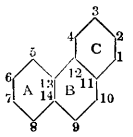
396. *Experiments on the Synthesis of Substances Related to the Sterols. Part XLVIII. Synthesis of a Tricyclic Degradation Product of Cholesterol.*

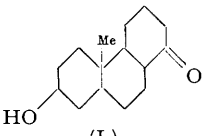
By J. W. Cornforth and Sir Robert Robinson.

A development of the method outlined in Part XLV (*J.*, 1946, 676) has led to the synthesis of the tricyclic diketone (V) in a form structurally and stereochemically identical with a degradation product of cholesterol (Reich, 1945). A summary of this work has already been published (*Nature*, 1947, **160**, 737).

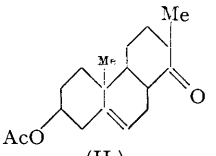
Oxidative degradation of sterols and bile acids has become an important means of preparing hormones and other valuable substances. In such partial syntheses, by-products are sometimes encountered which owe their origin to the removal of ring D of the steroid nucleus. Thus Köster and Logemann (*Ber.*, 1940, **73**, 299) isolated 1-keto-7-acetoxy-2 : 13-dimethyl-$\Delta^{9(14)}$-dodecahydrophenanthrene (II) from the oxidation products of cholesteryl acetate dibromide; hydrolysis and Oppenauer-oxidation of (II) gave the unsaturated ketone (III). Reich (*Helv.*

Chim. Acta, 1945, **28**, 892) similarly obtained 7-hydroxy-1-keto-2 : 13-dimethyl-Δ^2-dodecahydrophenanthrene (IV) from methyl diacetyldeoxycholate, and thence by reduction and oxidation 1 : 7-diketo-2 : 13-dimethylperhydrophenanthrene (V).

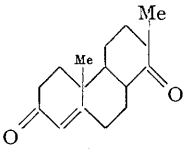




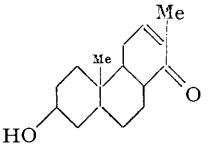
(I.)



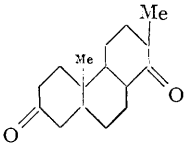
(II.)



(III.)



(IV.)



(V.)

We have now been able to correlate these two series : hydrogenation of (III) led smoothly to (V). Our thanks are due to Dr. K. Miescher and to Prof. T. Reichstein and Dr. H. Reich, who kindly furnished specimens of (II) and (V) respectively.

The method used (Part XLV, *loc. cit.*) to synthesise one stereoisomeride of 7-hydroxy-1-keto-13-methylperhydrophenanthrene (I) from 1 : 6-dihydroxynaphthalene promised an approach to the total synthesis of the steroid nucleus. It was obvious, however, that the completion of the task would be facilitated by a relay at the tricyclic stage. Identification of such a synthetic product with material derived from a natural steroid might have two great advantages. In the first place a large number of possible stereoisomerides would be eliminated from consideration and, secondly, the degradation product, if available in sufficient quantity, might serve as the raw material for the later stages of the synthesis. The diketone (V) was therefore chosen as the first objective : we already had reason to believe that the method used to prepare (I) produced a *cis*-configuration at the A/B ring-junction, and this configuration is present also in (V) because it was prepared from deoxycholic acid without disturbance at $C_{(14)}$ ($C_{(5)}$ in steroid numbering).

It was necessary to repeat the first steps of the synthesis on a much larger scale than heretofore, and we express our gratitude to Messrs. Imperial Chemical Industries Ltd. (Dyestuffs Division), for a generous supply of 1 : 6-dihydroxynaphthalene, prepared specifically for the present investigation. The earlier stages are shown on page 1857.

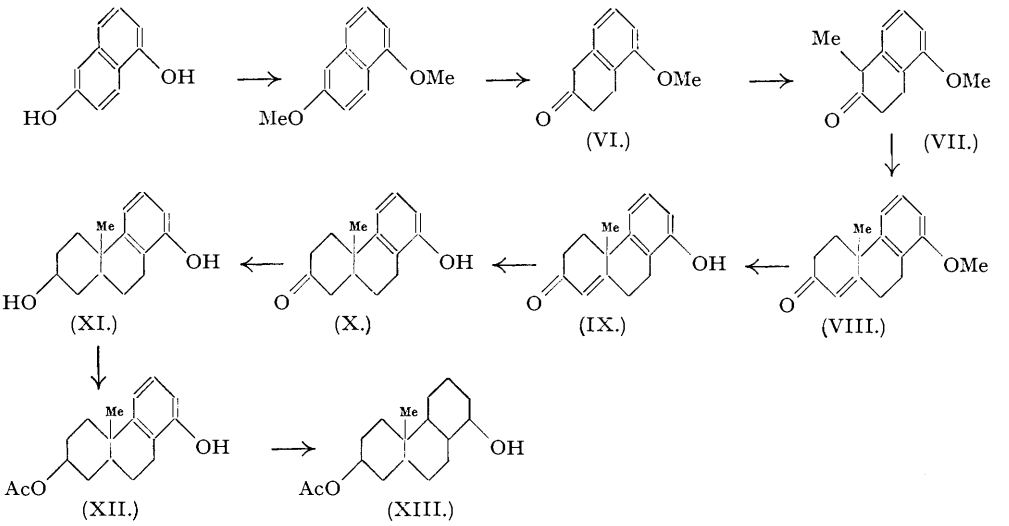
The preparation of 5-methoxy-2-tetralone (VI) in hectogram quantities presented no special difficulty ; the *C*-methylation of (VI) was modified to operate in batches of comparable size, and conditions for the separation of 5-methoxy-1-methyl-2-tetralone (VII) from unchanged (VI) and 5-methoxy-1 : 1-dimethyl-2-tetralone were standardised. The latter stage, however, is relatively the least satisfactory of the synthesis (maximum net yield, 62%).

In the next operation a successful departure was made from the usual technique for inducing reaction between alicyclic ketones and diethylaminobutanone methiodide. Instead of preparing a sodio-derivative of the ketone (VII) by means of sodamide and adding an alcoholic solution of the methiodide, the crystalline methiodide was prepared in the reaction vessel, a benzene solution of the ketone added, and reaction initiated by addition of alcoholic potassium ethoxide. The method is well adapted to large-scale working and should be useful when a stronger base than ethoxide ion is required. In the present instance it enabled us to prepare 7-keto-1-methoxy-13-methyl-5 : 6 : 7 : 9 : 10 : 13-hexahydrophenanthrene (VIII) in 70% yield.

Demethylation of (VIII) to 1-hydroxy-7-keto-13-methyl-5 : 6 : 7 : 9 : 10 : 13-hexahydrophenanthrene (IX) by means of hydrogen iodide in acetic acid was repeated with few modifications. Hydrogenation of (IX) was allowed to proceed through 1-hydroxy-7-keto-13-methyl-$\Delta^{1:3:11}$-octahydrophenanthrene (X) to 1 : 7-dihydroxy-13-methyl-$\Delta^{1:3:11}$-octahydrophenanthrene (XI), m. p. 171°. The mother-liquors from which (XI) was separated, doubtless contained the 7-epimeride and this could be oxidized by the Oppenauer method to give a further quantity of (X), and thence, by reduction, (XI).

With methyl sulphate (X) gave the methoxy-ketone that had previously been prepared by hydrogenation of (VIII). Bromination of the methoxy-ketone afforded a bromo-ketone which was evidently 8-bromo-7-keto-1-methoxy-13-methyl-$\Delta^{1:3:11}$-octahydrophenanthrene, because the unsaturated ketone (VIII) was readily regenerated by boiling it with pyridine. This

transformation provided additional evidence that the alicyclic rings in (X) and (XI) were fused in the *cis*-configuration, since it has always been found that the bromination of β-decalones



occurs preferentially at the α-position in *cis*-β-decalones and at the β′-position in *trans*-β-decalones. On the other hand, the suggestion (Part XLV) that the angular methyl and alcoholic hydroxyl groups have a *cis*-relationship in (XI) must now be withdrawn. It has been found that the reduction of (X) to (XI) gives a better yield in alcoholic than in acetic acid solution, so that no analogy with the case of coprostanone can be discerned. Indeed, the results recall the behaviour of 3-keto-groups in the bile acids, which tend to give 3(α)-hydroxy-steroids on reduction under acid or neutral conditions.

The partial acetylation of (XI) to 1-hydroxy-7-acetoxy-13-methyl-$\Delta^{1:3:11}$-octahydrophenanthrene (XII) required no modification. Hydrogenation of the acetoxy-phenol (XII) over platinum in an acetic acid medium was not found satisfactory on a larger scale; the use of Raney nickel in dioxan at high temperature and pressure gave some of the desired product but was attended by too much hydrogenolysis of the 1-hydroxyl group. Palladium–strontium carbonate in dioxan (Morton and Robinson, *J.*, 1943, 497) was the catalyst of choice; at 200° it afforded 1-hydroxy-7-acetoxy-13-methylperhydrophenanthrene (XIII) as a mixture of stereoisomerides in 70% yield.

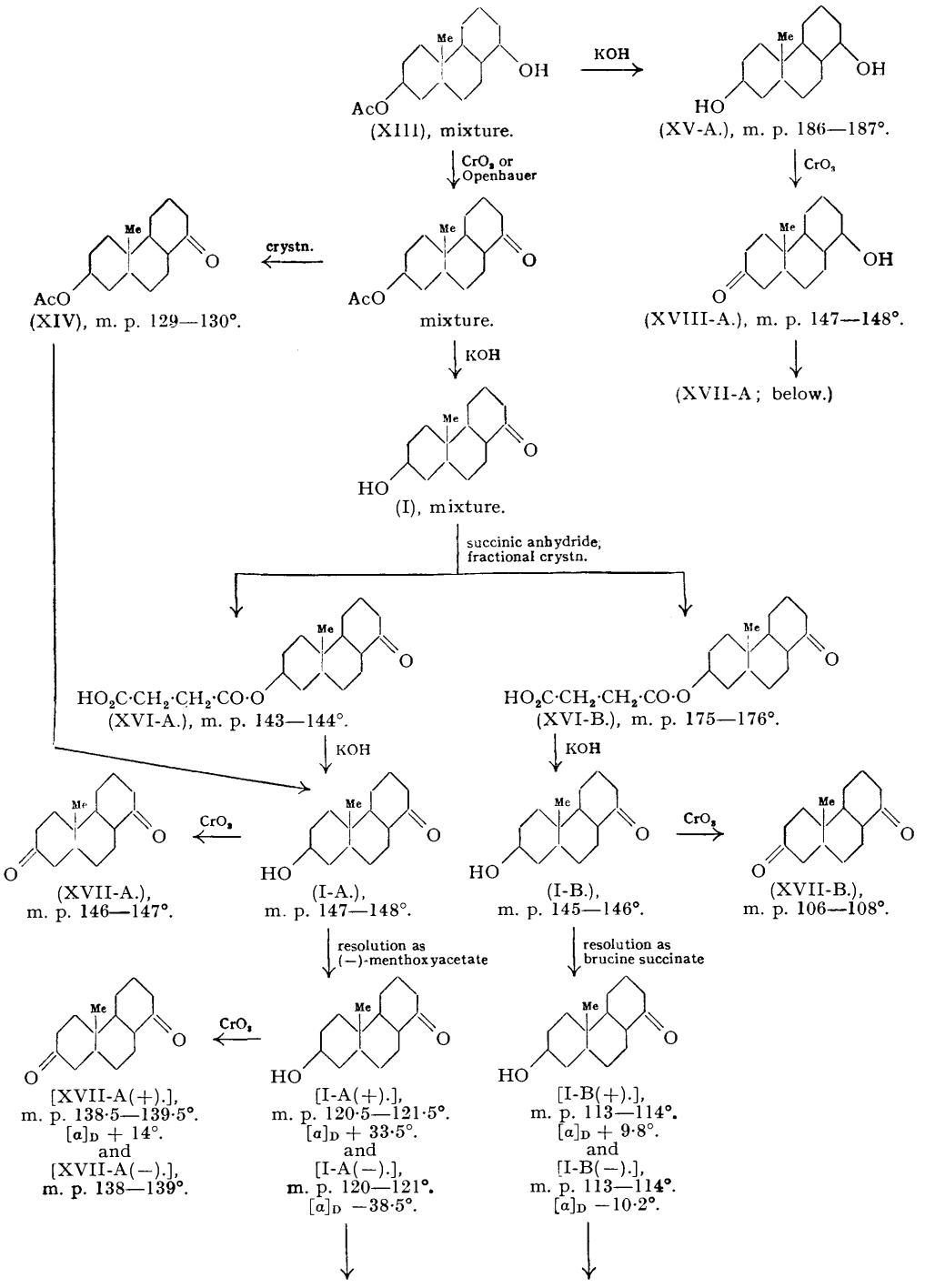
Oxidation of (XIII) with chromic acid or by the Oppenauer method gave a mixture of 1-*keto*-7-*acetoxy*-13-*methylperhydrophenanthrenes* (XIV) from which a crystalline individual could be separated; usually, however, the total oxidation product was hydrolysed. In this way a crystalline, hydrated mixture of hydroxy-ketones (I) was obtained, along with a 1 : 7-dihydroxy-13-methylperhydrophenanthrene (XV), the latter doubtless being derived from unoxidized (XIII).

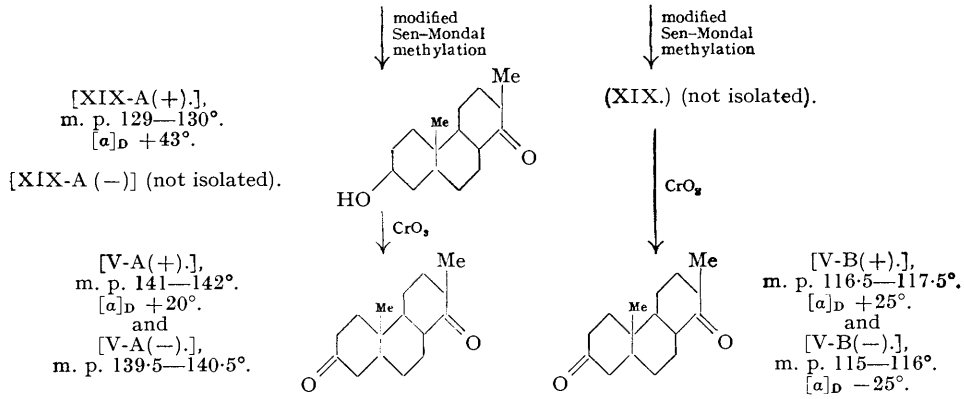
The hydroxy-ketone mixture was treated with succinic anhydride and pyridine; fractional crystallization of the product separated it into two stereoisomeric 1-*keto*-13-*methyl*-7-*perhydrophenanthryl hydrogen succinates* (XVI), and these on hydrolysis gave two 7-*hydroxy*-1-*keto*-13-*methylperhydrophenanthrenes* (I), from which two 1 : 7-*diketo*-13-*methylperhydrophenanthrenes* (XVII) were derived by oxidation.

We have already (Part XLV, *loc. cit.*) given reasons for supposing that the mixture of hydroxy-ketones (I) consists exclusively of *trans*-α-decalone types. Oxidation of the two individual hydroxy-ketones (I) to different diketones (XVII) provides a proof that the stereoisomerism is not wholly due to the 7-hydroxy-group; epimerization of this group is in any event unlikely to have taken place under the conditions of synthesis. Still less likely is a partial inversion at $C_{(14)}$. The probability is thereby established that the two hydroxy-ketones (I) are the two possible racemates, having rings B and C fused in the *trans*-relationship, which can be derived from the acetoxy-phenol (XII) without inversion at any of the existing asymmetric centres. This will not, however, be assumed in what follows; the stereochemical families will be termed A and B, corresponding to the lower-melting and higher-melting hydrogen succinates (XVI)

respectively, the difference between the series being understood to lie in the configuration of the bridgehead carbon atoms $C_{(11)}$, $C_{(12)}$, $C_{(13)}$, $C_{(14)}$.

The A-7-hydroxy-1-keto-13-methylperhydrophenanthrene (I-A) was found to give a semicarbazone identical with that described in Part XLV (*loc. cit.*); presence of the B-isomeride in the earlier crude preparation of (I) is not excluded however, for it would have been masked by

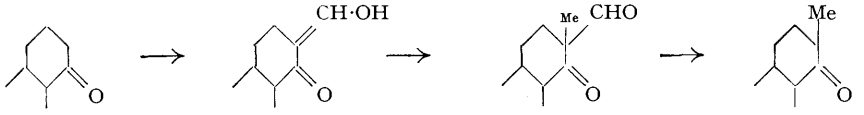




the more abundant A-isomeride. The crystalline acetoxy-ketone (XIV) gave the A-hydroxy-ketone (I-A) on hydrolysis. The diol (XV) mentioned above could be partly oxidized to a hydroxy-ketone differing from both (I-A) and (I-B); further oxidation gave the A-diketone (XVII-A), so that the diol (XV) is of the A series and, if epimerization at $C_{(7)}$ can be excluded, the intermediate oxidation product is *A*-1-*hydroxy*-7-*keto*-13-*methylperhydrophenanthrene* (XVIII).

Optical resolution of (I-A) (the more abundant isomeride) was first undertaken. No satisfactory alkaloidal salt of the hydrogen succinate (XVI-A) having been found, the hydroxy-ketone was esterified with (−)-menthoxyacetyl chloride. The resolution followed a somewhat unusual course: the diastereoisomerides formed a molecular compound of $[\alpha]_D$ about −43°, which was partly dissociated on recrystallisation to give the more sparingly soluble *A*(−)-1-*keto*-13-*methyl*-7-*perhydrophenanthryl* (−)-*menthoxyacetate*. Although several recrystallisations were necessary to separate the maximum amount of this ester, yet, arising from the circumstances mentioned, no progressive changes were observed in the optical rotation of the fractions which consisted of the molecular compound, or of substantially pure A(−)-ester of $[\alpha]_D$ about −77°. The course of resolution could actually be followed without polarimetric control, the form of the crystals being a sufficient guide. Hydrolysis of this A(−)-ester led to *A*(−)-7-*hydroxy*-1-*keto*-13-*methylperhydrophenanthrene* [I-A(−)]. Material in the mother-liquor of the menthoxyacetate crystallisation was similarly hydrolysed and gave a partly racemic product, separated by crystallisation into *A*(+)-7-*hydroxy*-1-*keto*-13-*methylperhydrophenanthrene* [I-A(+)] and a little of the racemic hydroxy-ketone (I-A). Oxidation of the purified enantiomorphs led to *A*(+)- and *A*(−)-1 : 7-*diketo*-13-*methylperhydrophenanthrenes* (XVII).

Introduction of a methyl group at $C_{(2)}$ was now necessary. We had long considered the method of Sen and Mondal (*J. Indian Chem. Soc.*, 1928, **5**, 609) as eminently suitable in a case of this kind. The operations involved are formylation, *C*-methylation, and hydrolysis, as follows:



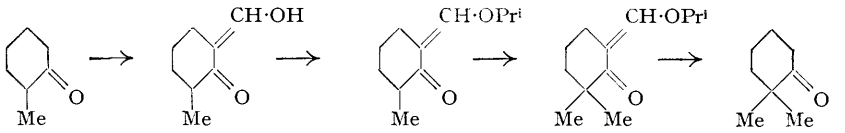
Sometimes the last two stages are combined in one operation.

Accordingly, the hydroxy-ketone [I-A(−)] was formylated, and the sodio-derivative of the resulting crude hydroxymethylene-ketone heated in methanol with methyl iodide. Oxidation of the neutral product gave a new ketone, A(−)-1 : 7-diketo-2 : 13-dimethylperhydrophenanthrene [V-A(−)]. This showed a considerably higher melting-point than the "natural" diketone (V), and thus provided the first indication that the A series was not the desired one.

Resolution of (I-B) was therefore necessary. The hydrogen succinate of (XVI-B) formed diastereosiomeric brucine salts of widely differing solubility, so as to render feasible the separation of brucine B(−)-1-keto-13-methyl-7-perhydrophenanthryl succinate in spite of the very small amount of available material. Successive treatment with acid and alkali gave *B*(−)-1-*keto*-13-*methyl*-7-*perhydrophenanthryl hydrogen succinate* [XVI-B(−)] and then *B*(−)-7-*hydroxy*-1-*keto*-13-*methylperhydrophenanthrene* [I-B(−)]. From the mother-liquors of the

recrystallisation of the brucine salt a crude hydrogen succinate was obtained and most of the sparingly soluble (±)-compound which it contained could be separated from this. After this process, hydrolysis of the remainder and crystallisation yielded *B*(+)-7-*hydroxy*-1-*keto*-13-*methylperhydrophenanthrene* [I-B(+)].

Experience with the Sen–Mondal methylation of [I-A(−)] had indicated the need of a gentler procedure, for, though the desired substance was eventually obtained, the yield and quality of the product were unsatisfactory. Johnson and Posvic (*J. Amer. Chem. Soc.*, 1947, **69**, 1361) have recently published a method for the *C*-methylation of ketones, illustrated below by the stages in the preparation of 2 : 2-dimethyl*cyclo*hexanone.



It will be appreciated that an alkoxymethylene group is here used to block *C*-methylation on one side of the carbonyl group, whereas in the Sen–Mondal method the hydroxymethylene group facilitates *C*-methylation on the same side. *iso*Propyl iodide and potassium carbonate in acetone were used by Johnson and Posvic for *O*-alkylation of the hydroxymethylene-ketone; methyl iodide had been tried first, but had afforded little *O*-methyl ether. It was assumed that *C*-methylation accounted for the rest of the product, and as this seemed probably correct an extremely mild method of carrying out the Sen–Mondal *C*-methylation was indicated.

The hydroxymethylene-ketone obtained by formylation of [I-A(+)] was therefore heated with potassium carbonate and methyl iodide in acetone solution and suspension. Gentle acid hydrolysis followed by extraction with alkali then removed the small proportion of hydroxymethylene-ketone which had undergone *O*-alkylation; the neutral product containing A(+)-7-hydroxy-1-keto-2-formyl-2 : 13-dimethylperhydrophenanthrene was then warmed with alkali. Crystalline *A*(+)-7-*hydroxy*-1-*keto*-2 : 13-*dimethylperhydrophenanthrene* (XIX) could be isolated at this stage, but chromic acid oxidation of the crude product gave the diketone *A*(+)-1 : 7-*diketo*-2 : 13-*dimethylperhydrophenanthrene* [V-A(+)] in better overall yield.

Methylation of [I-B(−)] was now carried out in the same manner. The resulting *B*(−)-1 : 7-*diketo*-2 : 13-*methylperhydrophenanthrene* [V-B(−)] was difficult to purify. This was possibly due to unnecessarily vigorous acid hydrolysis, which may have brought about contamination with some unmethylated diketone in the final product. However, the diketone [V-B(−)] melted at almost the same temperature as the " natural " diketone, and the optical rotation was of the same magnitude though opposite in sign.

Advantage of the experience gained was taken in effecting the *C*-methylation of [I-B(+)]; gentler conditions were used and the product, B(+)-1 : 7-diketo-2 : 13-dimethylperhydrophenanthrene [V-B(+)], was purified without trouble. It had the same melting point and, within experimental error, the same optical rotation as the " natural " diketone (V), and mixed-melting-point determination also indicated the identity of the synthetic and the " natural " specimens. Final confirmation of this, and also of the identity of the two " natural " specimens prepared from cholesterol and from deoxycholic acid, was sought in a comparison of the substances by *X*-ray crystallography. We are indebted for this comparison to Dr. D. M. Crowfoot, F.R.S., whose report follows.

" The three specimens, *A* from cholesterol, *B* from deoxycholic acid (Reich), and *C*, synthetic, were compared and found to be crystallographically identical.

" *A* and *C* had been crystallised in the form of good lath-shaped crystals or prisms suitable for single *X*-ray crystallographic examination. In *B*, the crystals were very small; a portion was therefore recrystallised from a few drops of ether; thin, clear plates formed by evaporation in a few hours.

" The specimens may be described as orthorhombic plates or prisms showing the forms 001, 101, and 011, and usually elongated along 010. The unit cell dimensions are approximately: $a = 8{\cdot}1$, $b = 7{\cdot}22$, $c = 23{\cdot}7$ A.; space group P2,2,2; $n = 4$ for ρ calc. = 1·18. The orientation of the optic axes is $n_\gamma//b$, $n_\alpha//c$, $n_\beta//a$. (19.9.47)."

Experimental.

All optical rotations were taken in chloroform solution. Melting points are uncorrected, a point to be noted because many corrected m. p.s are cited in the literature.

Hydrogenation of 1 : 7-*Diketo*-2 : 13-*dimethyl*-Δ^8-*dodecahydrophenanthrene* (III).—A solution of

1-keto-7-acetoxy-2 : 13-dimethyl-$\Delta^{9(14)}$-dodecahydrophenanthrene (II; 950 mg.) in methanol (15 c.c.) along with potassium hydroxide (1 g.) was heated under reflux for an hour. The neutral product was isolated by means of ether and dissolved in toluene (30 c.c.); water was then expelled by boiling. *cyclo*Hexanone (4 c.c.) and aluminium *iso*propoxide (0·5 g.) were added and the procedure of Köster and Logemann (*loc. cit.*) was then followed. Recrystallisation of the crude product from ether gave a first crop of (III) (443 mg.), m. p. 137·5—138·5°, raised by crystallisation from methanol to 138—139°; $[\alpha]_D$ +124° ± 3° (*c*, 0·716). Köster and Logemann gave m. p. 140—141°, $[\alpha]_D$ 128°. The unsaturated ketone (III) (441 mg.) in ethanol (5 c.c.) was hydrogenated at 20°/1 atm. in the presence of platinum oxide (22 mg.). Hydrogen (50 c.c.) was taken up within 5 minutes, the rate of absorption then slackened, and the process was stopped. Recrystallisation of the product from ether afforded colourless, prismatic rods, m. p. 116·5—117·5°, of 1 : 7-diketo-2 : 13-dimethylperhydrophenanthrene (V; "natural" *A* of Dr. Crowfoot's report); $[\alpha]_D^{24}$ +28° ± 2° (*c*, 1) (Found: C, 77·1; H, 9·5. Calc. for $C_{16}H_{24}O_2$: C, 77·4; H, 9·7%). A specimen of (V) prepared by Dr. H. Reich from deoxycholic acid and very kindly supplied to us, also had m. p. 116·5—117·5° under our conditions (Reich, *loc. cit.*, gave 119—120·5° as the corrected m. p. on the Kofler block); there was no depression in m. p. on admixture of the specimens.

5-Methoxy-2-tetralone (VI).—1 : 6-Dihydroxynaphthalene (200 g.) was mixed with 2N-sodium hydroxide (1120 c.c.), and methyl sulphate (250 c.c.) added at once. The mixture was shaken and prevented from actually boiling until reaction had subsided; 2N-sodium hydroxide (560 c.c.) and methyl sulphate (120 c.c.) were then added. When the second reaction slackened, excess of methyl sulphate was destroyed by warming for ½ hour on a steam-bath with frequent shaking. The warm liquid was acidified and extracted with chloroform; the chloroformic layer was washed twice with a little 2N-sodium hydroxide and evaporated. Sodium (190 g.) was added during 35 minutes to a solution of the crude 1 : 6-dimethoxynaphthalene (225 g.; 96%) in boiling alcohol (1900 c.c.); a large copper reflux condenser was used. Alcohol (400 c.c.) was then added and heating continued under reflux until the metal had disappeared (about 40 minutes). Water (600 c.c.) was cautiously added and most of the alcohol removed under diminished pressure. The residue was mixed with more water (300 c.c.), and the lower aqueous layer was separated as far as possible and extracted twice with a little dioxan which was then united with the oily upper layer. To this was added water (250 c.c.) and then hydrochloric acid (*d* 1·18) until the mixture was acid to Congo-red (about 100 c.c. required). More acid (30 c.c.) was added and the liquid kept hot and shaken occasionally for ½ hour. The lower oily layer was separated; the aqueous layer was diluted with water (1 l.), separated from more oil, and extracted thrice with small quantities of chloroform. The combined oil and chloroformic extracts were stirred with saturated aqueous sodium hydrogen sulphite (500 c.c.) until crystallisation set in. Next day the mass was triturated with ether; the solid was collected, washed well with ether, dissolved in hot water (2—3 l.) and treated with solid sodium carbonate until no more oil separated. The 5-methoxy-2-tetralone was extracted with chloroform and distilled; b. p. *ca.* 120°/0·5 mm. (157 g.). The material which did not react with sodium hydrogen sulphite could be reduced again with sodium and alcohol, but this gave only an additional 2 g. of ketone (total yield, 73% based on 1 : 6-dihydroxynaphthalene). On keeping, the ketone solidified in massive prisms, m. p. 36—37°.

5-Methoxy-1-methyl-2-tetralone (VII).—An ice-cooled mixture of 5-methoxy-2-tetralone (51 g.), dry methanol (50 c.c.), and methyl iodide (25 c.c.) was stirred under nitrogen during the addition (1 hour) of a solution of sodium (6·6 g.) in dry methanol (100 c.c.). The mixture was stirred for a further hour and then heated under reflux for a few minutes; dilute sulphuric acid was added with good stirring until a colour change (to brighter yellow) indicated that excess of alkali had been destroyed. Air was then admitted, a little water added, and the methanol removed under reduced pressure. The oil was separated and a little more recovered from the aqueous layer by extraction with chloroform. The solvent-free oil was shaken with saturated, aqueous sodium hydrogen sulphite (35 c.c.) until the mixture became solid (5—10 minutes); after 25 minutes had elapsed from the time of mixing, ether was added, to inhibit further reaction, and the solid collected and washed with ether. The bisulphite compound was decomposed as in the previous experiment and gave unchanged (VI) (13·7 g.). The ethereal filtrate was evaporated, the residue mixed with an equal volume of ethanol, shaken with saturated sodium hydrogen sulphite (100 c.c.) until crystallisation set in (about ½ hour), and kept for 36 hours. The bisulphite compound was then collected, washed, and decomposed as before. The crude monomethyl ketone (VII) was tested for unchanged (VI) by dissolving one drop in alcohol (1 c.c.) and adding one drop of 10% sodium hydroxide. A slight purple colour usually appeared at once; if this did not deepen appreciably on shaking for 1—2 minutes, the sample was satisfactory, otherwise treatment with a little more sodium hydrogen sulphite was necessary. The ketone was then distilled; b. p. about 120°/0·5 mm. (21 g.); it sometimes solidified and then had m. p. 42—43° after washing with a little light petroleum, but the entire distillate was used in the next stage. The unchanged (VI) was remethylated without distillation and afforded a further quantity of (VII). From 156 g. of (VI), 85 g. of (VII) and 8·5 g. of recovered (VI) were obtained by two successive methylations, a net yield of 62%.

7-Keto-1-methoxy-13-methyl-5 : 6 : 7 : 9 : 10 : 13-hexahydrophenanthrene (VIII).—Diethylaminobutanone (prepared according to Wilds and Shurk, *J. Amer. Chem. Soc.*, 1943, **65**, 471) (15·05 g.) was swirled gently in a 1-l. flask and cooled in ice during the addition of methyl iodide (15·0 g.) in portions during ½ hour. The swirling was regulated so as to obtain the crystalline methiodide as an even coating on the walls of the flask. When no more liquid remained, the flask was kept in ice for ½ hour and then under the tap for 45 minutes. A solution of the ketone (VII) (20·0 g.) in dry, thiophen-free benzene (100 c.c.) was added, air was expelled from the flask by dry nitrogen, and a solution of potassium (6·5 g.) in dry ethanol (100 c.c.) added with ice cooling during 5 minutes. Swirling was continued until the methiodide had all dissolved (about 30 minutes) and was replaced by a precipitate of potassium iodide. After it had been kept in ice for another hour, the mixture was boiled gently for 25 minutes. An excess of 2N-sulphuric acid was then added and the nitrogen stream stopped. After addition of enough water to dissolve the potassium sulphate the benzene layer was separated and the aqueous layer extracted twice with ether. The united extracts were washed with water, clarified with a little magnesium sulphate, and evaporated. The residue was distilled and 23·2 g. were collected up to 180°/0·1 mm. The distillate was

warmed until fluid, and ether added gradually until the total weight was 40 g. Crystallisation set in at once and was allowed to proceed at 0° overnight; the ketone (VIII) (17·0 g.; m. p. 115—117°) was then collected and washed with chilled ether. The mother-liquors after fractional distillation afforded an additional 1 g.; the total yield was thus 71%. This process has been carried out successfully on four times the above scale.

1-*Hydroxy*-17-*keto*-5 : 6 : 7 : 9 : 10 : 13-*hexahydrophenanthrene* (IX).—Hydriodic acid (51 c.c.; *d* 1·7; light yellow in colour) was added to a boiling solution of the methoxy-ketone (VIII) (68 g.) in pure acetic acid (1020 c.c.). Heating under reflux was continued for 30—35 minutes, and the mixture cooled quickly and poured into a stirred mixture of water (4 l.), containing a little sodium hydrogen sulphite, and ether (400 c.c.). The light-yellow ethereal layer was separated and the aqueous layer shaken twice with ether. The combined extracts were then repeatedly washed with water and finally with small successive portions of 2N-sodium hydroxide until all the acetic acid had been removed. 2N-Sodium hydroxide (140 c.c.) was then added and, after brief shaking, the deep-red lower layer was run into an excess of 2N-sulphuric acid with swirling. The ethereal layer was washed twice with a little water, extracted again with 2N-alkali, and washed again with water and finally with a little 2N-acid. All the alkaline washings were acidified immediately after separation. The precipitated phenol (IX) was collected, washed, dried at 100°, and triturated with cold ether; it was then ready for hydrogenation. From the neutral fraction, unchanged material was recovered by distillation at low pressure; the distillate was then demethylated as before. In this way 37 g. (70% net) of the phenol (IX) were obtained, along with 12 g. of recovered methoxy-ketone.

1 : 7-*Dihydroxy*-13-*methyl*-$\Delta^{1:3:11}$-*octahydrophenanthrene* (XI).—The phenol (IX) (37 g.) and platinum oxide (2·6 g.) were suspended in alcohol (200 c.c.) and hydrogenated at 20°/1 atm. The first stage was very rapid; (IX) dissolved and the saturated ketone (X) separated. Further reduction was slower; it could be accelerated by addition of a trace of ferrous sulphate (50 mg. in a little water). When absorption had ceased, catalyst and solvent were removed, the residue treated with enough chloroform to make it fluid and crystallisation allowed to proceed at 0°. Next day the diol (XI) (24·5 g.) was collected; m. p. 170°. The mother-liquors were reoxidized by the Oppenauer method with acetone (300 c.c.), aluminium *tert.*-butoxide (15 g.), and benzene (300 c.c.) (heating for 24 hours under reflux), and the product was isolated in the usual way and stirred for several hours with saturated aqueous sodium hydrogen sulphite solution, but no crystalline adduct separated. The mixture was washed with ether, and the aqueous layer and gummy precipitate were treated with an excess of sodium carbonate solution and extracted with ether. Crystallisation from ethanol gave the phenolic ketone (X), from which more of the diol (XI) (3·5 g.) was obtained by hydrogenation. The total yield of (XI) and (IX) combined was therefore 75%.

Transformation of the Phenolic Ketone (X) *into the Unsaturated Methoxy-ketone* (VIII).—1-Hydroxy-7-keto-$\Delta^{1:3:11}$-octahydrophenanthrene (0·7 g.) was methylated with methyl sulphate and N-sodium hydroxide in the usual manner to give 7-keto-1-methoxy-$\Delta^{1:3:11}$-octahydrophenanthrene (0·6 g.), m. p. 119—121° after crystallisation from ether. The m. p. was not depressed by admixture with material previously prepared (Part XLV, *loc. cit.*) by hydrogenation of (VIII). This methoxy-ketone (548 mg.) in acetic acid (7 c.c.) was treated with bromine (360 mg.) in acetic acid (1·8 c.c.). The deep-blue solution was diluted with water, and the product collected and crystallised from a little alcohol. Another recrystallisation gave 8-*bromo*-7-*keto*-1-*methoxy*-$\Delta^{1:3:11}$-*octahydrophenanthrene* as aggregated, colourless prisms, m. p. 136—137° (Found: C, 59·3; H, 5·9; Br, 23·8. $C_{16}H_{19}O_2Br$ requires C, 59·5; H, 5·9; Br, 24·8%). The bromo-ketone (400 mg.) was boiled with dry pyridine (12 c.c.) for 20 hours. Ether and dilute acid were added; the ethereal solution was dried, treated with charcoal, and evaporated. The residual gum crystallised on seeding with (VIII). Two crystallisations from light petroleum (b. p. 40—60°) gave colourless, prismatic needles, m. p. 118—120°, alone or mixed with a specimen of (VIII), m. p. 119—120°.

1-*Hydroxy*-7-*acetoxy*-13-*methyl*-$\Delta^{1:3:11}$-*octahydrophenanthrene* (XII).—The partial acetylation of (XI) (27·95 g.) was carried out as before (*loc. cit.*) affording (XII) (20·3 g.; recrystallised). After hydrolysis of the acetate in the mother-liquor, 9·8 g. of (XI) were recovered (net yield, 95%).

Hydrogenation of (XII).—The acetoxy-phenol (XII) (12·8 g.) in dioxan (190 c.c.; peroxide-free and anhydrous) was hydrogenated for 3 hours at 190—205°/*ca.* 150 atm. in the presence of palladium–strontium carbonate (6·5 g. of 2·5%), only a trace of the phenol escaping reaction. Distillation gave a lower fraction, b. p. 90—100°/0·005 mm., consisting largely of hydrogenolysed material (4·0 g.); the main fraction (8·3 g.) containing 1-hydroxy-7-acetoxy-13-methylperhydrophenanthrenes (XIII) distilled at 130—140°/0·01 mm. and was a vitreous mass when cold. A small further quantity could be recovered on redistillation of the lower fractions. In an earlier experiment when the hydrogenation was interrupted prematurely, the unchanged acetoxy-phenol (XII) crystallised out almost quantitatively when the product was (without distillation) mixed with an equal volume of ether and kept for a few days.

Oxidation of (XIII).—(*a*) The above glassy product (17·9 g.; b. p. 130—140°/0·1 mm.) in purified acetic acid (180 c.c.) was treated slowly at 10—20° with chromium trioxide (4·8 g.) in a little water and acetic acid (180 c.c.). After 22 hours the mixture was diluted with water (1500 c.c.) and extracted twice with ether. The clear yellow extract, freed from acetic acid, was evaporated, and the residue partly crystallised. This was dissolved in alcoholic potassium hydroxide (400 c.c of 0·4N), and the solution heated under reflux for one hour, concentrated to 150 c.c., and slowly diluted to 1 l. with water.

The crystalline precipitate (9·75 g.) was collected and recrystallised from moist ethyl acetate, giving a fraction (7·2 g.) melting indefinitely below 100°, consisting of hydrated hydroxy-ketones (I). The mother-liquor and aqueous-alcoholic filtrate were united and extracted continuously with ether; the product was treated with aqueous-alcoholic semicarbazide acetate and gave a crystalline semicarbazone mixture (4·1 g.). This was decomposed by keeping with a 15% solution of oxalic acid in methanol; the product on crystallisation from moist ethyl acetate gave a further 2·2 g. of the hydroxy-ketone mixture. From the semicarbazone mother-liquors a crystalline product, m. p. 181—182°, was obtained (0·8 g.); recrystallisation from ethyl acetate gave fine needles, m. p. 186—187°, of *A*-1 : 7-*dihydroxy*-13-*methylperhydrophenanthrene* (XV) (Found: C, 75·1; H, 10·6. $C_{15}H_{26}O_2$ requires C, 75·6; H, 10·9%).

(*b*) The glassy fraction, b. p. 130—140°/0·01 mm. (0·6 g.), was boiled under reflux for 45 hours with acetone (20 c.c.), benzene (20 c.c.), and aluminium *tert.*-butoxide (1 g.). The isolated product was crystallised from a little alcohol, giving 1-*keto*-7-*acetoxy*-13-*methylperhydrophenanthrene* (XIV) (150 mg.) in fine, solvated needles, m. p. 129—130°, after drying for several hours at 30°/15 mm. (Found : C, 73·4; H, 9·4. $C_{17}H_{26}O_3$ requires C, 73·5; H, 9·4%). After hydrolysis of the substances in the mother-liquors, the diol (XV) was obtained.

1-*Hydroxy*-7-*keto*-13-*methylperhydrophenanthrene* (XVIII).—A mixture of the diol (XV) (780 mg.), chromium trioxide (290 mg.), and acetic acid (15 c.c.) was kept for 24 hours. The neutral product was crystallised thrice from ethyl acetate, giving the *hydroxy-ketone* (XVIII) (0·3 g.) as colourless prisms, m. p. 147—148°, depressed sharply by both hydroxy-ketones-I-A and -I-B (Found : C, 76·4; H, 10·0. $C_{15}H_{24}O_2$ requires C, 76·2; H, 10·2%). The substances reacted with dinitrophenylhydrazine and with succinic anhydride in pyridine. On admixture with the diketone (XVII-A) there was a small but definite lowering of the m. p. (to 143—144°). The substance (110 mg.) was oxidised further with chromium trioxide (75 mg.) in acetic acid (3 c.c.). After 20 hours the product was isolated as usual and crystallised from ethyl acetate; m. p. 146·5—147·5°, alone or mixed with (XVII-A) (diketone), m. p. 146—147°.

1-*Keto*-13-*methyl*-7-*perhydrophenanthryl Hydrogen Succinates* (XVI-A) *and* (XVI-B).—The hydrated mixture of hydroxy-ketones (I) (8·2 g.) was heated with succinic anhydride (8 g.) and pyridine (16 c.c.) at 120° until a sample gave a clear solution in aqueous sodium carbonate (about 2 hours). An ether–chloroform solution of the product was washed with dilute acid and then repeatedly with water, evaporated to a syrup, and treated with ether (25 c.c.). Large prisms (6·9 g.), m. p. 140—141·5°, gradually separated; as soon as the crystallisation appeared complete the liquid was decanted and the crystals were washed quickly with ether. The mother-liquors and washings were evaporated to a syrup, using a little methanol to inhibit immediate crystallisation, then treated with ether, and allowed to crystallised as completely as possible. This gave a mixed crop (2·5 g.) which was dissolved in methanol, evaporated to a syrup, and treated with ether (10 c.c.). Irregular nodules (0·4 g.), m. p. 172—174°, separated; the mother-liquor was decanted before any of the prismatic form had separated, and evaporated with methanol. Ether (6 c.c.) was added and the volume maintained constant during the crystallisation. The crystals were separated by hand, giving 1·05 g. of prisms, m. p. 132—140°, and 1·0 g. of nodules, m. p. 155—165°. The prisms were recrystallised from ethyl acetate, and the purified product (0·65 g.) was united with the prisms obtained previously; recrystallisation of a sample from ethyl acetate gave the *A-hydrogen succinate* (XVI-A) as colourless prisms, m. p. 143—144° (Found : C, 67·6; H, 8·7; equiv., 335. $C_{19}H_{28}O_5$ requires C, 67·8; H, 8·4%; equiv., 336). Recrystallisation of the combined crops of nodules (m. p. 172—174° and 155—165°) from ethyl acetate (charcoal) gave the more sparingly soluble *B-hydrogen succinate* (XVI-B) in colourless, aggregated leaflets (1·05 g.), m. p. 175—176° (Found : C, 68·1; H, 8·4%). By similar processes the mother liquors gave small additional amounts of (XVI-A) and (XVI-B).

7-*Hydroxy*-1-*keto*-13-*methylperhydrophenanthrenes* (I-A) *and* (I-B).—The A-hydrogen succinate (200 mg.) was hydrolysed by warming with potassium hydroxide (0·3 g.) in water (8 c.c.) on a steam-bath for 20 minutes. After the mixture had cooled, the crystals were collected and recrystallised from moist ethyl acetate; m. p. about 100°. By drying for 2½ hours at 80°/15 mm. the anhydrous *hydroxy-ketone* (I-A) was obtained, having m. p. 147—148°; it formed prisms on recrystallisation from light petroleum (b. p. 60—80°) (Found : C, 76·1; H, 10·0. $C_{15}H_{24}O_2$ requires C, 76·3; H, 10·2%). The semicarbazone separated from *iso*butanol in diamond-shaped prisms, m. p. 245° (decomp.) undepressed by admixture with the semicarbazone described in Part XLV (*loc. cit.*). The same hydroxy-ketone, m. p. and mixed m. p. 147—148°, was obtained by hydrolysis of the acetoxy-ketone (XIV).

The B-hydrogen succinate (200 mg.) was hydrolysed in the same manner. The product on recrystallisation from ethyl acetate gave the anhydrous *hydroxy-ketone* (I-B) in colourless rectangular rods, m. p. 145—146°, depressed sharply by (I-A) (Found : C, 76·7; H, 10·1. $C_{15}H_{24}O_2$ requires C, 76·3; H, 10·2%). The *semicarbazone* crystallised from butanol in aggregated leaflets, m. p. 226—227° (decomp.) (Found : N, 13·7. $C_{16}H_{27}O_2N_3$ requires N, 14·3%).

1 : 7-*Diketo*-2 : 13-*dimethylperhydrophenanthrenes* (XVII-A) *and* (XVII-B).—A solution of hydroxy-ketone (I-A) (75 mg.) and chromium trioxide (30 mg.) in acetic acid (2 c.c.) was kept for 12 hours. The *diketone* (XVII-A) separated from ethyl acetate in well-formed, thick plates, m. p. 146—147°, depressed sharply by admixture with the parent hydroxy-ketone (Found : C, 76·8; H, 9·5. $C_{15}H_{22}O_2$ requires C, 76·9; H, 9·5%). The *bis*-2 : 4-*dinitrophenylhydrazone* was prepared by adding the diketone (16 mg.) to a solution of 2 : 4-dinitrophenylhydrazine (50 mg.) and a little sulphuric acid in alcohol (10 c.c.) and digestion of the mixture at the boiling point until the precipitate became granular; recrystallisation from dioxan gave small, orange-yellow prisms, m. p. 256—257° (decomp.) (Found : C, 54·7; H, 5·3. $C_{27}H_{30}O_8N_8$ requires C, 54·5; H, 5·1%).

Hydroxy-ketone (I-B) (72 mg.) was oxidized as described for (I-A); the *diketone* (XVII-B) was recrystallised by adding light petroleum to a solution in a little chloroform, and filtering quickly; it formed colourless leaflets, m. p. 106—108° (Found : C, 76·6; H, 9·4%). The *bis*-2 : 4-*dinitrophenylhydrazone* was prepared as in the A series; it separated from dioxan–alcohol in isolated, orange-yellow prisms, m. p. 257—258° (decomp.) depressed to 245—246° by admixture with the A-derivative (Found : C, 54·9; H, 5·2; N, 18·3. $C_{27}H_{30}O_8N_8$ requires C, 54·5; H, 5·1; N, 18·8%). It is uncertain whether the bisdinitrophenylhydrazone reported in Part XLV (*loc. cit.*) was of the A or B series, for all of the older sample was consumed for analysis; most likely it was of the more abundant A series.

Resolution of the Hydroxy-ketone (I-A).—The hydrogen succinate (XVI-A) (7·01 g.) was hydrolysed as described above, and the resulting hydroxy-ketone (I-A) freed from water by heating at 100°/15 mm. The hydroxy-ketone (4·90 g.) in anhydrous pyridine (25 c.c.) was treated with (−)-menthoxyacetyl chloride (5·3 g.; distilled) dropwise with swirling. After 24 hours the mixture was poured into water (400 c.c.), set aside with a little ether for 2 hours, and then extracted with ether, which was washed with 3N-hydrochloric acid, N-sodium hydroxide, and water, filtered through a little magnesium sulphate, and evaporated, finally *in vacuo*. The residue was mixed with an equal volume of light petroleum (b. p.

40—60°), cooled to about −40°, removed from the cooling bath, and scratched. The mass soon became solid; it was taken up in boiling light petroleum (15—20 c.c.) and set aside at 0°. Next day the crystals (7·0 g.; fluffy needles) were collected; m. p. 75—78°; $[\alpha]_D^{21}$ −43° (*c*, 1). A second crop (0·65 g.) was obtained by concentration of the mother-liquor to a small volume; this had m. p. 75—77° and $[\alpha]_D^{20}$ −45° (*c*. 1).

The subsequent course of the resolution can be recorded most succinctly by describing the recrystallisation of a typical fraction. This fraction (3·45 g.), m. p. 77—80°, $[\alpha]_D^{20}$ −45°, was boiled with light petroleum (b. p. 40—60°; 20 c.c.), leaving a slight residue of larger prisms. On cooling a further crop of prisms separated; this was collected after 1 hour and had m. p. 105—108°, $[\alpha]_D^{21}$ −76° (*c*, 1). The mother-liquor was concentrated to about 10 c.c. and kept at 0° overnight; a crop of fluffy needles (0·68 g.) was then collected; m. p. 77—79°; $[\alpha]_D^{24}$ −43° (*c*, 1). This crop was united with others of similar m. p. and specific rotation, and recrystallised as above to give more prisms.

The combined crops of prisms, m. p. 105° to 110°, $[\alpha]_D$ −75° to −77°, were recrystallised twice from ethyl acetate to give *A*(−)-1-*keto*-13-*methyl*-7-*perhydrophenanthryl menthoxyacetate*, m. p. 112—113°; $[\alpha]_D^{23}$ −77° ± 2° (*c*, 1) (Found: C, 74·6; H, 9·9. $C_{27}H_{44}O_4$ requires C, 75·0; H, 10·2%). The total amount obtained was 3·0 g. This product (2·85 g.) was heated under reflux with potassium hydroxide (1 g.) in methanol (12 c.c.) for 2½ hours; water was added and the mixture extracted thrice with chloroform. Some of the product was crystallised from ethyl acetate and some from chloroform–light petroleum (b. p. 40—60°); in each case long, colourless needles of *A*(−)-7-*hydroxy*-1-*keto*-13-*methylperhydrophenanthrene* [I-A(−)] were obtained; m. p. 120—121°; $[\alpha]_D^{23}$ −33·5° ± 2° (*c*, 1); this was a hydrate, and the m. p. was not changed by heating for several hours at 100°/20 mm. or by subliming at 120°/0·1 mm. (Found: C, 71·1; H, 10·5. $C_{15}H_{24}O_2,H_2O$ requires C, 70·9; H, 10·2%). The yield was 1·55 g.

The mother-liquors of the (−)-menthoxyacetate crystallisation, from which as much as possible of the material of $[\alpha]_D$ −43° had been separated, gave a gum on evaporation. This was hydrolysed with potassium hydroxide in methanol as described for the A(−)-ester. The crude product was recrystallised, first from ethyl acetate–light petroleum and then from large volumes of light petroleum (b. p. 40—60°); the light-petroleum solutions were concentrated to half their bulk before crystallisation was allowed to take place. In this way mixed crops of slender colourless needles and larger, slightly yellow prisms were obtained; the prisms were picked out where possible, and advantage was also taken of their slower rate of dissolution in light petroleum. The first crystallisation gave mixed material of m. p. 116—117·5° and $[\alpha]_D^{23}$ +31·5°; the prisms were gradually eliminated and finally a total of 1·35 g. of *A*(+)-7-*hydroxy*-1-*keto*-13-*methylperhydrophenanthrene* [I-A(+)] was obtained having m. p. 120—121·5°, and $[\alpha]_D^{24}$ +38·5° ± 2° (Found: C, 70·8; H, 10·3. $C_{15}H_{24}O_2,H_2O$ requires C, 70·9; H, 10·2%). As with the A(−)-siomeride, the water of crystallisation could be demonstrated by boiling the substance with benzene. The prisms separated by recrystallisation (0·25 g.) had m. p. 144—145°, undepressed by anhydrous (±)-A-hydroxy-ketone (I).

A(−)- *and A*(+)-1 : 7-*Diketo*-13-*methylperhydrophenanthrenes* (XVII).—The hydroxy-ketone [I-A(−)] was oxidized with chromic acid in the manner already described. The *diketone* [XVII-A(−)] separated from ether in clusters of prisms, m. p. 138—139° (Found: C, 77·0; H, 9·5. $C_{15}H_{22}O_2$ requires C, 76·9; H, 9·5%).

From the hydroxy-ketone [I-A(+)] the *diketone* [XVII-A(+)] was prepared similarly; small prisms from ether; m. p. 138·5—139·5°; $[\alpha]_D^{26}$ +14·5° ± 2° (*c*, 0·4) (Found: C, 76·7; H, 9·2%).

A(−)-1 : 7-*Diketo*-2 : 13-*dimethylperhydrophenanthrene* [V-A(−)].—The hydroxy-ketone [I-A(−)] (200 mg.) was boiled with benzene until free from water. The solution was mixed with ethyl formate (0·3 c.c.) and added to powdered potassium (50 mg.) in benzene (3 c.c.). Next day, water and ether were added; the aqueous layer was washed with ether, and the benzene–ether layer was extracted with N-sodium hydroxide, which was then added to the aqueous layer. Acidification and ether extraction gave the crude hydroxymethylene ketone (140 mg.; dried at 100°/20 mm.). This was heated with methyl iodide (0·3 c.c.) and a solution of sodium (11·5 mg.) in methanol (0·5 c.c.) under pressure at 100° for 6 hours. The product was boiled with N-hydrochloric acid for a few minutes and then taken up in ether, and a little hydroxymethylene ketone extracted with alkali; the neutral fraction obtained on evaporation of the ethereal solution was then extracted with light petroleum (b. p. 40—60°). The resulting yellow, petroleum-soluble gum was set aside in acetic acid (2 c.c.) with chromium trioxide (50 mg.). Next day the mixture was worked up as usual and the crystalline, neutral product recrystallised from ether–light petroleum (b. p. 40—60°) and then from ethyl acetate–light petroleum. The *diketone* [V-A(−)] formed small prisms, m. p. 139·5—140·5° (Found: C, 77·3; H, 9·6. $C_{16}H_{24}O_2$ requires C, 77·4; H, 9·7%). On admixture with the diketone [XVII-A(−)] the m. p. was depressed to 110°.

Resolution of the Hydroxy-ketone (I-B).—The hydrogen succinate (XVI-B) (11·319 g.) and anhydrous brucine (13·231 g.) were dissolved in acetone, and the solution was concentrated to 10 c.c. and set aside for 48 hours at 0°. The stout prisms (1·45 g.) were then collected; m. p. 129—130° (effervescence); $[\alpha]_D^{20}$ −41° (*c*, 1). Two recrystallisations by dissolution in chloroform, concentration to a syrup, and addition of acetone (8 c.c.) gave a product (1·20 g.), m. p. 132·5—133·5° (effervescence) and $[\alpha]_D^{20}$ −43°, unchanged by further crystallisation. A solution of this product in chloroform–acetone was poured into a mixture of hydrochloric acid (0·6 c.c.; *d* 1·18) and water (9 c.c.); the organic solvents were then removed by gentle heating at low pressure. The crystalline residue was triturated under several changes of water and then dried by evaporation of added carbon tetrachloride. The residue separated from ether–light petroleum (b. p. 40—60°) in irregular platelets, m. p. 116—117°, $[\alpha]_D^{21}$ −23° ± 2°, of *B*(−)-1-*keto*-13-*methyl*-7-*perhydrophenanthryl hydrogen succinate* [XVI-B(−)] (Found: equiv., 334. $C_{12}H_{28}O_5$ requires equiv., 336). The crystals and mother-liquor were warmed with dilute aqueous potassium hydroxide, and the neutral hydrolysis product crystallised from ether–light petroleum (b. p. 40—60°) (1 : 1). *B*(−)-7-*Hydroxy*-1-*keto*-13-*methylperhydrophenanthrene* [I-B(−)] was thus obtained in fine needles of a hemihydrate (280 mg.), m. p. 113—114°, $[\alpha]_D^{23}$ −10·2° ± 0·5° (*c*, 4·18) (Found: C, 73·5; H, 10·5. $C_{15}H_{24}O_2,0{\cdot}5H_2O$ requires,C, 73·4; H, 10·4%). The m. p. was not changed by prolonged heating at 80° *in vacuo*.

The mother-liquor from the initial crystallisation of brucine salt was evaporated and treated as above to recover the hydrogen succinate. This was left overnight in ether (1 c.c.), after nucleation with the (±)-hydrogen succinate (XVI-B). The solution was then decanted from the few crystals of (XVI-B) which had separated; after being washed with dilute hydrochloric acid the ether was removed and the residue warmed with aqueous potassium hydroxide. The neutral product on crystallisation from ether, gave long needles, m. p. 105—106°, apparently of a more solvated form, which reverted on drying at 80°/15 mm. to the hemihydrate (203 mg.), m. p. 113—114°, $[\alpha]_D^{20}$ +9·3° ± 0·5° (*c*, 4·16), of *B*(+)-1-*hydroxy*-7-*keto*-13-*methylperhydrophenanthrene* [I-B(+)] (Found: C, 73·8; H, 10·4. $C_{15}H_{24}O_2,0{\cdot}5H_2O$ requires C, 73·4; H, 10·4%). In order to test the optical purity of this product it was crystallised (*a*) from light petroleum (75% recovery) and (*b*) from benzene (50% recovery). The crystals obtained from (*a*), and both crystals and mother-liquor from (*b*), showed the same specific rotation as the original material.

A(+)-1 : 7-*Diketo*-2 : 13-*dimethylperhydrophenanthrene* [V-A(+)].—A benzene solution of the hydroxy-ketone [I-A(+)] (236 mg.) was boiled to expel water of crystallisation. A benzene suspension of sodium methoxide (from 92 mg. of sodium) was mixed with ethyl formate (0·33 c.c.) and the solution of the hydroxy-ketone; the volume was made up to 25 c.c. with benzene, and the mixture kept over-night in the absence of air. Water was then added; the benzene layer was twice extracted with N-sodium hydroxide, and the united alkaline solutions washed once with ether and acidified with hydrochloric acid. Extraction with ether and evaporation, finally at 80°/0·4 mm., gave the crude hydroxymethylene-ketone as a light-yellow gum (218 mg.). This was dissolved in acetone (1·25 c.c.) and heated under reflux with potassium carbonate (118 mg.; freshly ignited) and methyl iodide (0·2 c.c.) for 20 hours. The product was isolated and kept in 0·5N-aqueous-alcoholic hydrochloric acid for 2 hours; recovered hydroxymethylene-ketone was then removed by extraction with N-sodium hydroxide. The neutral fraction (150 mg.) slowly developed a faint colour with alcoholic ferric chloride; it was accordingly warmed for a few minutes with 2N-aqueous-alcoholic hydrochloric acid and then extracted with alkali as before. Hydrolytic removal of the formyl group was then carried out by gently heating the neutral product with potassium hydroxide in methanol (1 c.c. of 10%) for 10 minutes. After isolation in the usual way the neutral product was oxidised by means of chromium trioxide (50 mg.) in acetic acid (3 c.c.). Next day, the customary procedure gave the *diketone* [V-A(+)], m. p. 136—138° (100 mg.); recrystallisation from ether afforded colourless prisms, m. p. 141—142°, $[\alpha]_D^{25}$ +20° ± 2° (*c*, 1·36) (Found: C, 77·4; H, 9·6. $C_{16}H_{24}O_2$ requires C, 77·4; H, 9·7%). A mixture with the diketone [XVII-A(+)] had m. p. 110°.

The crude product before oxidation could be crystallised from light petroleum (b. p. 40—60°) to give small needles, m. p. 129—130°, $[\alpha]_D^{17}$ +43° ± 2° of *A*(+)-7-*hydroxy*-1-*keto*-2 : 13-*dimethylperhydrophenanthrene* [XIX-A(+)]. This apparently contained a trace of water not expelled by prolonged heating at 100° *in vacuo* (Found: C, 75·5, 75·8; H, 10·3, 10·4. $C_{16}H_{26}O_2$ requires C, 76·8; H, 10·4%). On admixture with the hydroxy-ketone [I-A(+)] (hydrate) the m. p. was intermediate. The presence of the 2-methyl group was confirmed by chromic acid oxidation, the product being the diketone [V-A(+)]. An alternative explanation of the low carbon content found in this case is that the product contained a little of the unchanged formyl derivative ($C_{17}H_{26}O_3$ requires C, 73·4; H, 9·3%). It is important to notice that the chromic acid oxidation would correct any incompleteness of hydrolysis, since $-CHO \longrightarrow -CO_2H \longrightarrow H$ (CO_2).

B(−)- *and* *B*(+)-1 : 7-*Diketo*-2 : 13-*dimethylperhydrophenanthrenes* [V-B(−)] *and* [V-B(+)].—Formylation and methylation of the hydroxy-ketone [I-B(−)] (150 mg.) was carried out as described for [I-A(+)] above. Acid hydrolysis of the total methylation product was carried out by warming for 15 minutes with 3N-aqueous-alcoholic hydrochloric acid. The subsequent operations again followed the procedure given above. The *diketone* [V-B(−)], after one recrystallisation from ether and two from light petroleum, had m. p. 115—116°, $[\alpha]_D^{25}$ −25° ± 2° (Found: C, 77·5; H, 9·8. $C_{16}H_{24}O_2$ requires C, 77·4; H, 9·7%).

The formylation and methylation of [I-B(+)] (175 mg.) were carried out as already indicated; all extractions with alkali, however, were done at 0° to minimise loss of the formyl group by hydrolysis. After the methylation, acid hydrolysis was effected by keeping with 1·5N-aqueous-alcoholic hydrochloric acid; alkaline extraction (at 0°), hydrolysis, and oxidation then followed as in the A(+)-series. The diketone [V-B(+)] (58·5 mg.) had m. p. 115·5—116·5° after one crystallisation from light petroleum (b. p. 40—60°); recrystallisation gave colourless rods or blades, m. p. 116·5—117·5°, $[\alpha]_D^{25}$ +25° ± 2° (*c*, 1·3) (Specimen *C* of Dr. Crowfoot's report) (Found: C, 77·2; H, 9·7. Calc. for $C_{16}H_{24}O_2$: C, 77·4; H, 9·7%). There was no depression in melting point on admixture with the specimen of (V) prepared from cholesterol.

NATIONAL INSTITUTE FOR MEDICAL RESEARCH, HAMPSTEAD.
DYSON PERRINS LABORATORY, OXFORD UNIVERSITY. [*Received, January 27th*, 1949.]