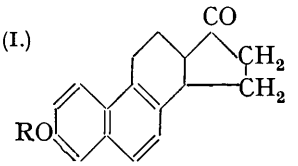
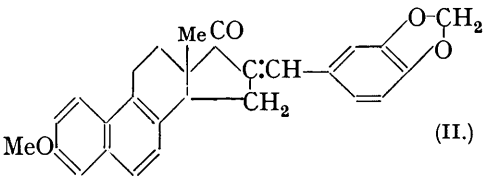
102. *Experiments on the Synthesis of Substances related to the Sterols. Part XXXVI (Continuation of Part XXII).*

By A. Koebner and Sir Robert Robinson.

In Part XXII (J., 1938, 1994) the synthesis of *x*-norequilenin methyl ether (I, R = Me) is described. It is now found that methylation of its *piperonylidene* derivative by means of potassium *tert.*-butoxide and methyl iodide in *tert.*-butyl alcoholic solution gives a *stereoisomeride* of *piperonylidene-equilenin methyl ether* (II).

(I.)

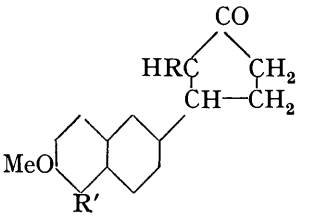


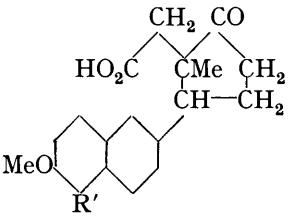


(II.)

Variations of the general line of Part XXII have been explored, especially with a view to the preparation of an acid of the type (IV) from (III, R′ = H), where R represents either the methyl group or the acetic acid residue. This has not been achieved, but other matters of interest have emerged from the work involved.

(III.)



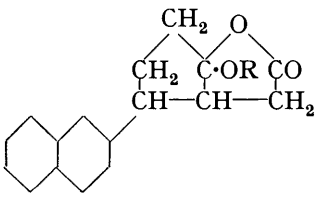


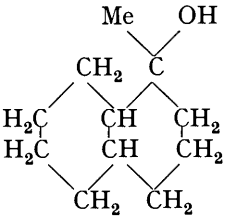
(IV.)

In attempting the cyclo-dehydration of 3-β-naphthyl*cyclo*pentan-1-one-2-acetic acid by a new method we have encountered an *isomeride* which is not soluble in aqueous sodium carbonate. It affords the semicarbazone of the original acid under mild conditions and must be either the *hydroxy-lactone* (V, R = H) or the hydrate of the enol-lactone, the former being the more probable hypothesis.

The *acetoxy-lactone* (V, R = Ac) also has been obtained.

(V.)

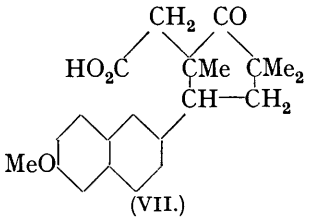




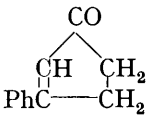
(VI.)

trans-1-*Methyl-α-decalol* (VI) has been prepared in the hope that it might serve as a model for the oxidative fission, in this case between positions 1 and 9. The possible use of the resulting diketones has been indicated in an earlier paper. The *tert.*-alcohol was found to be very resistant to oxidation. By dehydration it affords a 1-*methyloctalin* of undetermined

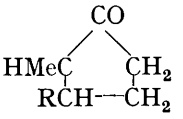
constitution. The direct methylation of methyl 3-6′-methoxy-2′-naphthyl*cyclo*pentan-1-one-2-acetate, and hydrolysis of the product, gave a trimethyl derivative, probably (VII).



(VII.)



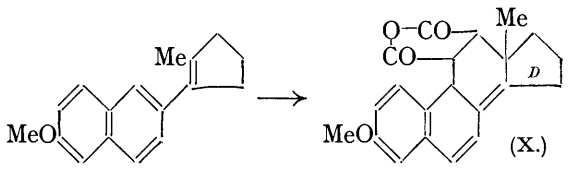
(VIII.)



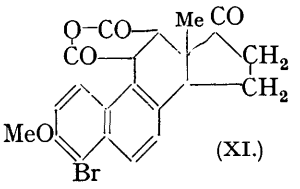
(IX.)

Borsche and Fels (*Ber.*, 1906, **39**, 1922) found that the hydrolysis of ethyl phenacylacetoacetate gave rise to the phenyl*cyclo*pentenone (VIII) and Borsche and Menz (*Ber.*, 1908, **41**, 190) reduced the substance to a saturated ketone and saturated *sec.*-alcohol. When ethyl propionylacetate is used in place of ethyl acetoacetate, substituted *cyclo*pentanones (IX) become accessible. We have prepared a number of such substances (R = phenyl, β-naphthyl, 6-methoxy-2-naphthyl, and halogenated derivatives), but have not been able to introduce the acetic acid residue ($CH_2 \cdot CO_2H$) in position 2 of the *cyclo*pentanone group. Although our main objective was not attained, a side issue is being followed up.

Wagner-Jauregg (*Annalen*, 1931, **491**, 1) showed that maleic anhydride forms a 2 : 1-adduct with *as.*-diphenylethylene, and by degradation phenylnaphthalene derivatives were obtained. Cohen and Warren (J., 1937, 1318) developed this method and synthesised a tetrahydrophenanthrenedicarboxylic acid anhydride from α-vinylnaphthalene and maleic anhydride. The idea of Bergmann and Bergmann (*J. Amer. Chem. Soc.*, 1937, **59**, 1443) to apply this method to the synthesis of chrysene derivatives was realised by Bachmann and Kloetzel (*J. Amer. Chem. Soc.*, 1938, **60**, 2204) in several cases, of which the most interesting is that shown below. It was assumed, presumably from formal analogy with



(X.)



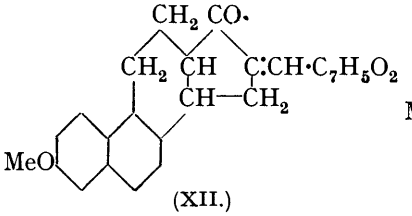
(XI.)

other " diene " syntheses, that the substance (X) is a 2 : 3 : 4 : 12-tetrahydrophenanthrene derivative, but no proof was offered of this and it seems possible that the aromatic naphthalene nucleus remains intact and the substance is a derivative of 1 : 2 : 3 : 4-tetrahydrophenanthrene. The anhydride (X) bears no reactive group in ring *D* and, although we thought it unlikely to succeed, it seemed desirable to attempt the addition of maleic anhydride to a substance of the type (VIII) in which R is a β-naphthyl radical. Such an adduct (XI) has been prepared and the transformations of this class of compound will, it is hoped, be studied in detail. The constitution figured is advanced provisionally pending further information.

In view of the expected neutralising action of the carbonyl group on the reactivity of the diene system it was surprising that an adduct was formed at all. Accepting this, however, the structure proposed seems the most natural. It is possible that the substance contains two, or even four, more hydrogen atoms and that it may be (XI, CH·OH instead of CO) or a substituted succinic anhydride; much further work is needed.

x-Norequilenin methyl ether (I, R = Me) has been demethylated, and x-*norequilenin acetate* (I, R = Ac) prepared. It is a weak oestrogenic agent. The experiments of Cook and Lawrence (J., 1937, 817) on the methylation of *trans*-α-decalone showed clearly that a direct methylation of *x*-norequilenin methyl ether could not be expected to yield *x*-equilenin methyl ether. We have therefore protected the 16-position by a piperonylidene group and submitted the derivative (XII) to the action of potassium *tert.*-butoxide and methyl iodide. One methyl group was introduced and the constitution of the product should be

(II). It is closely similar in properties to *piperonylidene-equilenin methyl ether* (also II), which was prepared for comparison. It is not, however, the *dl*-form of this substance, because the colour reactions with hot sulphuric acid are characteristic, reproducible with all specimens, and different. Examination of the models shows that the molecular shapes of the stereoisomeric piperonylidene-*dl*-equilenins are quite dissimilar and it is not surprising that the profound changes caused by hot sulphuric acid take divergent courses. Neither of the substances (II) is affected by further treatment with the methylating agents. Similarly, 6-*methoxy*-2-*piperonylidene*-α-*tetralone* (XIII) was recovered unchanged after attempted methylation under the same conditions, but 5-*methoxy*-2-*piperonylideneindan*-1-*one* (XIV) was converted in this way into an *isomeride* or dimeride.



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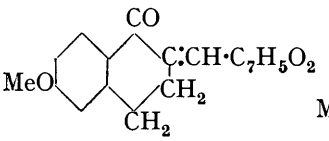
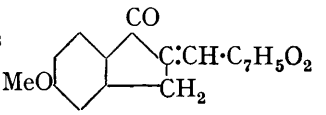


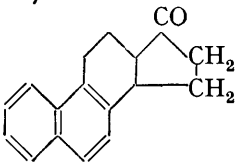
(XIII.)

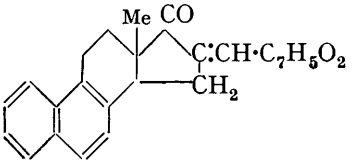


(XIV.)

The *x*-norequilenin methyl ether series has been paralleled by the preparation of 3′-*keto*-1 : 2 : 3 : 4-*tetrahydro*cyclo*pentenophenanthrene* (XV) by reduction of 3′ : 4-diketo-1 : 2 : 3 : 4-tetrahydro*cyclo*pentenophenanthrene (Koebner and Robinson, *loc. cit.*). The piperonylidene derivative was methylated by the usual method and afforded the 2-methyl derivative (XVI).

(XV.)

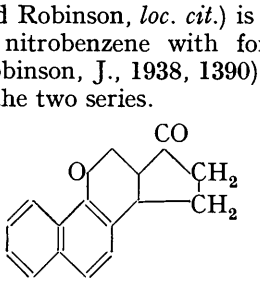


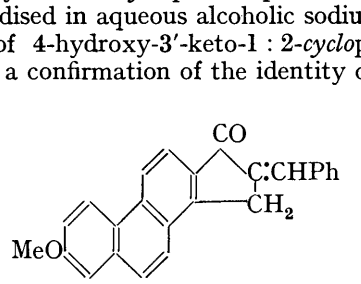


(XVI.)

Two observations bearing on the constitution of *x*-norequilenin methyl ether are the following. 3′ : 4-Diketo-1 : 2 : 3 : 4-tetrahydro-1 : 2-*cyclo*pentenophenanthrene (XVII) (Koebner and Robinson, *loc. cit.*) is easily oxidised in aqueous alcoholic sodium hydroxide solution by nitrobenzene with formation of 4-hydroxy-3′-keto-1 : 2-*cyclo*pentenophenanthrene (Robinson, J., 1938, 1390). This is a confirmation of the identity of the carbon skeletons in the two series.

(XVII.)





(XVIII.)

The dehydrogenated benzylidene derivative mentioned in the addendum to our last paper (*loc. cit.*) has been further examined and found to be 3′-*keto*-7-*methoxy*-4′-*benzylidene*-cyclo*pentenophenanthrene* (XVIII). The possibility of such dehydrogenation is a clear proof that catalytic reduction of the 3′ : 4-diketo-7-methoxy-1 : 2 : 3 : 4-tetrahydro*cyclo*-pentenophenanthrene eliminates oxygen in the 4-position as already assumed on other grounds.

Experimental.

Hydroxy-lactone Form of 3-β-*Naphthyl*cyclo*pentan*-1-*one*-2-*acetic Acid* (V, R = H).—The cyclo-dehydration of the acid was best effected by means of phosphoric oxide in syrupy phosphoric acid solution (Koebner and Robinson, *loc. cit.*), but a number of other methods were tried. In some of these the acid was converted into a product insoluble in aqueous sodium carbonate. For example, a 60% yield of this substance was obtained by the action of stannic chloride on the acid in carbon disulphide solution. The *hydroxy-lactone* crystallised from aqueous alcohol in small prisms, m. p. 60° (Found: C, 76·2; H, 6·3. $C_{17}H_{16}O_3$ requires C,

76·1; H, 6·1%). The semicarbazone, prepared in an aqueous alcoholic medium by the normal procedure, crystallised from methyl alcohol in rhombic plates, m. p. 217°, and was clearly the derivative of naphthyl*cyclo*pentanone-2-acetic acid already described (*loc. cit.*).

The action of boiling acetic anhydride on the keto-acid led to extensive decomposition in 30 minutes. If, however, a few drops of hydriodic acid were added and the time was reduced to 15 minutes, the *acetate* (V, R = Ac) of the hydroxy-lactone form could be isolated (yield, 30%). This substance crystallised from alcohol in colourless, monoclinic prisms, m. p. 157—158° (Found: C, 73·3; H, 6·0. $C_{19}H_{18}O_4$ requires C, 73·6; H, 5·8%). On hydrolysis with aqueous alcoholic potassium hydroxide, the salt of the keto-acid was regenerated. These substances were obtained incidentally and no attempt has been made to find the most satisfactory methods of preparation.

3-*Methyl*-Δ^2-cyclo*penten*-1-*one*-2-*acetic Acid*.—Acetonyl-lævulic acid (Kehrer and Igler, *Ber.*, 1899, **32**, 1178) (1·8 g.) was heated on the steam-bath with 2% aqueous potassium hydroxide (200 c.c.) for 2 hours. The solution was just acidified to Congo-red and evaporated to dryness, and the residue extracted with ethyl acetate. After removal of the solvent the product was crystallised from benzene–light petroleum (b. p. 40—60°) and then from a little chilled ethyl acetate (yield, 1 g.). The *acid* formed colourless, well-shaped, hexagonal plates, m. p. 109—110° (Found: C, 62·2; H, 6·4. $C_8H_{10}O_3$ requires C, 62·3; H, 6·5%). The substance is the simplest that can be made by this type of synthesis (starting from a furfurylideneketone); it is unsaturated to permanganate, readily soluble in most organic solvents, and moderately readily soluble in water.

*Reduction of Difurfurylidene*cyclo*hexanone*.—An attempt to apply the Kehrer–Igler method to difurfurylidene*cyclo*hexanone gave only intensely coloured decomposition products. No better results were obtained with the reduced compounds mentioned below and with these a fission by bromine was also unsuccessfully attempted. A solution of the unsaturated ketone (30 g.) in ethyl acetate (100 c.c.) was shaken under hydrogen with a palladised strontium carbonate catalyst (5 g.). In 15 minutes the absorption of hydrogen corresponded to saturation of three double bonds. The main product, 2 : 6-*di*-α-*furyl*cyclo*hexanol* (20 g.), was a colourless oil, b. p. 169°/2·5 mm., $n_D^{19°}$ 1·5070 (Found: C, 73·3; H, 7·9. $C_{16}H_{20}O_3$ requires C, 73·8; H, 7·7%). There was a fraction (4 g.) of lower b. p. and a residue.

If the hydrogenation was allowed to continue, two more mols. of hydrogen were taken up in 2 hours. The product (yield, 65%) was a viscous oil, b. p. 180°/1 mm., $n_D^{19°}$ 1·5272 (Found: C, 72·6; H, 9·1. $C_{16}H_{24}O_3$ requires C, 72·7; H, 9·1%). Reduction of the furan nucleus has evidently occurred, but it is not known whether one such nucleus gives a tetrahydro-derivative or whether the product is 1 : 3-bisdihydro-α-furyl*cyclo*hexanone. It is best described as *tetrahydro*-2 : 6-*di*-α-*furyl*cyclo*hexanol*.

trans-1-*Methyl*-α-*decalol* (VI).—The prefix "*trans*" refers to the decalin configuration and the material described below may be a mixture of stereoisomerides due to the two possible arrangements of the substituents.

A solution of *trans*-α-decalone (3 g.) in benzene (30 c.c.) was slowly added to one of methylmagnesium iodide (from methyl iodide, 3 g.; magnesium, 1 g.) in ether (30 c.c.) cooled in an ice-bath and vigorously stirred for 1 hour. The mixture was then kept at room temperature for 1 hour and refluxed for 2 hours. The product was an oil (2·8 g.), b. p. 83—88°/2 mm., $n_D^{20°}$ 1·4930 (Found: C, 78·5; H, 11·9. $C_{11}H_{20}O$ requires C, 78·6; H, 11·9%). The substance was resistant to oxidation by chromic acid or potassium permanganate. It was dehydrated with the greatest ease by passing sulphur dioxide into a solution in acetone (1 g. in 30 c.c.). 1-*Methyloctalin* (yield, 0·8 g.) had b. p. 60°/0·4 mm. and $n_D^{20°}$ 1·4985 (Found: C, 88·2; H, 11·9. $C_{11}H_{18}$ requires C, 88·0; H, 12·0%). Oxidation with lead tetra-acetate, followed by treatment with acetic and sulphuric acids, gave a ketone, but this indication was not followed up.

The methylation of *trans*-α-decalone (Cook and Lawrence, *loc. cit.*) in position 2 was effected by means of sodamide and methyl iodide. We have reproduced the results of these authors, employing potassium *tert.*-butoxide and methyl iodide in solution in *tert.*-butyl alcohol (3 vols.) and ether (4 vols.).

Under similar conditions 3′ : 4-diketo-1 : 2 : 3 : 4-tetrahydro-1 : 2-*cyclo*pentenophenanthrene ($C_{17}H_{14}O_2$) afforded a *derivative* that crystallised from alcohol in yellow needles, m. p. 191—192° (Found: C, 81·6, 81·3; H, 6·0, 6·3. $C_{18}H_{16}O_2$ requires C, 81·8; H, 6·0%). It thus appears to be a monomethyl derivative, but it is also possible that more extensive methylation and perhaps dehydrogenation has occurred. The m. p. was not very sharp and the ketonic properties were not well developed. Moreover we would not expect that the 2-methyl derivative, which might be weakly ketonic, would be a yellow substance.

3-*Phenyl*-2-*methyl*-Δ^2-cyclo*penten*-1-*one*.—Finely powdered sodium (1·2 g.) was suspended in ether (100 c.c.), and ethyl propionylacetate (7 g.) (Willstätter, *Ber.*, 1914, **47**, 298) slowly added; the mixture was refluxed on the steam-bath for 30 minutes. Phenacyl bromide (10 g.), dissolved in ether (25 c.c.), was added with shaking to the cooled solution, which was then refluxed for 3 hours. Water was added to the cooled mixture, the ethereal layer separated, and the aqueous solution twice extracted with ether. The combined ethereal solutions were washed and dried, and the solvent evaporated. A yellow oil was obtained, which was heated on the steam-bath with aqueous sodium hydroxide (250 c.c. of 5%) and alcohol (50 c.c.) for 20 minutes. The solution was extracted with ether, the solvent removed, and the residual oil distilled under diminished pressure. As the analysis gave low values for carbon, indicating the presence of an open-chain diketone, the oil was boiled with 10 times its weight of acetic anhydride for 30 minutes. The acetic anhydride was removed; the residual oil, b. p. 136—137°/6 mm., solidified completely on standing. The substance crystallised from light petroleum (b. p. 40—60°) in large, lath-shaped, colourless prisms, m. p. 50—51° (yield, 65%) (Weidlich and Daniels,* *Ber.*, 1939, **72**, 1590, give m. p. 47—48°) (Found: C, 84·0; H, 7·1. Calc. for $C_{12}H_{12}O$: C, 83·7; H, 6·9%). The 2 : 4-*dinitrophenylhydrazone*, twice crystallised from benzene, formed long, slender, dark red prisms, m. p. 232—233° (Found: N, 16·1. $C_{18}H_{16}O_4N_4$ requires N, 15·9%). On acidification of the aqueous solution from the cyclisation, β-benzoylpropionic acid was obtained in small amount.

3-*Phenyl*-2-*methyl*cyclo*pentan*-1-*one* (IX, R = Ph).—Phenylmethyl*cyclo*pentenone (5·5 g.) was shaken in an atmosphere of hydrogen with palladised strontium carbonate (3 g. of 2%) at 40° in alcoholic solution (30 c.c.). The absorption of hydrogen was complete in 2 hours. The hot solution was separated from the catalyst, which was extracted twice with small portions of hot alcohol. After the removal of the solvent a colourless oil remained (yield, 75%), b. p. 112—114°/0·4 mm., $n_D^{19°}$ 1·5335 (Found: C, 82·6; H, 8·3. Calc. for $C_{12}H_{14}O$: C, 82·8; H, 8·1%). The 2 : 4-*dinitrophenylhydrazone* crystallised from ethyl acetate in square, yellow plates, m. p. 203—204° (Found: N, 15·8. $C_{18}H_{18}O_4N_4$ requires N, 15·8%).

5-*Bromo*-6-*methoxy*-2-*naphthacyl Bromide*.—A solution of bromine (40 g.) in chloroform (200 c.c.) was slowly added to 2-methoxy-6-acetylnaphthalene (25 g.) in chloroform (200 c.c.); after 3 hours hydrogen bromide was removed in a stream of dry air, and the solvent evaporated under reduced pressure. The dark green residue was crystallised from benzene and then from ethyl acetate (yield, 75%). It formed long, pale green needles, m. p. 134—135° (Found: C, 43·6; H, 2·8. $C_{13}H_{10}O_2Br_2$ requires C, 43·6; H, 2·8%).

A small amount of a less readily soluble *tribromo*-derivative was also formed. It crystallised from acetic acid in pale yellow needles, m. p. 162—163° (Found: C, 36·1; H, 2·1. $C_{13}H_9O_2Br_3$ requires C, 35·7; H, 2·1%).

5′-*Bromo*-6′-*methoxy*-2′-*naphthacylpyridinium Bromide*.—The above dibromo-ketone (5 g.) was heated on the steam-bath with an excess of pyridine for 10 minutes. The *pyridinium bromide* separated immediately as a white, crystalline mass. After being washed free from pyridine with ether, it crystallised from 90% aqueous alcohol in colourless needles, m. p. 255—256° (decomp.) (Found: N, 3·1. $C_{18}H_{15}O_2NBr_2$ requires N, 3·1%).

5-*Bromo*-6-*methoxy*-2-*naphthoic Acid*.—The pyridinium bromide was dissolved in water (25 c.c.) and treated with aqueous sodium hydroxide (2 c.c. of 10%). The yellow hydroxide separated at once, but when the mixture was warmed on the steam-bath for 15 minutes a colourless solution was obtained. This was cooled and acidified. The crystalline precipitate was collected and recrystallised from alcohol; m. p. 292—293° (Haworth and Sheldrick, J., 1934, 864, give m. p. 292—293°). The methyl ester, m. p. 163—164°, was also prepared (H. and S., m. p. 162—163°).

Ethyl 5-*Bromo*-6-*methoxy*-2-*naphthacylacetoacetate*.—A solution of ethyl acetoacetate (6 g.) in ether (50 c.c.) was slowly added to a suspension of finely powdered sodium (1·1 g.) in ether (150 c.c.). The mixture was heated on the steam-bath for 20 minutes. 5-Bromo-6-methoxy-2-naphthacyl bromide (16 g.), dissolved in anhydrous benzene (100 c.c.), was introduced, and the mixture refluxed for 3 hours. After cooling and addition of water the ether–benzene layer was separated, and the aqueous solution extracted twice with ether. The brown oil from the extracts solidified and crystallised from alcohol in pale yellow plates, m. p. 78—80° (yield, almost theoretical) (Found: C, 56·0; H, 4·5. $C_{19}H_{19}O_5Br$ requires C, 56·0; H, 4·7%).

5-*Bromo*-6-*methoxy*-2-*naphthacylacetone*.—The above ester was heated for 30 minutes on the steam-bath with aqueous sodium hydroxide (150 c.c. of 5%) and alcohol (50 c.c.). Complete

* Our independent work on this topic was completed a long time before the date of this publication and, as it differs in detail, we submit an account of the experiments.

solution soon occurred, but yellow crystals separated after a short time. The mixture was cooled, and the solid collected and crystallised from benzene; m. p. 176—177°. A specimen was refluxed with 10 times its weight of acetic anhydride for 30 minutes and the unchanged substance was isolated (Found: C, 57·0; H, 4·5; Zerewitinoff H, 0·56. $C_{16}H_{15}O_3Br$ requires C, 57·2; H, 4·5; Zerewitinoff 2H, 0·59%).

The 2 : 4-*dinitrophenylhydrazone* crystallised from nitrobenzene in very long, fine needles that did not melt below 300° (Found: N, 11·0. $C_{22}H_{19}O_6N_4Br$ requires N, 10·9%).

When the substance was heated with ammonium acetate in acetic acid solution, a pyrrole *derivative* was produced; it formed buff-coloured prisms, m. p. 173—175°, from benzene (Found: N, 3·9. $C_{16}H_{14}ONBr$ requires N, 4·4%).

Ethyl β-5-*Bromo*-6-*methoxy*-2-*naphthacylpropionylacetate*.—A solution of ethyl propionylacetate (8 g.) in ether (50 c.c.) was added to a suspension of powdered sodium (1·1 g.) in ether (250 c.c.). The mixture was refluxed for 30 minutes and 5-bromo-6-methoxy-2-naphthacyl bromide (20 g.) in benzene (400 c.c.) was then added slowly to the cooled solution. After refluxing for 2 hours, the *product* was isolated in the usual manner. It separated from alcohol in rhombic plates (23 g.), m. p. 89—91° (Found: C, 56·7; H, 5·0; Br, 19·0. $C_{20}H_{21}O_5Br$ requires C, 57·0; H, 5·0; Br, 19·0%).

3-(5′-*Bromo*-6′-*methoxy*-2′-*naphthyl*)-2-*methyl*-Δ^2-cyclo*penten*-1-*one*.—A mixture of the above crude ester (23 g.), alcohol (75 c.c.), and aqueous sodium hydroxide (300 c.c. of 5%) was heated on the steam-bath for 1 hour. The yellow solid that separated crystallised from ethyl acetate in large, pale buff-coloured prisms, m. p. 177—178° (yield, 85%) (Found: C, 61·5; H, 4·6. $C_{17}H_{15}O_2Br$ requires C, 61·6; H, 4·5%). The 2 : 4-*dinitrophenylhydrazone* crystallised from pyridine in long, crimson needles, m. p. 292—293° (decomp.) (Found: N, 11·1. $C_{23}H_{19}O_5N_4Br$ requires N, 11·0%). The alkaline filtrate from the decarboxylation and *cyclo*dehydration was acidified, and the precipitate crystallised from acetic acid and then from alcohol. β-5-*Bromo*-6-*methoxy*-2-*naphthoylpropionic acid* was so obtained in buff-coloured plates, m. p. 204—205° (Found: C, 53·2; H, 3·8. $C_{15}H_{13}O_4Br$ requires C, 53·4; H, 3·8%).

3-(6′-*Hydroxy*-2′-*naphthyl*)-2-*methyl*-Δ^2-cyclo*penten*-1-*one*.—A solution of bromomethoxynaphthylmethyl*cyclo*pentenone (2 g.) in acetic acid (10 c.c.) and hydriodic acid (20 c.c., *d* 1·7) was refluxed for 8 hours. The mixture was decolorised with sulphur dioxide, poured into water, rendered alkaline, and extracted with ether. The solid obtained on saturating the aqueous solution with carbon dioxide was collected and dried, and its benzene solution passed through an alumina column. After removal of the solvent the compound gave low values of carbon on analysis and was found to contain traces of iodine. The solution of the product in aqueous sodium hydroxide (30 c.c. of 5%) was therefore boiled with zinc dust (1 g.) for 2 minutes. The recovered phenol crystallised from alcohol in large, very faintly yellow plates (0·75 g.), m. p. 204—205° (Found: C, 80·4; H, 5·9. $C_{16}H_{14}O_2$ requires C, 80·6; H, 5·9%).

3-(6′-*Methoxy*-2′-*naphthyl*)-2-*methyl*cyclo*pentan*-1-*one*.—Bromomethoxynaphthylmethyl*cyclo*pentenone (5 g.) in alcohol (50 c.c.) was shaken with palladised strontium carbonate (3 g.) under hydrogen at 60° for 18 hours. After hydrogen (1 mol.) had been absorbed, the catalyst was reactivated by shaking with air for ½ hour; a further equal volume of hydrogen was then absorbed. The alcoholic solution and extract of the catalyst was evaporated to dryness, and the residue extracted several times with small volumes of hot benzene. The benzene solution was passed through an alumina column and then mixed with light petroleum (b. p. 40—60°). The *ketone* crystallised from benzene in stout prisms (3 g.), m. p. 116—117° (Found: C, 80·4; H, 7·1. $C_{17}H_{18}O_2$ requires C, 80·3; H, 7·1%).

In all subsequent preparations which were carried out in a similar way a more soluble form of the ketone was isolated, m. p. 84—86° (Found: C, 80·4; H, 7·4%). A mixture of the two specimens had m. p. 116°. It would appear that this substance is dimorphic.

The preparation of 3-(6′-methoxy-2′-naphthyl)-2-methyl*cyclo*pentan-1-one-2-acetic acid from this methoxy-ketone was attempted under a variety of conditions, but without result.

3-(6′-*Hydroxy*-2′-*naphthyl*)-2-*methyl*cyclo*pentan*-1-*one*.—A mixture of the methyl ether (2 g.), acetic acid (10 c.c.), and hydriodic acid (20 c.c., *d* 1·75) was refluxed for 20 minutes. The solution was cooled, decolorised with sulphur dioxide, poured into water, rendered alkaline, and extracted with ether. Carbon dioxide was passed through the aqueous solution and the precipitated phenol was collected and dried. Its benzene solution was passed through an alumina column and, on concentration, the *phenol* crystallised. Recrystallised from ethyl acetate–light petroleum (b. p. 40—60°), it formed colourless prisms (1·5 g.), m. p. 143—144° (Found: C, 80·0; H, 6·8. $C_{16}H_{16}O_2$ requires C, 80·0; H, 6·7%).

Anhydride of 8-*Bromo*-3′-*keto*-7-*methoxy*-2-*methyltetrahydro*-1 : 2-cyclo*pentenophenanthrene*-

3 : 4-*dicarboxylic Acid* (?) (XI).—A mixture of 3-(5′-bromo-6′-methoxy-2′-naphthyl)-2-methyl-Δ^2-*cyclo*penten-1-one (2 g.), maleic anhydride (6 g.), and xylene (25 c.c.) was refluxed for 5 hours; the solution became dark red. Alcohol (50 c.c.) was added; after 2 weeks at 0°, a yellow solid had crystallised (0·75 g.). The *adduct* separated from alcohol as a crystalline powder, m. p. 147—148° (Found: C, 58·1; H, 4·7. $C_{21}H_{17}O_5Br$ requires C, 58·7; H, 4·0%). It is proposed to make a further examination of this, or an analogous substance. The analysis establishes the region of composition, taking into consideration the nature of the components, but a better agreement is obtained if reduction is assumed ($C_{21}H_{19}O_5Br$ requires C, 58·5; H, 4·4%. $C_{21}H_{21}O_5Br$ requires C, 58·2; H, 4·8%).

5-*Chloro*-6-*methoxy*-2-*naphthacyl Bromide*.—On a large scale the method of Robinson and Willenz (this vol., p. 395) for the preparation of 5-chloro-6-methoxy-2-acetonaphthone was modified, and the yield of 80% maintained. The quantities used were: 1-chloro-2-methoxynaphthalene (70 g.), acetyl chloride (30 g.; 1 mol.), nitrobenzene (800 c.c.), and aluminium chloride (105 g.).

The ketone (25 g.) was treated with bromine (20 g.) in cold chloroform (300 c.c.) and after 3 hours the solvent was removed under diminished pressure. The residue crystallised from benzene in pale green, slender prisms (yield, 80%), m. p. 116—117° after recrystallisation from ethyl acetate (Found: C, 49·8; H, 3·4. $C_{13}H_{10}O_2ClBr$ requires C, 49·8; H, 3·3%). When the pyridinium bromide obtained from this *bromo-ketone* was heated with aqueous sodium hydroxide, an almost quantitative yield of 5-chloro-6-methoxy-2-naphthoic acid, slender prisms, m. p. 308—310°, was obtained (Robinson and Thompson, J., 1938, 2006, give m. p. 308—310°).

Ethyl β-5-*Chloro*-6-*methoxy*-2-*naphthacylpropionylacetate*.—This was prepared like the corresponding bromo-compound (above), except that the bromide was introduced as a fine powder instead of in benzene solution, and the yield was almost theoretical. The *ester* crystallised from methyl alcohol in colourless prisms, m. p. 87—89° (Found: C, 63·6; H, 5·6. $C_{20}H_{21}O_5Cl$ requires C, 63·7; H, 5·6%). Hydrolysis at 60° with an excess of aqueous sodium hydroxide (2%) was carried out for 3 hours, and the liquid then boiled for 10 minutes. The solid was collected and extracted (Soxhlet) with ethyl acetate, and the solution concentrated. The *cyclo*pentenone *derivative* separated (yield, 60%) and was recrystallised from alcohol, forming prisms, m. p. 165—166° (Found: C, 71·1; H, 4·9. $C_{17}H_{15}O_2Cl$ requires C, 71·2; H, 5·2%). The 2 : 4-*dinitrophenylhydrazone* separated from nitrobenzene in deep red, prismatic needles, m. p. 296—297° (decomp.) (Found: N, 12·1. $C_{23}H_{19}O_5N_4Cl$ requires N, 12·0%). The alkaline filtrate from the crude ketone (above) was acidified and afforded β-5-chloro-6-methoxy-2-naphthoylpropionic acid (0·5 g.); glistening plates from alcohol, m. p. 196—197° (Robinson and Thompson, *loc. cit.*, give m. p. 198—199°).

3-(5′-*Chloro*-6′-*methoxy*-2′-*naphthyl*)-2-*methyl*cyclo*pentan*-1-*one*.—The conditions of the catalytic hydrogenation of the chloro-*cyclo*pentenone derivative (2 g.) were closely similar to those used for the corresponding bromo compound, but the chlorine atom was not eliminated completely. When a hot benzene solution of the product was diluted with light petroleum (b. p. 40—60°), a *substance* separated; recrystallised from methyl alcohol, it formed colourless prisms (0·2 g.), m. p. 137—139° (Found: C, 71·1; H, 5·6. $C_{17}H_{17}O_2Cl$ requires C, 70·8; H, 5·9%). The filtrate was evaporated, and the residue crystallised from light petroleum (b. p. 60—80°) and then from methyl alcohol (yield, 1·0 g.). The colourless prisms had m. p. 84—86°, alone or mixed with methoxynaphthylmethyl*cyclo*pentanone obtained from the 5-bromo-derivative as above.

x-*Norequilenin Acetate* (I, R = Ac).—A mixture of *x*-norequilenin methyl ether (250 mg.), hydriodic acid (6 c.c., *d* 1·75), and acetic acid (3 c.c.) was heated to 130—140° during 10 minutes and kept at this temperature for 5 minutes longer. It was then cooled, poured into water, and decolorised with sulphur dioxide. The solid (230 mg.) was collected and dissolved in aqueous sodium hydroxide, the solution filtered and acidified, and the phenol (150 mg.), which was very sparingly soluble in most solvents, was at once acetylated by means of acetic anhydride (5 c.c.) and pyridine (5 c.c.). The mixture was heated on the steam-bath for 4 hours, poured into water, and extracted with ether. The ethereal extract was washed with dilute alkali, dilute acid, and with water. After removal of the solvent the yellow solid residue crystallised from aqueous alcohol (charcoal) in flat needles, m. p. 135—136° (Found: C, 77·5; H, 6·0. $C_{19}H_{18}O_3$ requires C, 77·6; H, 6·1%). Professor E. C. Dodds has kindly examined this *acetate* and reports that it is oestrogenic in doses of 10 mg. Like the methyl ether, it gives a yellow solution in sulphuric acid and an intense green fluorescence is developed on heating. The reaction resembles that exhibited by equilenin. The acetate forms an orange-red picrate.

3′-*Keto*-1 : 2 : 3 : 4-*tetrahydro*-1 : 2-cyclo*pentenophenanthrene* (XV).—A solution of 3′ : 4-diketo-1 : 2 : 3 : 4-tetrahydro-1 : 2-*cyclo*pentenophenanthrene (500 mg.) in alcohol (30 c.c.) was shaken at room temperature with platinised charcoal (1 g. of 10%) and a saturated alcoholic solution of palladous chloride (2 c.c.) under hydrogen. The theoretical volume of hydrogen was absorbed in 4 hours and no further absorption occurred, although the conditions were maintained for 4 hours longer. The catalyst was removed from the hot solution and extracted with hot alcohol. The combined alcoholic solutions were concentrated; the new *ketone* then crystallised. It separated from methyl alcohol or from aqueous alcohol in white prisms, m. p. 111—112° (Found : C, 86·2; H, 6·5. $C_{17}H_{16}O$ requires C, 86·4; H, 6·8%).

The 2 : 4-*dinitrophenylhydrazone* crystallised from acetic acid in bright yellow needles, m. p. 255—256° (Found : N, 13·3. $C_{23}H_{20}O_4N_4$ requires N, 13·5%).

3′-*Keto*-4′-*piperonylidene*-1 : 2 : 3 : 4-*tetrahydro*-1 : 2-cyclo*pentenophenanthrene*.—A solution of sodium ethoxide (10 c.c. of 1%) was gradually added to one of the above ketone (0·6 g.) and piperonal (0·4 g.) in alcohol (10 c.c.). The mixture was then heated on the steam-bath; on cooling, a yellow solid separated (0·7 g.), which was collected and washed with aqueous sodium carbonate. It was crystallised from acetic acid and then from benzene–light petroleum (b. p. 40—60°), forming pale yellow prisms, m. p. 173—174° (Found : C, 81·2; H, 5·3; CMe, 0·9. $C_{25}H_{20}O_3$ requires C, 81·5; H, 5·5; CMe, 0·0%. 2-Methoxynaphthalene gave CMe, 0·8% by the Kuhn–Roth method).

3′-*Keto*-4′-*piperonylidene*-2-*methyl*-1 : 2 : 3 : 4-*tetrahydro*-1 : 2-cyclo*pentenophenanthrene* (XVI).—The above piperonylidene derivative (250 mg.) was dissolved in a solution of potassium (0·8 g.) in *tert.*-butyl alcohol (15 g.). Methyl iodide (5 c.c.) was added, and the mixture refluxed for 1 hour on the steam-bath and kept overnight. Most of the alcohol was then evaporated and the residue was treated with water and dilute hydrochloric acid and extracted with ether. The solvent was evaporated; the residue, a yellow solid, crystallised from ethyl acetate–light petroleum (b. p. 40—60°) in flat prisms, m. p. 158—159° (Found : C, 81·7; H, 5·8; CMe, 2·5. $C_{26}H_{22}O_3$ requires C, 81·7; H, 5·8; 1CMe, 3·2%).

3′-*Keto*-7-*methoxy*-4′-*piperonylidene*-1 : 2 : 3 : 4-*tetrahydro*-1 : 2-cyclo*pentenophenanthrene* (XII).—A solution of the methoxy-ketone (0·9 g.) and piperonal (0·5 g.) in alcohol (30 c.c.) was gently heated on the steam-bath, and 5N-sodium hydroxide (10 c.c.) added slowly; the yellow *piperonylidene* compound began to separate almost at once. After cooling and keeping, the solid was collected; it crystallised from benzene–light petroleum (b. p. 40—60°) in pale yellow, rhombic plates, m. p. 187—188° (Found : C, 78·4; H, 5·5; CMe, 1·4. $C_{26}H_{22}O_4$ requires C, 78·4; H, 5·5; CMe, 0%).

A 2 : 4-dinitrophenylhydrazone could not be obtained. The compound gave an intense yellow coloration in *tert.*-butyl-alcoholic sodium *tert.*-butoxide.

3′-*Keto*-7-*methoxy*-4′-*piperonylidene*-2-*methyl*-1 : 2 : 3 : 4-*tetrahydro*-1 : 2-cyclo*pentenophenanthrene*, *Piperonylidene*-x-*equilenin Methyl Ether* (II).—The above piperonylidene compound (0·5 g.) was dissolved in a solution of potassium (1·6 g.) in *tert.*-butyl alcohol (30 g.), methyl iodide (10 c.c.) added, and the mixture refluxed on the steam-bath for 2 hours. Most of the *tert.*-butyl alcohol was evaporated, and the residue treated with water and dilute hydrochloric acid and extracted with ether. The solvent was evaporated; the residue, a bright yellow solid (0·5 g.), crystallised from benzene–light petroleum (b. p. 40—60°) in pale yellow plates, m. p. 180—181°, mixed m. p. with the unmethylated material, 166—170° (Found : C, 78·7; H, 6·1; CMe, 2·6. $C_{27}H_{24}O_4$ requires C, 78·6; H, 5·8; 1CMe, 3·6%). The *compound* showed no ketonic properties and, when dissolved in an alcoholic solution of sodium ethoxide, gave no coloration. Its orange-red solution in cold concentrated sulphuric acid became brown on heating. This reaction was repeated on many occasions and always with the same result; it constitutes a distinction from piperonylidene-equilenin methyl ether (*q.v.*). The colorations developed by the isomerides in the cold reagent are identical in tone and intensity.

16-*Piperonylidene-equilenin Methyl Ether* (II).—This derivative was prepared from the methyl ether of natural equilenin by condensation with piperonal in ethyl-alcoholic solution containing a little potassium hydroxide. It crystallised from alcohol in colourless plates, m. p. 208—209° (Found : C, 78·7; H, 6·1; CMe, 3·1. $C_{27}H_{24}O_4$ requires C, 78·6; H, 5·8; 1CMe, 3·6%). This compound was treated with potassium and methyl iodide in hot *tert.*-butyl-alcoholic solution, and was recovered unchanged, though slightly yellow, m. p. 206°, mixed m. p. with the original sample, 207—208°. The derivative gave no coloration in alcoholic sodium ethoxide solution. In cold concentrated sulphuric acid it gave an orange-red solution, which slowly became brownish-green on heating.

6-*Methoxy*-2-*piperonylidene*-α-*tetralone* (XIII).—This *substance* was obtained in almost

quantitative yield by the condensation of 6-methoxy-α-tetralone and piperonal in alcoholic solution with the help of sodium hydroxide. It crystallised from alcohol in pale yellow needles, m. p. 171—172° (Found: C, 74·0; H, 5·1. $C_{19}H_{16}O_4$ requires C, 74·0; H, 5·2%). It was submitted to the methylation process (boiling *tert.*-butyl-alcoholic potassium *tert.*-butoxide, and methyl iodide) under the usual conditions and was recovered unchanged, m. p. 171—172° alone or mixed with the original specimen.

5-*Methoxy*-2-*piperonylidene*-α-*hydrindone* (XIV), also obtained in theoretical yield from the components in aqueous alcoholic sodium hydroxide solution, crystallised from benzene–light petroleum (b. p. 40—60°) in pale yellow prisms, m. p. 226—227° (Found: C, 73·5; H, 4·9. $C_{18}H_{14}O_4$ requires C, 73·5; H, 4·8%). Attempted methylation in boiling *tert.*-butyl-alcoholic potassium *tert.*-butoxide by means of methyl iodide afforded in this case an *isomeride* (or dimeride) that crystallised from alcohol–benzene in colourless needles, m. p. 253—254° (Found: C, 73·2; H, 4·9. $C_{18}H_{14}O_4$ requires C, 73·5; H, 4·9. $C_{19}H_{16}O_4$ requires C, 74·0; H, 5·2%). Mixed with the starting material, it melted at 210°. A further study of this interesting change is projected.

4-*Hydroxy*-3′-*keto*-1 : 2-cyclo*pentenophenanthrene*.—A mixture of 3′ : 4-diketo-1 : 2 : 3 : 4-tetrahydro-1 : 2-*cyclo*pentenophenanthrene (0·6 g.), nitrobenzene (2 c.c.), alcohol (24 c.c.), and 5N-sodium hydroxide (6 c.c.) was boiled for 3 minutes, cooled, and shaken with acetic anhydride (12 c.c.). The solid obtained crystallised from acetic acid in needles, m. p. 207° alone or mixed with 3′-keto-4-acetoxy-1 : 2-*cyclo*pentenophenanthrene (Robinson, *loc. cit.*). The phenol obtained on hydrolysis had all the properties (including diazo-coupling) of the specimen previously obtained. On methylation it afforded the methyl ether, which crystallised from alcohol in needles, m. p. 179° alone or mixed with an authentic specimen.

3′-*Keto*-7-*methoxy*-4′-*benzylidene*-1 : 2-cyclo*pentenophenanthrene* (XVIII).—A mixture of *x*-norequilenin methyl ether (0·3 g.), benzaldehyde (3 c.c.), alcohol (10 c.c.), and 5N-sodium hydroxide (4 c.c.) was boiled for 15 seconds and then left exposed to the air. Alcohol was added to dissolve some oil that had separated; the product crystallised from ethyl acetate–alcohol in bright yellow threads, m. p. 223° (Found in material dried at 100°: C, 84·0, 84·2; H, 5·5, 5·6. $C_{25}H_{18}O_2,0{\cdot}5H_2O$ requires C, 83·6; H, 5·3%). The *substance* was dissolved in benzene, a little alcohol added, and the solution concentrated by distillation. On cooling, slender yellow needles, m. p. 224°, separated (Found in material dried at 110° in a high vacuum: C, 85·6; H, 5·3. $C_{25}H_{18}O_2$ requires C, 85·7; H, 5·1%). The orange-red solution in sulphuric acid (salmon-red when very dilute) exhibited an intense greenish-yellow fluorescence. On heating, the colour changed to bluish-red and then orange-red and the fluorescence became still more intense and yellower in tone. The solution in alcohol was yellow and exhibited a bluish-green fluorescence; the addition of sodium hydroxide produced no change.

The following is reported by Dr. H. M. E. CARDWELL.—

Various attempts to modify the carbonyl group of 3′-keto-4 : 7-dimethoxy-1 : 2-*cyclo*pentenophenanthrene have been made.

The cyanohydrin could not be prepared, although there was evidence of its occurrence in the products in some cases. Applications of the Francis and the Strecker reaction were also found to be impracticable. Reduction with sodium and amyl, butyl, or propyl alcohol never took a simple course. The chief product was a very sparingly soluble, yellow substance that crystallised from nitrobenzene in slender needles, m. p. 313°, and dissolved in sulphuric acid to a purple solution. Analytical results were not consistent, owing to the difficulty of complete combustion, but they pointed to the condensation of two molecules. Reduction of 7-methoxy-4-ethoxyketo*cyclo*pentenophenanthrene by means of aluminium *iso*propoxide and *iso*propyl alcohol gave an inseparable mixture, m. p. 100—320°, and chiefly the self-condensation product.

Reduction of 4-hydroxy-7-methoxyketo*cyclo*pentenophenanthrene by sodium amalgam gave amorphous non-phenolic material, and by Raney nickel in alkaline solution (Wintersteiner, *J. Biol. Chem.*, 1937, **118**, 789) left the phenol unchanged.

4 : 7-*Dimethoxy*-1 : 2-cyclo*pentenophenanthrene*.—Ketodimethoxy*cyclo*pentenophenanthrene (2·9 g.) in acetic acid (80 c.c.) was reduced by shaking with hydrogen for 20 hours at 75° in the presence of Adams's catalyst (0·1 g.) and aqueous ferric chloride (5 c.c. of N/2). After 1200 c.c. had been absorbed, the catalyst coagulated. Evaporation of the filtered solution left a residue, which was extracted with alcohol (Soxhlet). On crystallisation of the product from butyl

alcohol the first fraction (0·93 g.) had m. p. 114—130°, raised to 175—185° by recrystallisation from amyl acetate; it consisted of unchanged ketone. The second fraction (0·45 g.) had m. p. 112—116° and, after three crystallisations from acetic acid, m. p. 119—122°, with shrinking at 114° (Found : C, 81·8; H, 6·8. $C_{19}H_{18}O_2$ requires C, 82·0; H, 6·5%).

3′-*Keto*-7-*methoxy*-4-*ethoxy*-1 : 2-cyclo*pentenophenanthrene oxime* (12·6 g.) was obtained by the pyridine method from the ketone (15 g.). It crystallised from toluene in pale yellow needles, m. p. 244—246° (Found : C, 74·6; H, 6·1. $C_{20}H_{19}O_3N$ requires C, 74·8; H, 5·9%).

Reduction by hydrogen in the presence of Adams's catalyst in acetic anhydride solution at 70—80° gave two-thirds of the material back as the *acetate* of the oxime. This crystallised from toluene in clusters of rectangular prisms, m. p. 209—210° alone or mixed with a specimen made from the oxime and acetic anhydride (Found : C, 72·9; H, 5·7; N, 3·7. $C_{22}H_{21}O_4N$ requires C, 72·8; H, 5·8; N, 3·9%). The mother-liquor afforded 3′-*acetamido*-7-*methoxy*-4-*ethoxy*-1 : 2-cyclo*pentenophenanthrene* (yield, about 30%), which crystallised from aqueous methyl alcohol and then from benzene in light yellow plates, m. p. 219—221° (Found : C, 75·9; H, 6·5; N, 4·1. $C_{22}H_{23}O_3N$ requires C, 75·7; H, 6·7; N, 4·0%). An attempt to hydrolyse this derivative by means of a hot mixture of acetic and hydrochloric acids resulted in the production of a bluish-green hydrochloride, but the corresponding base could not be purified.

Isomeric Forms of Methyl 3-(6′-*Methoxy*-2′-*naphthyl*)cyclo*pentan*-1-*one*-2-*acetate*.—The ester already described (Koebner and Robinson, *loc. cit.*) has m. p. 61°, and is obtained by catalytic reduction of the substituted *cyclo*pentenone in alcoholic solution. It is probably the *cis*-ester. On hydrolysis it affords an acid, m. p. 147°, which is probably a *trans*-form. Re-esterification gives the trans-*ester*, needles from methyl alcohol, m. p. 101—102° (Found : C, 73·3; H, 6·6. $C_{19}H_{20}O_4$ requires C, 73·1; H, 6·4%). Hydrolysis of this ester gives the acid, m. p. 147°.

Hydrogenation of the *cyclo*pentenone acid in acetic acid solution gave a gummy acid and a little of the acid, m. p. 147°. The gum, heated with aqueous sodium hydroxide for 30 minutes, was converted into the acid, m. p. 147°, which was recovered on acidification. Cyclisation of the gummy acid and the acid, m. p. 147°, gave the same results.

3-6′-*Methoxy*-2′-*naphthyl*-2 : 5 : 5-*trimethyl*cyclo*pentan*-1-*one*-2-*acetic Acid* (VII).—Methyl 3-6′-methoxy-2′-naphthyl*cyclo*pentan-1-one-2-acetate (3·2 g., m. p. 100°) and then methyl iodide (7 c.c.) were added to *tert.*-butyl-alcoholic potassium *tert.*-butoxide (4 g. of potassium), and the mixture refluxed for 2 hours. The solvent was removed, and water added. Neutral ester products were collected by means of ether and hydrolysed by heating with aqueous sodium hydroxide (5%) in the steam-bath. Acidification of this solution and of that from which the ester was extracted yielded the same *acid*, collected by means of ether in both cases. It was crystallised from a little acetic acid and then from benzene–light petroleum (b. p. 40—60°) and obtained in hexagonal plates, m. p. 193—195° (Found : C, 74·3; H, 7·3. $C_{21}H_{24}O_4$ requires C, 74·1; H, 7·1%).

3′-*Hydroxy*-3′-*methyl*-1 : 2 : 3 : 4-*tetrahydro*-1 : 2-cyclo*pentenophenanthrene*.—A solution of ketotetrahydro*cyclo*pentenophenanthrene (1·5 g.) in benzene (30 c.c.) was slowly added to one of methylmagnesium iodide (2 g. of methyl iodide; 0·4 g. of magnesium) in ether (30 c.c.), stirred at 0° for 2 hours, kept for 12 hours, and finally refluxed for 1 hour. The product was isolated in the known manner as a yellow oil and later crystallised from alcohol (20 c.c.) (charcoal) (yield, 70%). On recrystallisation, it was obtained in long, colourless needles, m. p. 112—113° (m. p. 85—90° when mixed with the starting material) (Found : C, 85·4; H, 7·8. $C_{18}H_{20}O$ requires C, 85·7; H, 7·9%). This *substance* is devoid of ketonic properties.

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