.) was stirred at room temperature for 7 hours in a stream of nitrogen and then

refluxed for ½ hour. A solution of 4-diethylaminobutan-2-one methiodide (16 g.) in alcohol (10 c.c.) was gradually added to the cold mixture and after 12 hours the whole was refluxed for ½ hour. Dilute hydrochloric acid and ether were added and the ethereal layer was separated, dried, and distilled. Methoxytetralone (0·9 g.), b. p. 136°/0·3 mm., was recovered and the next considerable fraction was a pale yellow oil (2·4 g.), b. p. 180—195°/0·3 mm.; redistilled, b. p. 178—181°/0·3 mm. The red 2 : 4-*dinitrophenylhydrazone* from this crystallised from ethyl acetate–toluene in prisms, m. p. 186—187° (Found: C, 61·7; H, 5·1; N, 13·7. $C_{21}H_{20}O_5N_4$ requires C, 61·8; H, 4·9; N, 13·7%).

From the considerable gummy residue, obtained as the result of decomposition or more complex condensations, a crystalline *substance* was extracted by boiling *n*-butyl alcohol. It was very sparingly soluble and crystallised from butyl alcohol in needles, m. p. 247° (Found: C, 80·1; H, 5·4. $C_{22}H_{18}O_3$ requires C, 80·0; H, 5·4%). This may be $2C_{11}H_{12}O_2 - H_2O - 2H_2$, that is, a dehydrogenated dimethoxytetrylidenetetralone. Particularly, but not exclusively, when an excess of diethylaminobutanone methiodide was employed, an ether-insoluble part of the crude product was obtained. This had m. p. 228° after crystallisation from alcohol (Found: C, 75·0; H, 8·5. C_6H_8O requires C, 75·0; H, 8·3%). The *substance* is probably a polymeride of the simple formula indicated; it has no ketonic properties.

3 : 4-*Dihydrophenanthrene*-2-*carboxylic Acid*.—γ-1-Naphthylbutyric acid (Haworth, J., 1932, 1128) was esterified with alcoholic sulphuric acid (90% yield, b. p. 209—210°/13 mm. Cf. Fieser and Hershberg, *J. Amer. Chem. Soc.*, 1935, **57**, 1853). This ester (15 g.) and *iso*-amyl formate were condensed (4·32 g. of sodium ethoxide) as described above in another case. The resulting formyl derivative (7·8 g.) was mixed with phosphoric acid (15 c.c., *d* 1·75) and sulphuric acid (60 c.c.) at − 5° and after 3 hours at this temperature the mixture was poured on ice and the esters were isolated and hydrolysed by refluxing with aqueous sodium hydroxide (30 c.c. of 20%). The *acid* (6 g.) obtained on acidification crystallised from toluene in waxy plates, m. p. 234° (Found: C, 80·1; H, 5·4. $C_{15}H_{12}O_2$ requires C, 80·3; H, 5·3%). The *ethyl* ester, obtained by the use of alcoholic sulphuric acid, had b. p. 192—193°/0·4 mm. (Found: C, 80·8; H, 6·2. $C_{17}H_{16}O_2$ requires C, 81·0; H, 6·3%).

7-*Methoxy*-3 : 4-*dihydrophenanthrene*-2-*carboxylic Acid* (V).—γ-6-Methoxy-3 : 4-dihydro-1-naphthylbutyric acid (Robinson and Walker, J., 1937, 63) was dehydrogenated by heating with sulphur to γ-6-methoxy-1-naphthylbutyric acid, m. p. 151°, which was esterified with alcoholic hydrogen chloride (ethyl ester, b. p. 169°/0·2 mm. Cf. Cohen, Cook, and Hewett, J., 1936, 53).

The formylation of the ester (14·8 g.) followed the method already described (*iso*amyl formate, 7·6 g., and sodium ethoxide, 3·74 g.). A mixture of the formyl derivatives (6 g.), phosphoric acid (25 c.c., *d* 1·75), and sulphuric acid (55 c.c.) was kept for 3 hours at − 10°, then worked up as usual and the cyclised product hydrolysed by boiling with aqueous sodium hydroxide (30 c.c. of 20%). The *acid* (4·7 g.) was precipitated on acidification of the diluted solution and after three crystallisations from acetic acid was obtained in almost colourless plates, m. p. 242° (Found: C, 75·5; H, 5·6. $C_{16}H_{14}O_3$ requires C, 75·6; H, 5·5%).

Derivatives of 6-*Methoxy*-3 : 4-*dihydronaphthalene*-1 : 2-*dicarboxylic Acid* (VI).—Alcohol (20 c.c.) was added to a suspension of finely divided potassium (5·4 g.) in ether (100 c.c.) and, when the formation of ethoxide was complete, ethyl oxalate (26 g.) was introduced with cooling. After ½ hour ethyl γ-*m*-methoxyphenylbutyrate (30 g.) was added, and the red mixture kept for about 12 hours. The potassium salt that had separated was washed with ether and decomposed with ice and dilute sulphuric acid. The product (31·5 g.) was isolated by means of ether. The whole quantity was carefully mixed with well-stirred sulphuric acid (150 c.c. of 96%) at − 15°. After 2 hours the solution was added to ice and the condensed product was isolated by means of ether (sodium carbonate washing) and distilled, finally as a pale yellow oil, b. p. 189—190°/0·7 mm. (Found: C, 66·9; H, 6·6. $C_{17}H_{20}O_5$ requires C, 67·1; H, 6·6%). When this *diethyl* ester (of VI) was hydrolysed with boiling 20% potassium hydroxide solution, and the resulting acid liberated, it was obtained as a precipitate containing some of the anhydride. In order to obtain the latter substance the crude product was boiled with chloroform for 10 minutes. The solution acquired an intense greenish-yellow fluorescence and, on cooling, pale yellow needles (m. p. 166°, b. p. 193—195°/0·6 mm.) of the *anhydride* (of VI) separated (Found: C, 67·6; H, 4·5. $C_{13}H_{10}O_4$ requires C, 67·8; H, 4·3%). Owing to the ease of dehydration the dicarboxylic acid could not be fully purified. This anhydride is formed instead of the ester if the cyclisation of the ethoxalyl derivative is conducted at − 5° instead of − 15°, but in this case some sulphonation also occurs.

The *imide* of (VI) was obtained by heating a mixture of the anhydride (9 g.) and urea (4 g.)

at 190° until frothing ceased. The product (7·6 g.) crystallised from butyl alcohol in elongated yellow prisms, m. p. 263° (Found: N, 6·1. $C_{13}H_{11}O_3N$ requires N, 6·1%).

6-*Methoxy*-1 : 2 : 3 : 4-*tetrahydronaphthalene*-1 : 2-*dicarboxylic Acid, Ethyl Ester, and Methylimide.*—A solution of the ethyl methoxydihydronaphthalenedicarboxylate (13 g.), described above, in alcohol (50 c.c.) was shaken with palladised strontium carbonate (2 g. of 2%) under hydrogen; the theoretical volume was absorbed in ½ hour. The residue (12·9 g.), after filtration and removal of the solvent, distilled as a colourless oil, b. p. 192°/0·66 mm. (Found: C, 66·7; H, 7·2. $C_{17}H_{22}O_5$ requires C, 66·7; H, 7·2%).

The *acid* was obtained on hydrolysis with hot 15% sodium hydroxide solution and subsequent acidification; it crystallised from aqueous alcohol in colourless prisms, m. p. 191° (Found: C, 62·5; H, 5·7. $C_{13}H_{14}O_5$ requires C, 62·4; H, 5·6%).

The acid was dissolved in an excess of 33% aqueous methylamine, the solution distilled, and the residue heated (bath at 200°) for 1 hour and finally distilled under 0·6 mm. The distillate crystallised from methyl alcohol in colourless prisms, m. p. 126° (Found: C, 68·8; H, 6·2. $C_{14}H_{15}O_3N$ requires C, 68·6; H, 6·1%). This *methylimide* was prepared as a reference compound in connexion with an entirely different investigation.

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DYSON PERRINS LABORATORY, OXFORD UNIVERSITY. [*Received, November 8th,* 1938.]