

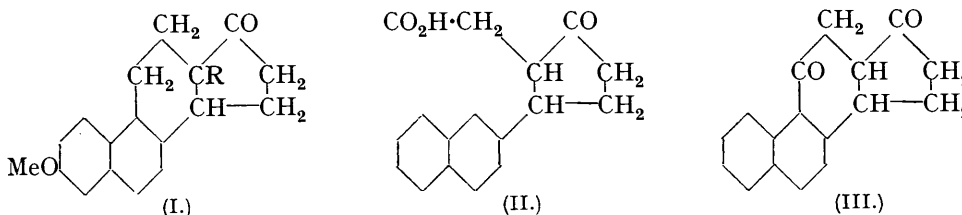
376. *Experiments on the Synthesis of Substances related to the Sterols.*
Part XXII. Synthesis of α -Norequilenin Methyl Ether.

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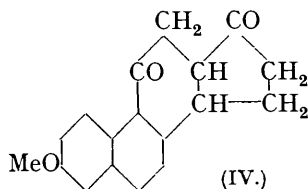
3- β -Naphthyl- Δ^2 -cyclopenten-1-one-2-acetic acid and its 6'-methoxy-derivative have already been shown to undergo ready cyclisation under the influence of acetic anhydride with formation of aromatic phenanthrene derivatives (this vol., p. 1390). The dihydro-acids have now been prepared and dehydrated to diketones which are related to tetrahydrocyclopentenophenanthrene. Following a method due to Zelinsky, the catalytic reduction of 4 : 3'-diketo-7-methoxytetrahydrocyclopentenophenanthrene has afforded a ketomethoxytetrahydrocyclopentenophenanthrene (I, R = H) which is closely related to equilenin methyl ether (I, R = Me) and may be termed α -norequilenin methyl ether, the prefix indicating undetermined stereochemical configuration.

HYDROGENATION of 3- β -naphthyl- Δ^2 -cyclopenten-1-one-2-acetic acid or of its methyl ester in methyl-alcoholic solution in the presence of palladised strontium carbonate proceeds smoothly to the dihydro-stage and the product is a ketone (*semicarbazone*) (II for the acid). Cyclisation does not occur under many of the conditions applicable in other keto-tetrahydrophenanthrene syntheses and the desired *diketone* (III) was first obtained by the use of phosphoric oxide in benzene solution. Later the yield was improved by employing phosphoric anhydride in syrupy phosphoric acid solution. The assumed direction of ring closure is in accord with many analogies.

3' : 4-Diketo-1 : 2 : 3 : 4-tetrahydro-1 : 2-cyclopentenophenanthrene (III) yields a *monosemicarbazone*, a *mono-2 : 4-dinitrophenylhydrazone* and a *monohydrazone*. As the substance bears carbonyl groups in the same relative positions as those of cholestane-3 : 6-dione, it was anticipated that condensation with hydrazine would afford a pyridazine derivative. It is clear that one of the carbonyl groups is inert and this must be that which is situated in position 4 of the phenanthrene nucleus.



The yield of (III) was moderately good, but when (IV) was prepared in a similar fashion by way of 3- β -6'-methoxynaphthylcyclopentan-1-one-2-acetic acid, the yield in the cyclisation was only 20%; other methods of dehydration were still less successful.



In this substance, also, only one carbonyl group reacts with 2 : 4-dinitrophenylhydrazine. Reduction of (IV) by hydrogen in presence of a platinum-palladium-charcoal catalyst gave a monoketone, and this is regarded as (I, R = H) because (a) the method used has been shown by Zelinsky (*Ber.*, 1933, **66**, 872) to be effective in the reduction of carbonyl groups directly attached to the aromatic nucleus and (b) reduction of the 3'-keto-group should yield an alcohol. Furthermore (c) the product readily yields a 2 : 4-dinitrophenylhydrazone. The investigation is being pursued with the object of introducing the angle-methyl group present in (I, R = Me).

EXPERIMENTAL.

Methyl 3- β -Naphthyl- Δ^2 -cyclopenten-1-one-2-acetate.—A solution of the crude acid (5 g.) (Robinson, *loc. cit.*) in methyl-alcoholic hydrogen chloride (100 c.c. of 3%) was refluxed for 3 hours. The resulting methyl ester crystallised from aqueous methyl alcohol in long colourless needles, m. p. 100° (Found : C, 77.0; H, 5.7. $C_{18}H_{16}O_3$ requires C, 77.1; H, 5.7%).

3- β -Naphthylcyclopentan-1-one-2-acetic Acid (II) and its Methyl Ester.—A mixture of the above methyl ester (3 g.), methyl alcohol (30 c.c.) and palladised strontium carbonate (1.5 g. of 2%) was shaken under hydrogen at 40° for 8 hours. The product (yield, almost theoretical) crystallised from aqueous methyl alcohol in small, colourless needles, m. p. 79–80° (Found : C, 76.6; H, 6.4. $C_{18}H_{18}O_3$ requires C, 76.6; H, 6.4%). The corresponding acid was obtained by hydrolysis of the ester in the usual way or by hydrogenation of 3- β -naphthyl- Δ^2 -cyclopenten-1-one-2-acetic acid (10 g. of acid, 100 c.c. of methyl alcohol, and 5 g. of catalyst, warmed for 12 hours at 40°). It crystallised from aqueous methyl alcohol (about 10 parts of 50%) in colourless needles, m. p. 132° (Found : C, 76.2; H, 6.1. $C_{17}H_{16}O_3$ requires C, 76.2; H, 6.0%). The *semicarbazone* of the acid crystallised from methyl alcohol in rhombic plates, m. p. 217° (Found : N, 12.9. $C_{18}H_{19}O_3N_3$ requires N, 12.9%).

3' : 4-Diketo-1 : 2 : 3 : 4-tetrahydro-1 : 2-cyclopentenophenanthrene (III).—A solution of 3- β -naphthylcyclopentan-1-one-2-acetic acid (6 g.) in syrupy phosphoric acid (20 c.c., *d* 1.75) was made by gentle heating, and phosphoric oxide (50 g.) gradually but quickly added with vigorous shaking. The temperature rose above 100° and a faint odour of naphthalene became perceptible. After 1 hour, ice was added to the dark green mixture and the product was isolated by extraction with ether and also with ethyl acetate. The solutions were washed with aqueous sodium carbonate and then with water, dried, and evaporated. The residue crystallised from a little alcohol in colourless needles (3.5 g.), m. p. 115° (Found : C, 81.6; H, 5.6. $C_{17}H_{14}O_2$ requires C, 81.7; H, 5.6%). The *semicarbazone* crystallised from alcohol in colourless prisms, m. p. 245° (Found : N, 13.3. $C_{18}H_{17}O_2N_3$ requires N, 13.1%), and the 2 : 4-dinitrophenylhydrazone from ethyl acetate as a deep orange-coloured crystalline powder, m. p. 240° (Found : N, 12.9. $C_{23}H_{18}O_5N_4$ requires N, 13.0%). The *hydrazone*, obtained by the

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use of an excess of hydrazine hydrate, crystallised from methyl alcohol in pale yellow prisms, m. p. 156° (Found: C, 77.3; H, 6.0; N, 10.9. $C_{17}H_{16}ON_2$ requires C, 77.3; H, 6.1; N, 10.6%).

The above ring closure was also effected by means of 80% sulphuric acid at 98° and by means of phosphoric oxide in a benzene medium, but the yields were unsatisfactory.

3-β-6'-Methoxynaphthylcyclopentan-1-one-2-acetic Acid.—The preparation of methoxynaphthyldiketoheptioic acid from furfurylidene-6-methoxy-2-acetylnaphthalene (Robinson, *loc. cit.*) is accompanied by partial demethylation. We have found it convenient to carry the mixed product a stage further and to methylate the mixed methoxy- and hydroxy-naphthylcyclopentenoneacetic acids. The acids obtained by the action of 2% aqueous potassium hydroxide on the crude diketo-acids (20 g.) in the manner already described (*loc. cit.*) were dissolved in aqueous sodium hydroxide (130 c.c. of 10%) and vigorously stirred; methyl sulphate (14 c.c.) was then gradually added at 40–50°. Further quantities of methyl sulphate (56 c.c.) and 2N-sodium hydroxide (280 c.c.) were alternately added in portions and the solution was finally heated on the steam-bath in order to hydrolyse the methyl ester produced. The solution was cooled and acidified, and the product collected and dried (19.2 g.). This material was refluxed for 4 hours with methyl-alcoholic hydrogen chloride (200 c.c. of 4%); the ester separated on cooling (11.2 g.) and a further quantity (5.5 g.) was obtained from the mother-liquor. *Methyl 3-β-6'-methoxynaphthyl-Δ²-cyclopenten-1-one-2-acetate* crystallised from methyl alcohol in lath-shaped prisms, m. p. 115–116° (Found: C, 73.6; H, 5.8. $C_{19}H_{17}O_4$ requires C, 73.5; H, 5.8%). Its alcoholic solutions exhibited a blue fluorescence.

When the crude, unmethylated acids were similarly esterified, the above ester separated first from methyl alcohol. The mother-liquor was added to water, and the precipitate collected and crystallised from methyl alcohol. *Methyl 3-β-6'-hydroxynaphthyl-Δ²-cyclopenten-1-one-2-acetate* was so obtained in slender prisms, m. p. 164–165° (Found: C, 72.9; H, 5.4. $C_{18}H_{16}O_4$ requires C, 73.0; H, 5.4%), soluble in aqueous sodium hydroxide to a yellow solution. It readily coupled with *p*-nitrobenzenediazonium chloride to a crimson azo-compound.

In the present case it is advantageous to hydrogenate the methyl ester rather than the acid, because the former is the more readily soluble and is the more readily purified. A mixture of the methyl ester (10 g., m. p. 115–116°), methyl alcohol (75 c.c.), and palladised strontium carbonate (3 g. of 2%) was shaken under hydrogen for 7 hours at about 40°. Absorption ceased when the theoretical volume of hydrogen had been utilised. The filtered solution, combined with hot methyl-alcoholic extracts of the residue, was mixed with aqueous potassium hydroxide (resulting solution to contain 50% H₂O and 5% KOH) and, after refluxing for 4 hours, was cooled and acidified; the crystalline precipitate was collected and dried (9.6 g.). The substance crystallised from aqueous acetic acid in small, colourless needles, m. p. 146–147° (Found: C, 72.3; H, 5.9. $C_{18}H_{18}O_4$ requires C, 72.5; H, 6.0%). The alkaline solutions were colourless; those of the unsaturated acid were yellow. The *methyl* ester crystallised from methyl alcohol in plates, m. p. 61–62° (Found: C, 73.1; H, 6.4. $C_{19}H_{20}O_4$ requires C, 73.1; H, 6.4%).

3' : 4-Diketo-7-methoxy-1 : 2 : 3 : 4-tetrahydro-1 : 2-cyclopentenophenanthrene (IV).—This was obtained in the same way as the preceding diketone, the crude methoxynaphthylcyclopentanone-acetic acid (5 g.), syrupy phosphoric acid (15 c.c., *d* 1.75), and phosphoric oxide (50 g.) being used. The product crystallised from alcohol (charcoal) in well-shaped prisms (0.9 g.), m. p. 126–127° (Found: C, 77.2; H, 5.7. $C_{18}H_{16}O_3$ requires C, 77.1; H, 5.7%). The **2 : 4-dinitrophenylhydrazone** separated from ethyl acetate as a dark red, crystalline powder, m. p. 243° (decomp.) (Found: C, 62.4; H, 4.3; N, 12.0. $C_{24}H_{26}O_6N_4$ requires C, 62.6; H, 4.3; N, 12.2%).

3'-Keto-7-methoxy-1 : 2 : 3 : 4-tetrahydro-1 : 2-cyclopentenophenanthrene (x-Norequilemin Methyl Ether) (I, R = H).—The catalyst was prepared by heating powdered active charcoal (10 g.) with a solution of platinum chloride (H₂PtCl₆ equivalent to 1 g. of platinum) at 40°, after which the mixture was rendered alkaline by the addition of sodium carbonate and a few drops of hydrazine hydrate were added. The solid was collected, thoroughly washed with water and then with alcohol, and suspended in alcohol (100 c.c.). A mixture of the above methoxydiketone (1.3 g.), the well-shaken suspension of the platinised charcoal (10 c.c.), and a solution of palladous chloride (0.1 g.) in alcohol (20 c.c.) was shaken with hydrogen at room temperature. Hydrogen equivalent to 2 mols. was absorbed during 2 hours and reduction then ceased. The filtered solution, combined with hot alcoholic extracts of the catalyst, was concentrated. The new *ketone* crystallised, on cooling, in prisms of fine appearance and was recrystallised from methyl alcohol; m. p. 116–117° (Found: C, 81.2; H, 6.8; MeO, 11.8. $C_{18}H_{18}O_2$ requires C, 81.2; H, 6.8; IMeO, 11.7%). The **2 : 4-dinitrophenylhydrazone**, readily produced in acetic

acid solution, crystallised from this solvent in large, orange-yellow, rhombic plates, m. p. 246—247° (decomp.) (Found: N, 12.7. $C_{21}H_{22}O_5N_4$ requires N, 12.6%).

Addendum.—The constitution attributed to the diketone (III) has been confirmed by its conversion into *cyclopentenophenanthrene*. A mixture of 3':4-diketo-1:2:3:4-tetrahydro-1:2-*cyclopentenophenanthrene* (2 g.), amalgamated zinc (10 g.), water (45 c.c.), concentrated hydrochloric acid (10 c.c.), acetic acid (1 c.c.), and toluene (10 c.c.) was refluxed for 24 hours, further concentrated hydrochloric acid (total 15 c.c.) being added from time to time. The toluene layer was separated, combined with ethereal extracts of the aqueous layer, dried, and distilled (the yellow solution exhibited blue fluorescence). The residue distilled, b. p. *ca.* 200°/1 mm., as a light yellow, blue-fluorescent oil. This (1.2 g.) was mixed with palladised charcoal (0.2 g.) and heated at 330°; hydrogen was then rapidly evolved. When the process appeared to be finished, the cooled mass was powdered and extracted with boiling light petroleum (b. p. 60—80°). The solutions were washed with dilute aqueous sodium hydroxide, dried, and evaporated; the residue crystallised in pale yellow needles (0.4 g.). It was partly dissolved in light petroleum (b. p. 40—60°) (charcoal), and the filtered solution concentrated. Colourless leaflets separated and the substance was thrice recrystallised from methyl alcohol and obtained in colourless leaflets, m. p. 130—132°. The m. p. of a mixture with *cyclopentenophenanthrene*, m. p. 135° (kindly supplied by Dr. G. A. R. Kon), was 133—134°. The reddish-mauve solutions of the two specimens in hot sulphuric acid were identical.

When the supposed α -norequilenin methyl ether was condensed with an excess of benzaldehyde in the presence of methyl-alcoholic sodium hydroxide, and the mixture exposed to the air, a bright yellow substance separated after 2 days. This crystallised from alcohol in yellow needles, m. p. 222°; it dissolved in sulphuric acid to a cherry-red solution exhibiting yellow fluorescence and its yellow neutral solutions had an intense green fluorescence. The piperonylidene derivative on the other hand was nearly colourless and exhibited neither the halochromic (orange in sulphuric acid) nor the fluorescent properties of the benzylidene compound. It is evident that the benzylidene derivative suffered dehydrogenation under the conditions, whereas the sparingly soluble piperonylidene derivative separated so quickly that this change did not occur. The analysis of the benzylidene compound indicated retention of solvent at 100°, but even the qualitative results support the view that the ketone described in this communication is α -norequilenin methyl ether.