75. *Experiments on the Synthesis of Substances related to the Sterols. Part XXXII.*

By Sir Robert Robinson and J. Willenz.

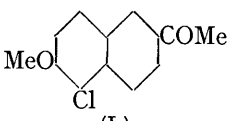
6-Methoxy-2-acetonaphthone is the starting point of a convenient synthesis of 3′-keto-1 : 2-*cyclo*pentenophenanthrene derivatives and the work described in this communication was undertaken in order to ascertain whether any advantages accrue from the use of 5-*chloro*-6-*methoxy*-2-*acetonaphthone* in an analogous series.

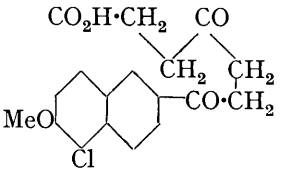
It was expected that the chlorine would be readily eliminated in reduction processes, but this did not prove to be the case. Moreover the tetracyclic substances investigated were characterised by inconvenient sparing solubility. The details follow in most respects those disclosed in Part XXI and the following special points may be noted.

5-Chloro-6-methoxy-2-acetonaphthone (I) is readily accessible in 80% yield by application of the Friedel–Crafts reaction. On hydrolysis of its *furfurylidene* derivative, demethylation does not occur, whereas in the case of the analogous unchlorinated compound an additional stage of remethylation is necessary. An interesting transformation of the keto*cyclo*pentenophenanthrene nucleus has been observed and it has been made probable that the first stage of reduction is in the 9 : 10-position.

The constitution of 5-*chloro*-6-*methoxy*-2-*acetonaphthone* (I) obtained by the action of aluminium chloride on 1-chloro-2-methoxynaphthalene and acetyl chloride in nitrobenzene solution is proved by its oxidation to 5-chloro-6-methoxynaphthoic acid, which Robinson and Thompson (J., 1938, 2009) obtained by chlorination of an undoubted 6-substituted 2-methoxynaphthalene and subsequent degradation. Hydrolysis of its *furfurylidene*

derivative by means of aqueous alcoholic hydrochloric acid affords 4 : 7-*diketo*-7-(5′-*chloro*-6′-*methoxy*-2′-*naphthyl*)*heptoic acid* (II) in about 50% yield. This is smoothly converted


(I.)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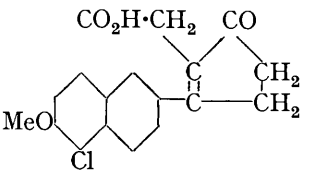
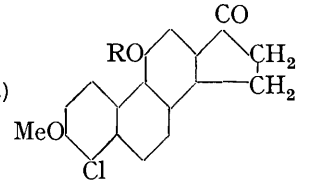
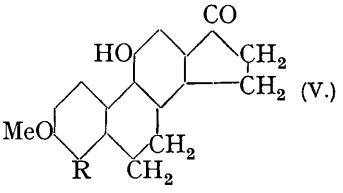

(III.)

into a cyclo*pentenoneacetic acid* (III) in hot 2% potassium hydroxide solution. Cyclisation by means of boiling acetic anhydride gives (IV, R = Ac), and this *substance* is, on the whole, more easy to prepare than the unchlorinated analogue. Various attempts to eliminate the chlorine atom by reduction processes failed. In the course of these trials the action of hot hydriodic acid was studied and the demethylated product was found to have curious properties. As some reduction occurred, the hydriodic acid was replaced by hydrobromic acid. The action of a boiling mixture of acetic acid and concentrated hydrobromic acid on (IV, R = Ac) gave a *substance*, $C_{17}H_{11}O_3Cl$, which therefore has the composition of a chlorodihydroxyketo*cyclo*pentenophenanthrene. But its colour reactions were quite inconsistent with this hypothesis as to its nature and moreover the keto-group, if present, is inactive and no evidence of the presence of a keto-methylene group could be obtained. On methylation the *dimethyl* ether, $C_{19}H_{15}O_3Cl$, was produced and this substance was not identical with 8-*chloro*-3′-*keto*-4 : 7-*dimethoxy*-1 : 2-cyclo*pentenophenanthrene* (IV, R = Me). It was then found that analogous transformation products could be obtained in the series unsubstituted in position 8. We designate these new substances of unknown constitution by the prefix *apo*.

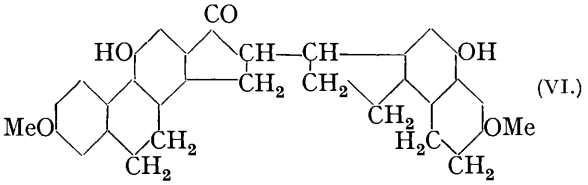
(IV.)




(V.)

In regard to the constitution of these *apo*-compounds we prefer to reserve our speculations; it is not helpful to regard them as keto*cyclo*hexenophenanthrenes formed by migration of the carbonyl group from position 2 to position 10 of the phenanthrene nucleus, because such products should also be distinctly reactive as ketones and keto-methylenes (cf. Bachmann and Kloetzel, *J. Amer. Chem. Soc.*, 1937, **59**, 2207). A series of experiments on the reduction of (IV, R = Ac) has been carried out on a considerable scale, pressure hydrogenation at elevated temperatures being used in the presence of Raney nickel and in acetic acid solution. The surprising point was noted that all the crystalline products were ketonic. The necessary laborious and complicated fractionations are not described in detail in the experimental section. One product was the *dihydro*-derivative (V, R = Cl).

Similar experiments in the unchlorinated series gave as one product (V, R = H) a substance already described by Robinson and Rydon (J., 1939, 1400) but regarded as a *sec.*-alcohol on the basis of analysis only. It is probable that the acetate, m. p. 145°, mentioned in the same paper is the acetate of (V, R = H). Another *substance* obtained in the course of these reduction experiments is regarded as having the structure (VI).


(VI.)

Experimental.

5-Chloro-6-methoxy-2-acetonaphthone (I).—Powdered aluminium chloride (33·5 g.) was added in small portions with shaking and cooling during 20 minutes to a mixture of 1-chloro-2-methoxynaphthalene (96·3 g.) (Autenrieth, *Ber.*, 1897, **30**, 2379), nitrobenzene (492 g.), and acetyl chloride (43·2 g.) cooled in ice and then kept at room temperature for 48 hours. The mixture was treated with ice (*ca.* 800 g.) and concentrated hydrochloric acid (120 c.c.). The organic layer was washed twice with water by decantation and then steam-distilled to remove nitrobenzene (about 4 hours). The residue solidified on cooling; it crystallised from methyl alcohol (charcoal) in white leaflets or needles, m. p. 124°, b. p. 192°/1·7 mm. (yield, 95·5 g.) (Found: C, 66·6; H, 4·7. $C_{13}H_{11}O_2Cl$ requires C, 66·5; H, 4·7%).

The 2 : 4-*dinitrophenylhydrazone* crystallised from dioxan–ethyl acetate in orange-red needles, m. p. 298° (decomp.) (Found: N, 13·8. $C_{19}H_{15}O_5N_4Cl$ requires N, 13·5%). The *piperonylidene* derivative crystallised from benzene in clusters of yellow, microscopic needles, m. p. 199—201° (Found: C, 69·0; H, 4·1. $C_{21}H_{15}O_4Cl$ requires C, 68·8; H, 4·1%). Its solution in sulphuric acid had a wine-red colour.

5-Chloro-6-methoxy-2-naphthoic Acid.—5-Chloro-6-methoxy-2-acetonaphthone (2 g.) was added to a solution of sodium hydroxide (4 g.) and sodium hypochlorite (3·75 g., added as 18% solution) in water (200 c.c.). The mixture was heated for 20 minutes on the steam-bath, then refluxed for 10 minutes. The mixture was cooled, and sulphur dioxide passed through the suspension of the sodium salt which had separated. The precipitate was collected and crystallised from alcohol, being obtained in white felted needles (1·5 g.), m. p. 301° after sintering, unchanged by admixture with an authentic specimen (Robinson and Thompson, *loc. cit.*).

Furfurylidene-5-chloro-6-methoxy-2-acetonaphthone.—Chloromethoxyacetonaphthone (31 g.), furfuraldehyde (14 g.), and alcohol (200 c.c.) were mixed, and a solution of sodium (1·7 g.) in alcohol (70 c.c.) gradually added at room temperature. The mixture was kept at 50° for 20 minutes and at room temperature for 1—2 hours. The separated solid was collected (40 g.) and washed with alcohol. It was recrystallised from alcohol (charcoal), being obtained in yellow needles, m. p. 151—152° (Found: C, 68·8; H, 4·0. $C_{18}H_{13}O_3Cl$ requires C, 69·1; H, 4·1%). The solution in sulphuric acid had a deep red colour.

4 : 7-*Diketo-7-(5′-chloro-6′-methoxy-2′-naphthyl)heptoic Acid* (II).—The above furfurylidene compound (20 g.) was refluxed for 15—20 hours on the steam-bath with a mixture of alcohol (250 c.c.) and concentrated hydrochloric acid (60 c.c.). The alcohol was evaporated under diminished pressure, and the solid residue refluxed with concentrated hydrochloric acid (110 c.c.), acetic acid (150—170 c.c.), and water (250 c.c.) (oil-bath at 145°) for 10—12 hours. The hot solution was carefully decanted from the dark residue; on cooling, the acid crystallised. It was collected and the filtrate used to extract the residue by further boiling and decantation of the hot clear liquid. After 8 or 9 extractions no further *diketo-acid* could be obtained on cooling the solution. The crude substance (11·3 g.) so obtained was dried and recrystallised from acetic acid (charcoal), forming white needles or plates having a nacreous lustre; m. p. 193—194° (Found: C, 61·7; H, 4·8. $C_{18}H_{17}O_5Cl$ requires C, 61·9; H, 4·9%). The orange-coloured solution in sulphuric acid became mauve on heating. Apparently demethylation, observed in the analogous case of the unchlorinated substance (Robinson and Rydon, *loc. cit.*), does not occur in this process. This was established by study of the next two stages, because identical results were obtained whether the *cyclo*pentenone acid was methylated or not.

3-(5′-*Chloro-6′-methoxy-2′-naphthyl*)-Δ^2-cyclo*penten*-1-*one*-2-*acetic Acid* (III).—A mixture of the above diketo-acid (10 g.), potassium hydroxide (20 g.), and water (1 l.) was heated on the steam-bath for 1 hour. The solution was cooled and acidified with concentrated hydrochloric acid. The precipitate was collected, dried (9·5 g.), crystallised from aqueous acetic acid (80%) (charcoal), and recrystallised from ethyl acetate. The *acid* formed white needles, which turned yellow on exposure to air; m. p. 215° (decomp.), after sintering (Found in material dried at 100° in a high vacuum: C, 65·7; H, 4·7. $C_{18}H_{15}O_4Cl$ requires C, 65·4; H, 4·5%).

8-*Chloro*-3′-*keto*-4-*acetoxy*-7-*methoxy*-1 : 2-cyclo*pentenophenanthrene* (IV, R = Ac).—The *cyclo*pentenoneacetic acid (30 g.) was refluxed with acetic anhydride (300 c.c.) for ½ hour. Acetic anhydride (230 c.c.) was removed by distillation, and the semi-solid residue mixed with methyl alcohol (450 c.c.). The product (21 g.) was collected and washed with a small amount of benzene. It crystallised from acetic acid in pale yellow needles, m. p. 254—255° (decomp.) after sintering (Found in material dried in a high vacuum at 100°: C, 67·5; H, 4·4. $C_{20}H_{15}O_4Cl$ requires C, 67·7; H, 4·2%). A further quantity of the *substance* (2 g.) was obtained on keeping the mother-liquor, concentrated to 20 c.c.

The substance gives a dinitrophenylhydrazone. Its solution in sulphuric acid is yellow. 85 C.c. of boiling acetic acid are necessary to dissolve 1 g. of the pure product. It is readily soluble in hot pyridine and hot dioxan and sparingly soluble in the simple alcohols, acetone and benzene.

The *oxime*, prepared by the pyridine method, crystallised from pyridine in stout, microscopic needles that darkened from 280° to 320° but did not melt at 370° (Found : N, 4·0. $C_{20}H_{16}O_4NCl$ requires N, 3·8%).

8-*Chloro*-4-*hydroxy*-3′-*keto*-7-*methoxy*-1 : 2-cyclo*pentenophenanthrene* (IV, R = H).—A mixture of the acetyl derivative (1 g.), sodium hydroxide (0·5 g. in a little water), and alcohol (175 c.c.) was refluxed for 5 hours. After acidification the solid was collected, dried (0·8 g.), and crystallised from nitrobenzene, being obtained in stout, microscopic needles, m.p. 335° (decomp. from 300°) (Found : C, 69·2; H, 4·2. $C_{18}H_{13}O_3Cl$ requires C, 69·1; H, 4·2%). The *keto-phenol* gives a yellow solution in aqueous sodium hydroxide.

8-*Chloro*-3′-*keto*-4 : 7-*dimethoxy*-1 : 2-cyclo*pentenophenanthrene* (IV, R = Me).—The above hydroxymethoxy-compound (3 g.) was dissolved by heating in a solution of sodium hydroxide (2·5 g.) in the minimum quantity of water and alcohol (450 c.c.). It was then treated at 40—50° with a large excess of methyl sulphate, and with aqueous sodium hydroxide (10%) to maintain alkalinity, until the methylated product was precipitated and the solution became practically colourless. Water was added, and the product collected, washed with alcohol and ether, and dried (2·9 g.). It crystallised from nitrobenzene in microscopic needles, m. p. 247°, or by slow evaporation of a solution in ethyl acetate in large rhombic prisms (Found : C, 69·7; H, 4·6. $C_{19}H_{15}O_3Cl$ requires C, 69·8; H, 4·6%). This *dimethyl* ether gives a 2 : 4-dinitrophenylhydrazone and a yellow solution in sulphuric acid.

apo*Chlorodihydroxyketo*cyclo*pentenophenanthrene*.—A mixture of 8-chloro-3′-keto-4-acetoxy-7-methoxy-1 : 2-*cyclo*pentenophenanthrene (3 g.), acetic acid (240 c.c.), and hydrobromic acid (26·5 c.c., *d* 1·5) was refluxed for 22 hours. After cooling, water was added, and sulphur dioxide passed through the suspension for a few minutes. The green solid that separated was collected, dried (2·6 g.), and crystallised from pyridine (about 70 c.c.), being obtained in intensely yellow, microscopic needles. The crystals were washed with boiling alcohol and with boiling acetic acid, recrystallised from pyridine and washed several times with boiling benzene and with dry ether. The *substance* did not melt or decompose below 380° (Found in material dried in a high vacuum at 100° : C, 68·7; H, 3·9; Cl, 11·5. $C_{17}H_{11}O_3Cl$ requires C, 68·3; H, 3·7; Cl, 11·9%). The substance is freely soluble in aqueous sodium hydroxide to an intense red solution; its solution in sulphuric acid is purple. It does not sublime when heated in a high vacuum before decomposition occurs. The substance is characterised by extreme sparing solubility in most solvents (0·4 g. of pure material requires more than 40 c.c. of boiling pyridine for complete solution). A dinitrophenylhydrazone or an oxime could not be obtained, nor could a piperonylidene derivative be prepared. The acetyl derivative gave analytical figures that showed it to be a diacetate, but the substance could not be crystallised.

apo*Chloroketodimethoxy*cyclo*pentenophenanthrene*.—The compound last described (0·4 g.) was methylated in alcohol (100 c.c.) by means of aqueous sodium hydroxide (75 c.c. of 10%) and methyl sulphate (20 c.c.). The product (0·4 g.) crystallised from nitrobenzene in microscopic yellow needles, m. p. 335° (decomp.) (Found in material dried at 100° in a high vacuum : C, 69·8; H, 4·5. $C_{19}H_{15}O_3Cl$ requires C, 69·8; H, 4·6%). The *substance* is insoluble in aqueous alkalis; it gives an intense blue coloration in sulphuric acid solution, which is destroyed on heating.

apo*Dihydroxyketo*cyclo*pentenophenanthrene*.—3′-Keto-4-acetoxy-7-methoxy-1 : 2-*cyclo*pentenophenanthrene was demethylated on a test-tube scale (Robinson, *loc. cit.*) by boiling with hydriodic acid (*d* 1·96) for a few seconds. The product had the properties of the true dihydroxy-compound later examined by Robinson and Rydon (*loc. cit.*), but it was not studied in detail at that time. All that was done was to note that it was a new substance (different azo-dye from that obtained from the hydroxymethoxy-compound) and that it furnished the dimethoxy-compound on methylation. A profound change is brought about by more leisurely procedure. A mixture of ketoacetoxymethoxy*cyclo*pentenophenanthrene (2·5 g.), acetic acid (70 c.c.), and hydrobromic acid (19·5 c.c., *d* 1·50) was refluxed for 20 hours. The dark green product (2·2 g.) was thrice extracted with boiling alcohol (50 c.c.), leaving 2·1 g. The solutions contained a ketone as shown by reaction with Brady's reagent. The solid crystallised from pyridine (30 c.c.) in well-shaped, yellow, microscopic needles which did not melt at 380° (Found in dried material : C, 76·7, 77·2; H, 4·6, 4·8. $C_{17}H_{12}O_3$ requires C, 77·3; H, 4·5%. $C_{17}H_{10}O_3$ requires C, 77·9; H, 3·8%). The solution in cold sulphuric acid was magenta-coloured and became dark purple on heating. That in aqueous sodium hydroxide was red and all the properties of the substance

were similar to those of the chloro-derivative described above. It is obvious that this *apo*-compound is quite different from the dihydroxyketo*cyclo*pentenophenanthrene, m. p. 338° (decomp.), described by Robinson and Rydon (*loc. cit.*). The dimethyl ether has m. p. 301° (decomp.). It crystallises from nitrobenzene in yellow needles and dissolves in sulphuric acid to a deep reddish-violet solution.

Reduction of 8-*Chloro*-3′-*keto*-4-*acetoxy*-7-*methoxy*-1 : 2-cyclo*pentenophenanthrene*.—In one experiment out of seven, reduction of the related hydroxy-compound by means of sodium and *iso*amyl alcohol gave a phenolic, non-ketonic product that crystallised from nitrobenzene in clusters of slender, pale yellow needles, m. p. 292° after sintering from 270° (Found : C, 68·1; H, 4·7; Cl, 10·1%). This analysis indicates about 10% dechlorination and either a dihydro- or a tetrahydro-derivative of the original substance. Many experiments on the catalytic hydrogenation of the chloro-ketone, using Raney nickel in acetic acid solution, have been made and the results may be summarised. At 105°/37 atms. for 24 hours, the starting material and a dihydro-derivative of the chlorohydroxyketomethoxy*cyclo*pentenophenanthrene were isolated. With twice the relative amount of catalyst at 158°/57 atms. for 25 hours, the results were similar. Most, but not all, of the starting material recovered was deacetylated and the hydroxymethoxydihydro-compound was also isolated. Mixed crystals gave much trouble in the tedious separations by fractional crystallisation. Indications of a more fully reduced crystalline product were obtained, but this could not be completely separated from the dihydro-compound. About 10% of the product was still more fully reduced and uncrystallisable. The dihydro-compound was eventually separated by taking advantage of its ready solubility in alcoholic sodium hydroxide. It was crystallised from dioxan and from acetic acid and obtained in colourless needles, m. p. 236—237° (Found in material dried at 100° in a high vacuum : C, 68·6; H, 4·7. $C_{18}H_{15}O_3Cl$ requires C, 68·7; H, 4·7%). It was expected that this substance would prove to be the secondary alcohol produced by reduction of the carbonyl group in position 3′, but it is definitely a ketone. An orange precipitate was obtained when Brady's reagent was added to an acetic acid solution, and condensation with piperonal in aqueous alcoholic solution in the presence of sodium hydroxide gave a red solution from which acid precipitated a yellow piperonylidene derivative. This crude material decomposed without melting below 360° and gave the usual characteristic wine-red solution in sulphuric acid. Hence this substance is almost certainly 8-*chloro*-4-*hydroxy*-3′-*keto*-7-*methoxy*-9 : 10-*dihydro*-1 : 2-cyclo*pentenophenanthrene* (V, R = Cl).

Reduction of 3′-*Keto*-4-*acetoxy*-7-*methoxy*-1 : 2-cyclo*pentenophenanthrene*.—Reduction at 125°/30 atms. for 15 hours was not effective and much starting material was recovered. Laborious fractional crystallisations led to the isolation of a substance that crystallised from methyl alcohol in colourless microscopic needles, m. p. 140° (Found : C, 77·6; H, 5·6. $C_{18}H_{16}O_3$ requires C, 77·1; H, 5·7%). Direct comparison showed that this substance was identical with the dihydro-derivative, m. p. 140°, described by Robinson and Rydon (*loc. cit.*) as 4 : 3′-dihydroxy-7-methoxy-1 : 2-*cyclo*pentenophenanthrene. This must be corrected; the substance is a ketone, probably 4-*hydroxy*-3′-*keto*-7-*methoxy*-9 : 10-*dihydro*-1 : 2-cyclo*pentenophenanthrene* (V, R = H). It gives an orange 2 : 4-dinitrophenylhydrazone and a yellow piperonylidene derivative exhibiting the usual properties. With twice the relative amount of catalyst (155°/50 atms., 25 hours) much intractable tar was produced. There were isolated mixed crystals of ketonic products and a very sparingly soluble substance of reduced *cyclo*pentylidene*cyclo*pentanone type. The components appear to be the hydroxymethoxydihydro-compound and a hydroxymethoxytetrahydro-compound. More probably it is derived by condensation of two molecules of the dihydro-compound, followed by reduction of the resulting αβ-unsaturated ketone. This *substance* (VI) crystallised from dimethylaniline in colourless, microscopic, hexagonal plates, m. p. 313° after slight sintering (Found : C, 81·4; H, 5·8. $C_{36}H_{32}O_4$ requires C, 81·8; H, 6·1%). Its solution in alcoholic sodium hydroxide is light yellow and in sulphuric acid it gives a mauve solution. When relatively much more catalyst (175°/50 atms., 32 hours) was used, a dark tar resulted from which crystals could not be isolated. High-vacuum distillation afforded a light-coloured oil in at least two distinct fractions. Crystals could not be isolated from either of these.

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