Experiments on the Synthesis of Substances Related to the Sterols. Part LIII. Stereospecific Synthesis of a Tricyclic Ketone.*

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The first steps to improve the formal total synthesis of androgenic hormones and cholesterol described earlier involved studies of the *C*-methylation of appropriate naphthalene derivatives and of the hydrogenation of model substances as well as of the compounds actually required for the synthesis. First, for the preparation of 5-methoxy-1-methyl-2-tetralone, it was found advantageous to proceed from 5-acetamido-1-naphthol rather than from 1 : 6-dihydroxynaphthalene as heretofore. Next a procedure was devised which avoided an irksome demethylation.

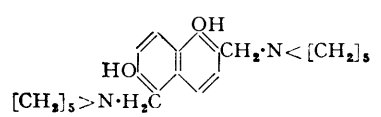
From this point a *cis*-A/B-ring was formerly set up largely as a matter of urgency to enable use to be made of the more accessible relay points.

A device for producing the *trans*-A/B-decalin system has now been successfully adopted and the new synthetic scheme has been taken as far as a tricyclic keto-ester in which only the asymmetric centre added last is of undetermined configuration.

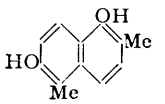
IN an earlier communication it was stated that the formal total syntheses recorded in this series (*J.*, 1946, 676; 1949, 1855; 1953, 361) should be regarded as scaffolding; the first steps in construction, within this framework, of a more seemly edifice are now reported.

The initial stages, before problems of stereoisomerism arose, were capable of improvement in several respects: in particular, it was desirable to improve or to circumvent the mono-*C*-methylation of 5-methoxy-2-tetralone. Many attempts to raise the yield in the process were made and one such is described in the Experimental section. The yield of crude product was about 50% in the best trials but even so the separations involved were tedious and the results not fully reproducible.

Hence we turned to the *C*-methylation of naphthalene derivatives by catalytic reduction of piperidinomethyl compounds. Unfortunately 1 : 6-dihydroxynaphthalene could not be converted into a mono(piperidinomethyl) derivative but always gave the disubstituted substance (I). This base could be converted into a diacetyl derivative by treatment with



(I)



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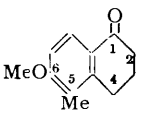

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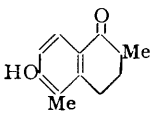


(IV)

acetyl chloride in cold acetone or into a tetra-acetate (replacement of piperidine groups by acetoxyl) by heating with acetic anhydride. It was catalytically reduced with palladised strontium carbonate or Raney nickel to 1 : 6-dihydroxy-2 : 5-dimethylnaphthalene (II). The constitution of this substance was proved by its synthesis from 6-methoxy-5-methyl-1-tetralone (III) (Martin and Robinson, *J.*, 1943, 491) by way of a 2-formyl derivative, *C*-methylation of this, hydrolysis, dehydrogenation, and demethylation.

After extensive study of the nuclear hydrogenation of piperidinomethylnaphthols, the base (I) was hydrogenated under pressure over W-7 Raney nickel in alcohol to a number of products, one of which proved to be 6-hydroxy-2 : 5-dimethyl-1-tetralone (IV). This could be methylated with formation of the 2-methyl derivative of (III), an intermediate in the above-mentioned synthesis of (II).

As we were unable to effect the mono-*C*-methylation of 1 : 6-dihydroxynaphthalene we turned to the use of the more readily available 5-acetamido-2-naphthol (V) as the starting material. Reaction with piperidine and formaldehyde gave the piperidinomethyl derivative (VI), which was reduced smoothly to 5-acetamido-1-methyl-2-naphthol

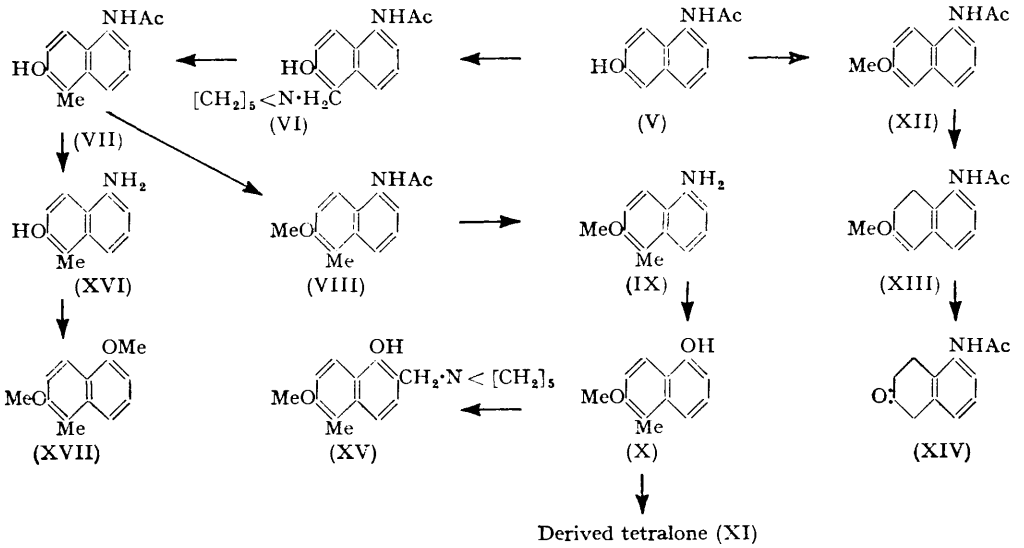
* Part LII, preceding paper.

(VII) by catalytic hydrogenation over palladium–strontium carbonate in the presence of oxalic acid. High temperature and pressure were unnecessary; thus the procedure is more convenient than the high-pressure hydrogenation which was used by Caldwell and Thompson (*J. Amer. Chem. Soc.*, 1939, **61**, 765) for other dialkylaminomethylphenols and by us in earlier experiments.

Methylation of the naphthol (VII) was followed by hydrolysis to the amine (IX). The Bucherer reaction worked well with this amine, and afforded 6-methoxy-5-methyl-1-naphthol (X) in high yield. An alternative preparation of this naphthol, and its reduction by sodium in ethanol–liquid ammonia, followed by hydrolysis to the β-tetralone (XI), were reported in Part XLV (*loc. cit.*, 1946).

Some alternative routes from 5-acetamido-2-naphthol were investigated as possible variants of the preferred scheme indicated above.

Reduction of 1-acetamido-6-methoxynaphthalene (XII) by sodium in ethanol–liquid ammonia gave, by way of the enol ether (XIII), 5-acetamido-2-tetralone (XIV), though the yield was poor. Again, the naphthol (X) was treated with formaldehyde and piperidine to give the base (XV), with a view to early introduction of the future C/D angular methyl group. A third approach involved hydrolysis of the methylnaphthol (VII) and exchange of the amino-group in the product (XVI) for hydroxyl; methylation then gave 2 : 5-dimethoxy-1-methylnaphthalene (XVII). The reduction of this substance, in moderate yield, to 6-methoxy-5-methyl-2-tetralone was mentioned in an earlier paper; attempts to improve the yield by using a liquid ammonia medium were not successful.

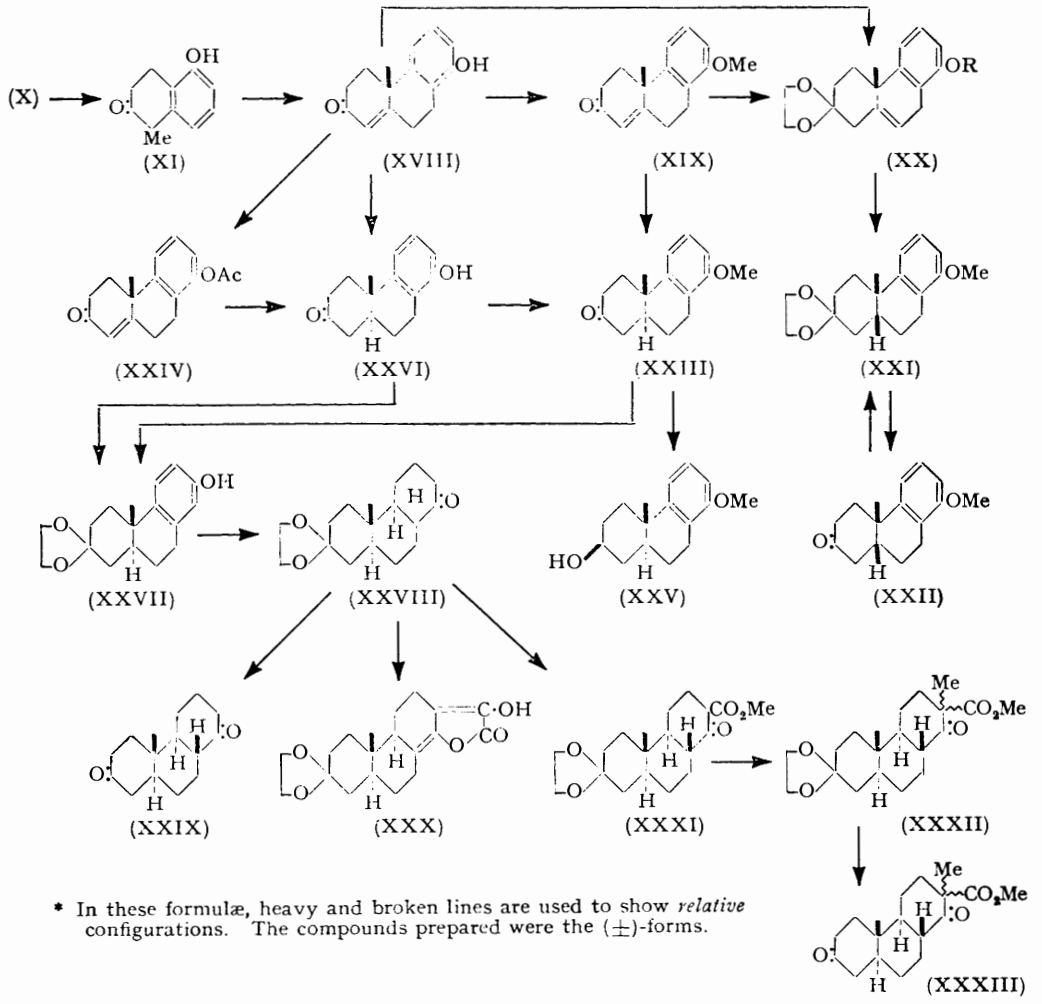


By using three equivalents of potassium ethoxide, condensation of the tetralone (XI) with 4-diethylaminobutan-2-one methiodide was effected without difficulty, to yield the known 5 : 6 : 7 : 9 : 10 : 13-hexahydro-1-hydroxy-13-methyl-7-oxophenanthrene (XVIII). Thus the two least favourable stages of the earlier synthesis have been avoided. In the present procedure the yields obtained in the last two stages (~50%) leave room for improvement; all the other stages proceed in excellent yield.

In choosing a procedure for setting up the second asymmetric centre we were concerned to make a *trans*-junction of the alicyclic rings. This has been slown (Renfrow and Cornforth, *J. Amer. Chem. Soc.*, 1953, **75**, 1347) to favour formation of the *anti-trans*-configuration when the aromatic ring is hydrogenated, whereas a *cis*-junction favours the *syn-trans*-configuration. In the earlier synthesis we hydrogenated the double bond in the ketone (XVIII) catalytically, obtaining a *cis*-junction, and were certainly fortunate at the perhydrophenanthrene stage to obtain even a minor proportion of the desired *cis-anti-trans*-isomeride along with a much larger amount of *cis-syn-trans*-material.

The ketone (XVIII) and its methyl ether (XIX) were readily converted into the ethylene ketals (XX). The shift of the double bond is presumed by analogy with many known examples. Catalytic addition of hydrogen to this double bond in the ketal (XX; R = Me) occurred, unfortunately, on the β-side, the product (XXI) being identical with a ketal prepared from the known *cis*-methoxy-ketone (XXII), to which it could be hydrolysed by acid. Evidently the α-oxygen atom, in the ketal group, is able to force β-addition of hydrogen, as it does in *epi*cholesterol (Lewis and Shoppee, *Chem. and Ind.*, 1953, 897).

Reduction by dissolving metals usually produces the thermodynamically stable isomeride when more than one may theoretically be formed (for bibliography see Arth *et al.*, *J. Amer. Chem. Soc.*, 1954, **76**, 1717). When the methoxy-ketone (XIX) was reduced with lithium in liquid ammonia the *trans*-ketone (XXIII) was isolated in 65% yield, a better result than could be obtained (Renfrow and Cornforth, *loc. cit.*) by reduction with sodium and pentyl alcohol followed by re-oxidation. When the methoxy-ketone (XIX) was



* In these formulæ, heavy and broken lines are used to show *relative* configurations. The compounds prepared were the (±)-forms.

reduced with lithium and ethanol in ammonia, or when its hydro-derivative (XXIII) was reduced with lithium aluminium hydride, the β-alcohol (XXV) was formed; the acetate of this alcohol had already been reported (Renfrow and Cornforth, *loc. cit.*). Reduction of

the acetate (XXIV) of the phenolic ketone (XVIII) by lithium in liquid ammonia gave the *trans*-ketone (XXVI) in similar yield; the phenolic ketone (XVIII) itself gave a lower yield.

The keto-group was then protected before reduction of the aromatic ring. Treatment of the ketone (XXVI) with ethylene glycol gave the ketal (XXVII), which could also be prepared quite conveniently from the methoxy-ketone (XXIII) by reaction with ethylene glycol and demethylation with potassium hydroxide in methanol at 190°.

Hydrogenation of the phenolic ketal (XXVII) over W2 Raney nickel in alkaline ethanol, followed by oxidation of the total product with chromium trioxide–pyridine (Sarett *et al.*, *J. Amer. Chem. Soc.*, 1953, **75**, 422) afforded a good yield of the ketonic monoketal (XXVIII). The *trans-anti-trans*-configuration of this substance was checked by hydrolysis to the diketone (XXIX) which was proved by m. p., mixed m. p., and infrared spectrum to be identical with the ketone previously prepared (Renfrow and Cornforth, *loc. cit.*) and correlated with the Köster–Logemann ketone derived from cholesterol. Thus four of the six asymmetric centres determining configuration of the steroid ring system had been set up in correct relation by a stereospecific procedure.

Reaction of the diketone monoketal (XXVIII) with sodium hydride and methyl carbonate led smoothly to the keto-ester (XXXI). An attempt to make this keto-ester *via* the glyoxylate gave a somewhat surprising result: reaction of the ketal ketone (XXVIII) with methyl oxalate and sodium methoxide in benzene afforded, as the sole crystalline product, the enol lactone (XXX), characterised as its methyl ether.

Methylation of the keto-ester (XXXI) gave in about 70% yield, a single stereoisomeride (XXXII); no epimer has yet been isolated. The diketo-ester (XXXIII) was obtained on hydrolysis. Experiments are now in progress to determine configuration at the new asymmetric centre.

The preferred route of syntheses is by the stages; V, VI, VII, VIII, IX, X, XI, XVIII, XXVI, XXVII, XXVIII, XXXI, XXXII, XXXIII.

Experimental

5-Methoxy-1-methyl-2-tetralone.—5-Methoxy-2-tetralone was prepared by the procedure described by Cornforth and Robinson (*J.*, 1942, 689; 1946, 676). 1 : 6-Dihydroxynaphthalene (200 g.) afforded 125 g. (57%) of distilled ketone, m. p. 33—35° (lit., m. p. 36—37°). The *semicarbazone*, prepared in the usual manner, crystallised from aqueous ethanol in needles, m. p. 165° (Found: C, 57·6; H, 7·0. $C_{12}H_{15}O_2N_3,H_2O$ requires C, 57·3; H, 6·8%).

A solution of 5-methoxy-2-tetralone (3·5 g.) in light petroleum (75 c.c.; b. p. 100—120°) was stirred under nitrogen with finely divided potassium (0·8 g.) for 4 hr. at room temperature and for ½ hr. at 65—70°. Methyl iodide (5·6 g.) was added and the temperature maintained for ½ hr. After cooling, the mixture was acidified and evaporated under reduced pressure; the mixture of ketones was separated by the usual procedure with sodium hydrogen sulphite (Cornforth and Robinson, *loc. cit.*), giving recovered 5-methoxytetralone (0·4 g.), 5-methoxy-1-methyl-2-tetralone (1·8 g.), and a residue containing 5-methoxy-1 : 1-dimethyl-2-tetralone (0·1 g.).

The crude monomethylated ketone from a number of runs was shaken in ether with saturated sodium hydrogen sulphite solution and distilled. The product, b. p. 127—129°/0·8 mm., solidified and formed colourless, elongated prisms, m. p. 46—47°.

This material (6·9 g.) gave 6·5 g. of 5 : 6 : 7 : 9 : 10 : 13-hexahydro-1-methoxy-13-methyl-7-oxophenanthrene which, on crystallisation from ether (yield, 4·3 g.), had m. p. 112—114°. Cornforth and Robinson (*loc. cit.*) give m. p. 115—116° for the pure substance.

1 : 6-Dihydroxy-2 : 5-bispiperidinomethylnaphthalene (I).—Technical dihydroxynaphthalene was recrystallised from benzene by a Soxhlet extraction procedure (recovery 92%) and distilled at 260—270°(bath)/0·1 mm. A mixture of aqueous formaldehyde (7·5 c.c. of 40%) in ethanol (15 c.c.) was added with gentle agitation under nitrogen to a solution of 1 : 6-dihydroxynaphthalene (8·0 g.) and piperidine (10·2 g.) in ethanol (40 c.c.), kept at 15—20°. Deposition of crystals began after ½ hr. at room temperature. The product (14·6 g.), washed with methanol and dried at room temperature, consisted of colourless plates, m. p. 133°, unchanged by recrystallisation from ethanol or *cyclo*hexane (Found: C, 74·8; H, 8·3; N, 8·1. $C_{22}H_{30}O_2N_2$ requires C, 74·5;

H, 8·5; N, 7·9%). The *base* is photosensitive, and slowly decomposed by heat, acid, or alkali into piperidine and a yellow to brown polymer which does not contain nitrogen. It was unaffected by diazomethane in ether–methanol. Its OO-*diacetyl derivative* was obtained when acetyl chloride (2 c.c.) was added to a solution of the base (1 g.) in acetone (15 c.c.). The precipitate was washed with ether, covered with ether, and treated with a saturated solution of sodium hydrogen carbonate. The diacetate, obtained from the ethereal layer, crystallised from light petroleum (b. p. 80—100°) as colourless prisms, m. p. 118—119° (Found: C, 71·5; H, 7·5. $C_{26}H_{34}O_4N_2$ requires C, 71·2; H, 7·8%).

A mixture of the base (I) (1 g.) and acetic anhydride (8 c.c.) was heated on the steam-bath for 3 hr. Enough water was added to give a clear solution on warming; this was treated with charcoal, filtered, and chilled. 1 : 6-*Diacetoxy*-2 : 5-*bisacetoxymethylnaphthalene* (0·6 g.) was obtained as prisms, m. p. 82—83°, after crystallisation from aqueous methanol (1 : 1) (Found: C, 61·6; H, 5·3. $C_{20}H_{20}O_8$ requires C, 61·8; H, 5·2%).

1 : 6-*Dihydroxy*-2 : 5-*dimethylnaphthalene* (II).—(*a*) Attempted hydrogenation of the base (I) using a copper–chromium oxide catalyst at 165° gave only piperidine and polymeric decomposition products.

(*b*) A mixture of the base (3 g.), 2% palladised strontium carbonate (1·5 g.), and ethanol (90 c.c.) was shaken with hydrogen at atmospheric pressure. Absorption of the gas was slow and stopped after slightly more than two equivalents had been taken up in 15 hr. Addition of fresh catalyst after 5 and 10 hr. failed to accelerate the process. The residue after removal of catalyst and solvent was taken up in ether and washed with dilute hydrochloric acid, causing the separation of much tar. Evaporation of the dried ethereal solution left a reddish, semi-crystalline mass from which no crystalline product could be isolated. It was accordingly methylated by means of methyl sulphate and aqueous sodium hydroxide. The crude product (0·4 g.) had m. p. 81—84°. Two crystallisations from methanol gave 1 : 6-*dimethoxy*-2 : 5-*dimethylnaphthalene* as cream-coloured plates, m. p. 88° (Found: 78·0; H, 7·6. $C_{14}H_{16}O_2$ requires C, 77·7; H, 7·5%).

(*c*) Similarly, when the base (2 g.) in ethanol (60 c.c.) was shaken with fresh W-7 Raney nickel and hydrogen at 45 lb./sq. in. absorption stopped after 22 hr. The product was isolated as above, and again methylated directly to give the dimethyl ether (0·3 g.).

(*d*) The base (3·5 g.) with oxalic acid (1·8 g.) in aqueous methanol (70 c.c. of 50%) was hydrogenated over palladised strontium carbonate (3 g.) at the ordinary temperature and pressure. Absorption of hydrogen stopped after slightly more than half of the theoretical amount had been taken up; addition of more catalyst led to no further absorption. The filtrate and washings from the catalyst were concentrated at 30—40° under reduced pressure, and diluted with water; the microcrystalline precipitate (0·7 g.) was twice crystallised from 35% aqueous methanol, to give 1 : 6-*dihydroxy*-2 : 5-*dimethylnaphthalene* as cream-coloured prisms, m. p. 127—129° (Found: C, 76·2; H, 6·2. $C_{12}H_{12}O_2$ requires C, 76·6; H, 6·4%). Some unreduced base (0·5 g.) was recovered from the filtrate by addition of aqueous ammonia. The dihydric phenol gave an orange colour with diazobenzenesulphonic acid, changed to deep purple by addition of alkali. It developed a light colour in very dilute solution with 2 : 6-dichloroquinone *N*-chloroimide. The ferric reaction was negative. Methylation gave the dimethyl ether, m. p. 87—88°.

2-*Formyl*-6-*methoxy*-2 : 5-*dimethyl*-1-*tetralone*.—A solution of 2-hydroxymethylene-6-methoxy-5-methyl-1-tetralone (E. B. Smith, D.Phil. Thesis, Oxford, 1949) (3·7 g.) and methyl iodide (4·5 g.) in acetone (25 c.c.) was heated on the steam-bath with freshly ignited, powdered potassium carbonate (2·5 g.); more methyl iodide (2 g.) and acetone (10 c.c.) were added after 15 hr. After 21 hr. the ferric reaction was negative. Dry ether (25 c.c.) was added to the cooled solution, which was filtered and evaporated, leaving a solid residue. (On addition of 2 drops of alcoholic ferric chloride a methanolic solution of this material slowly developed a green colour, indicating the presence of a small proportion of the *O*-methyl derivative.) Two crystallisations from light petroleum (b. p. 60—80°) gave colourless plates of the *keto-aldehyde*, m. p. 52—54° (Found: C, 72·6; H, 7·1. $C_{14}H_{16}O_3$ requires C, 72·4; H, 6·9%).

6-*Methoxy*-2 : 5-*dimethyl*-1-*tetralone*.—The entire crude formylmethoxydimethyltetralone, obtained as last described, was kept for ½ hr. with a solution of hydrochloric acid (3 c.c.) in 50% aqueous methanol (17 c.c.). The mixture was basified with 5% potassium hydroxide solution (100 c.c.) and extracted with ether. Acidification of the aqueous layer gave recovered hydroxymethylenemethoxymethyltetralone (0·4 g.), presumably formed by hydrolysis of its *O*-methyl derivative. The residue left after evaporation of the ethereal layer was heated for 10 min. with a solution of potassium hydroxide (3 g.) in methanol (30 c.c.). Addition of dilute

hydrochloric acid to the cooled solution precipitated the methylated tetralone (2·3 g.). Distillation of the crude ketone, b. p. 175—180° (air-bath)/0·1 mm., and crystallisation from 80% aqueous methanol gave colourless plates or needles, m. p. 114—115°. Martin and Robinson (*loc. cit.*, p. 494, line 51) give m. p. 113°. The dark red 2 : 4-dinitrophenylhydrazone had m. p. 226—229° (lit., 229°).

6-*Methoxy*-2 : 5-*dimethyl*-1-*naphthol*.—The tetralone (2 g.) was heated with sulphur (0·25 g., 75% of the theoretical amount) at 220—225° for 1·5 hr. A boiling benzene extract (charcoal) of the product was filtered, and extracted with three portions of 5% sodium hydroxide solution. Acidification of the combined alkaline extracts precipitated the *naphthol*. Two crystallisations from light petroleum (b. p. 60—80°) gave clusters of yellowish prisms, m. p. 79—80° (Found : C, 77·0; H, 6·9. $C_{13}H_{14}O_2$ requires C, 77·2; H, 7·0%).

1 : 6-*Dimethoxy*-2 : 5-*dimethylnaphthalene*.—The above naphthol was recovered unchanged after being kept overnight with an excess of ethereal diazomethane. The naphthol (0·4 g.) was methylated with methyl sulphate (1 c.c.) and 10% sodium hydroxide (5 c.c.) in the usual way. The product (0·4 g.) solidified on cooling, and after two crystallisations from 90% aqueous methanol had m. p. 87—88°, alone or mixed with a specimen from the successive hydrogenation and methylation of the base (I).

Hydrogenation of 2-*Methoxy*-1-*naphthaldehyde*.—The aldehyde was prepared from 2-methoxynaphthalene, *N*-methylformanilide, and phosphoryl chloride (cf. Wood and Bost, *Org. Synth.*, 1940, **20**, 11). The crude product was crystallised from ethanol (charcoal) and recrystallised from aqueous ethanol, to give colourless needles or plates, both forms melting at 84—85° and being interconvertible by seeding. The needles change into plates on prolonged contact with the saturated solution. From the mother-liquors, more aldehyde was obtained by evaporation and steam-distillation (total yield, 77%).

The aldehyde (20 g.), ethanol (60 c.c.), acetic acid (1 c.c.), and Raney nickel (2 g.) were heated and stirred with hydrogen at 100 atm. (cold). Four equiv. of hydrogen were taken up in 3½ hr. at 110°. The residue after removal of catalyst and solvent was mixed with twice its volume of methanol, and crystallised in the cold overnight. More crystals were obtained by cooling the mother-liquors to −60°. This product (8·8 g., 47%) was identified as 5 : 6 : 7 : 8-tetrahydro-2-methoxy-1-methylnaphthalene by its m. p. 50—51°, alone or mixed with an authentic specimen, and by oxidation to the tetralone, m. p. 112—113°.

The residue obtained by evaporation of the mother-liquors was steam-distilled and the volatile oil (5 g., 27%) had b. p. 85—86°/0·2 mm., n_D^{20} 1·5408. It was probably 1 : 2 : 3 : 4-*tetrahydro*-2-*methoxy*-1-*methylnaphthalene* (Found : C, 81·9; H, 8·9. $C_{12}H_{16}O$ requires C, 81·8; H, 9·2%.

The non-volatile residue from the steam-distillation solidified, and crystallised from light petroleum (b. p. 40—60°) or from water in colourless needles, or squat rhomboids, both of m. p. 67—68° and interconvertible by seeding. The needles changed into rhomboids in contact with the saturated solution. The product (2·2 g., 11%) reacted with acetyl chloride and dimethylaniline to give an oil which gave a positive hydroxamic acid test, and was therefore considered to be 5 : 6 : 7 : 8-*tetrahydro*-1-*hydroxymethyl*-2-*methoxynaphthalene* (Found : C, 74·9; H, 8·6. $C_{12}H_{16}O_2$ requires C, 75·0; H, 8·4%). Confirmation of the structure of this substance was obtained by synthesis.

5 : 6 : 7 : 8-*Tetrahydro*-2-*methoxy*-1-*naphthaldehyde*.—5 : 6 : 7 : 8-Tetrahydro-2-naphthol (3·5 g.; m. p. 60—61°) was converted into 5 : 6 : 7 : 8-tetrahydro-2-hydroxy-1-naphthaldehyde by the Reimer–Tiemann reaction following the procedure described by Arnold, Zaugg, and Sprung (*J. Amer. Chem. Soc.*, 1941, **63**, 1314). The product (0·9 g.), colourless plates from 35% aqueous ethanol, had m. p. 83—84° (lit., 86°).

The hydroxy-aldehyde was methylated with methyl sulphate and sodium hydroxide solution, and the *methoxy-aldehyde* crystallised from methanol as long, thin, colourless prisms, m. p. 63—64° (Found : C, 75·1; H, 7·8. $C_{12}H_{14}O_2$ requires C, 75·7; H, 7·4%). The substance is photosensitive.

5 : 6 : 7 : 8-*Tetrahydro*-1-*hydroxymethyl*-2-*methoxynaphthalene*.—4M-Ethereal lithium aluminium hydride (1 c.c.) was added to a solution of the above methoxy-aldehyde (25 mg.) in ether (10 c.c.). Excess of the hydride was decomposed by moist ether and dilute hydrochloric acid. The ethereal layer was washed with water, dried ($MgSO_4$), and evaporated, leaving the alcohol as a crystalline residue. After recrystallisation from water, this had m. p. 67—68°, alone or mixed with a specimen from the hydrogenation of 2-methoxy-1-naphthaldehyde.

Hydrogenation of Mannich Bases from β-*Naphthol*.—(*a*) 1-Piperidinomethyl-2-naphthol (12 g.; m. p. 96°) in ethanol (60 c.c.) was hydrogenated over copper–chromium oxide catalyst

(1·5 g.) at 160°/90 atm. (cold). Absorption of hydrogen was slow after 3 hr., and was then stopped. Removal of catalyst and solvent left a pale yellow oil. This was dissolved in benzene and extracted successively with dilute hydrochloric acid, water, and three portions of 10% sodium hydroxide solution. No starting material was found in the acid extract. Acidification of the alkaline extracts gave crude 1-methyl-2-naphthol (2·6 g.); crystallisation from water gave small felted needles, m. p. and mixed m. p. 110—111°.

The neutral material left by evaporation of the benzene was distilled, giving a colourless oil (4·3 g., b. p. 101—102°/0·1 mm., n_D^{20} 1·5587) which is probably 1 : 2 : 3 : 4-tetrahydro-1-methyl-2-naphthol. McKusick (*J. Amer. Chem. Soc.*, 1948, **70**, 2196) gives b. p. 105—107°/0·2 mm., n_D^{25} 1·5570.

(*b*) The above base (3 g.) in ethanol (50 c.c.) was hydrogenated over palladised strontium carbonate at the ordinary temperature and pressure, one equiv. of hydrogen being taken up in 1½ hr. 1-Methyl-2-naphthol (1·55 g., 77%) was isolated as described above.

(*c*) The base (4 g.) in ethanol (60 c.c.) was hydrogenated over fresh W-7 Raney nickel in the Burgess–Parr apparatus. No hydrogenation occurred at a pressure of less than 35 lb./sq. in., but when that pressure was maintained the hydrogenation was complete in 3 hr., giving 1-methyl-2-naphthol (1·8 g., 67%) isolated as before. The need for a certain minimum hydrogen pressure in the use of W-7 Raney nickel was also observed with other phenolic bases, as well as in the reduction of benzyl alcohol and acetophenone to hydrocarbons, but not in the hydrogenation of *cyclo*hexene or cinnamic acid.

(*d*) 1-Dimethylaminomethyl-2-naphthol (40·2 g.; m. p. 74°) in ethanol (80 c.c.) was hydrogenated over W-7 Raney nickel at 50—60°/100 atm. (cold). Absorption of hydrogen was stopped after the drop in pressure corresponded to approximately 1 equiv. (1 hr.). Isolation by the usual procedure gave 1-methyl-2-naphthol (23·1 g., 73%) and some neutral material (6 g., not investigated).

(*e*) The same base (20 g.) in ethanol (75 c.c.) was hydrogenated at 80—100°/100 atm. (cold) with an aged specimen of W-7 Raney nickel. The pressure remained constant after the absorption of about 3 equiv. (6 hr.). Isolation as described above gave only a trace of phenolic material together with an apparently neutral oil (13 g., b. p. 100—102°/0·1 mm., n_D^{20} 1·5605). The distillate deposited some long needles in the cold, but it was not possible to remove adhering oil without melting the crystals; some of the oil removed had n_D^{20} 1·5595. When the hydrogenation was repeated on five times the scale, the product was worked up in the manner described for the isolation of 1 : 2 : 3 : 4-tetrahydro-2-naphthol (Dauben, McKusick, and Muller, *J. Amer. Chem. Soc.*, 1948, **70**, 4170). A benzene solution of the product was washed with 10% sodium hydroxide solution (3 × 30 c.c.) (the alkaline extracts yield only 2 g. of phenolic product), evaporated, and distilled. The product, b. p. 102°/0·1 mm., n_D^{20} 1·5583 (55 g., 66%), was probably 1 : 2 : 3 : 4-tetrahydro-1-methyl-2-naphthol (Found: C, 81·4; H, 9·0. Calc. for $C_{11}H_{14}O$: C, 80·8; H, 8·7%). The residue from the distillation was dissolved in warm 20% sodium hydroxide solution, clarified with charcoal, and acidified, giving 5 : 6 : 7 : 8-tetrahydro-1-methyl-2-naphthol (15 g., 18%), which crystallised from light petroleum (b. p. 60—80°) in colourless needles, m. p. and mixed m. p. 113°.

(*f*) Acetic acid (7 g.) was added before a hydrogenation carried out as under (*e*). After the uptake of three equiv. of hydrogen, the phenolic product (6·5 g.) and a neutral oil (7 g.) were isolated. After this process had been repeated with five times the given quantities, the solvent-free reaction product and 20% sodium hydroxide solution were distilled with steam. Acidification of the alkaline solution gave the phenol (39·5 g., 46%). The neutral isomeride (28 g., 35%) was isolated from the distillate.

1-*Acetoxymethyl*-2-*naphthyl Acetate*.—1-Dimethylaminomethyl-2-naphthol (3 g.) and acetic anhydride (21 c.c.) were heated on the steam-bath for 3 hr. Enough water was added to give a clear solution on warming. The colourless *diacetate* (3·5 g.) crystallised on cooling; recrystallisation from 60% aqueous methanol gave square plates, m. p. 76° (Found: C, 69·8; H, 5·6. $C_{15}H_{14}O_4$ requires C, 69·8; H, 5·5%).

Hydrogenation. (*a*) The diacetate (2·8 g.) was hydrogenated in ethanol over 10% palladised charcoal (1 g.) at room temperature and pressure. One equiv. of hydrogen was taken up in 1½ hr. Methanolic 2N-potassium hydroxide (15 c.c.) was added to the filtrate from the catalyst, and the solution was heated on the steam-bath for 15 min. After removal of the solvent, water (15 c.c.) and dilute hydrochloric acid (30 c.c.) were added, giving 1-methyl-2-naphthol (1 g., 66%), m. p. 109—111°.

(*b*) The diacetate (14 g.) in methanol (85 c.c.) was hydrogenated over W-7 Raney nickel (3 g., aged six weeks) at 80—95°/90 atm. (cold), until the pressure drop corresponded to three

equiv. of hydrogen. Alkaline hydrolysis, evaporation, and acidification gave an oil, which was taken up in benzene, and extracted with dilute alkali; acidification gave the phenolic 5-methyl-6-hydroxytetralin (3·6 g., 64%). Evaporation of the benzene left an oil, presumably containing the non-phenolic isomeride (1 g., 18%).

Perhydrogenation Experiments.—(*a*) 1-Piperidinomethyl-2-naphthol (6 g.) in ethanol (50 c.c.) was hydrogenated over fresh W-7 Raney nickel. Absorption of approx. 6 equivs. of hydrogen was complete after 7 hr. at 100—110°/*ca.* 100 atm. (cold). Removal of catalyst and solvent left a colourless oil (3·8 g.). This material, in acetic acid (40 c.c.), was oxidised at 15—20° by the dropwise addition of chromic anhydride (4 g.) in water (4 c.c.) and acetic acid (36 c.c.). The excess of chromic acid was decomposed with sodium hydrogen sulphite solution, and most of the acetic acid removed by concentration under reduced pressure. The ketone, isolated by means of ether, was obtained as a colourless oil (2·7 g.). After this product had been heated with methanolic potassium hydroxide (50 c.c.) for 4 hr., derivatives were prepared. The 2 : 4-dinitrophenylhydrazone had m. p. 169—170° after two crystallisations from ethanol–ethyl acetate. The semicarbazone had m. p. 206—208° (decomp.) after three crystallisations from aqueous ethanol. These melting points were not depressed on admixture with authentic specimens of the derivatives of *trans*-1-methyl-2-decalone.

(*b*) Essentially the same procedure was applied to 2-piperidinomethyl-1-naphthol. After homogenisation with boiling methanolic potassium hydroxide solution as above, the ketone obtained gave a semicarbazone, m. p. 218—220° (decomp.) (from aqueous ethanol), and a 2 : 4-dinitrophenylhydrazone, m. p. 237—238° (from ethanol–benzene), undepressed on admixture with authentic specimens of the respective derivative of *trans*-2-methyl-1-decalone.

(*c*) The base (I) (7 g.) in ethanol (90 c.c.) was hydrogenated over fresh W-7 Raney nickel at 90—105°/110 atm. (cold). Absorption of hydrogen corresponded to about 7 equiv. and stopped after 2 hr. After removal of catalyst and solvent the gummy product was extracted with cold dilute hydrochloric acid and then with ether; evaporation of the ether and evaporative distillation gave two fractions: (i) a viscous colourless liquid, b. p. (bath) 90—100°/0·001 mm. (Found: C, 78·3; H, 8·5%), and (ii) a light yellow, gummy solid which reddened on exposure to air and had b. p. *ca.* 115°/0·001 mm. (Found: C, 76·0; H, 8·1%); the analyses indicated that in spite of the pressure hydrogenation had been incomplete. Both fractions were therefore dissolved in ether and extracted with 10% sodium hydroxide solution. The solid precipitate obtained on acidification of the aqueous layer (2·9 g.) was distilled; the distillate (b. p. *ca.* 120°/0·002 mm., slight decomp.) solidified and had m. p. 175—180°. Crystallisation from 35% aqueous methanol, sublimation at 130°/0·02 mm., and recrystallisation from 35% methanol gave slender yellow prisms, m. p. 180—182° (Found: C, 75·7; H, 7·5. $C_{12}H_{14}O_2$ requires C, 75·7; H, 7·4%). Methylation of the product with methyl sulphate and alkali gave a methyl ether, m. p. 114—115°, which was identified as 6-methoxy-2 : 5-dimethyl-1-tetralone by direct comparison and by preparation of the 2 : 4-dinitrophenylhydrazone, m. p. 227—229°. The phenolic ketone was therefore 6-*hydroxy*-2 : 5-*dimethyl*-1-*tetralone* (IV).

The 2 : 4-*dinitrophenylhydrazone*, needles from ethanol–ethyl acetate, had m. p. 260—263° (decomp.) (Found: C, 58·0; H, 5·1. $C_{18}H_{18}O_5N_4$ requires C, 58·4; H, 4·9%). The action of boiling acetic anhydride and pyridine gave the *acetoxy-ketone*, colourless prisms (from 80% aqueous methanol), m. p. 78—79° (Found: C, 72·1; H, 7·0. $C_{14}H_{16}O_3$ requires C, 72·4; H, 6·9%). Benzylation was accomplished by heating the phenolic ketone, benzyl chloride, and potassium carbonate in acetone until the diazo-coupling reaction was negative; after absorption on alumina and elution with benzene–light petroleum (1 : 1), the *benzyloxy-ketone* crystallised from light petroleum (b. p. 60—80°) as colourless prisms, m. p. 102—103° (Found: C, 81·4; H, 7·4. $C_{19}H_{20}O_2$ requires C, 81·4; H, 7·2%).

Evaporation of the ethereal solution from which the phenolic ketone had been extracted left a small amount of residue, the amount of which varied with the temperature at which the hydrogenation had been conducted. No residue was obtained from reactions at 100° or below. In one run the temperature was allowed to reach 160°; the residue then obtained (0·6 g.) was a mixture of oil and needles. Some of the needles were separated mechanically, washed with light petroleum (b. p. 40—60°), and recrystallised from this solvent. The product, m. p. 95—96°, was probably 5 : 6 : 7 : 8-*tetrahydro*-1 : 6-*dimethyl*-2-*naphthol* (Found: C, 82·3; H, 9·5. $C_{12}H_{16}O$ requires C, 81·8; H, 9·1%). The remaining product was stirred with four small portions of cold methanol, which dissolved the needles and some of the oil. The gummy residue solidified on being rubbed with cold methanol, and crystallisation from this solvent afforded small, squat prisms. This material, m. p. 105—107°, was probably 1 : 2 : 3 : 4-*tetrahydro*-1 : 6-*dihydroxy*-2 : 5-*dimethylnaphthalene* (Found: C, 74·4; H, 8·7. $C_{12}H_{16}O_2$ requires C, 75·0; H, 8·4%).

(*d*) 1 : 6-Dihydroxynaphthalene (8 g.) in ethyl acetate (100 c.c.) was hydrogenated over palladised strontium carbonate (5 g.) at 175°/92 atm. (cold) for 8 hr. Removal of catalyst and solvent left a solid residue (6·2 g.). Two crystallisations from 20% aqueous methanol gave light tan prisms (3·9 g.), m. p. 149—152°, which is the m. p. of 6-hydroxy-1-tetralone. Methylation in the usual way gave 6-methoxy-1-tetralone, m. p. and mixed m. p. 75—77°.

5-*Acetamido*-1-*piperidinomethyl*-2-*naphthol* (VI).—Commercial 5-acetamido-2-naphthol was purified by extraction in a Soxhlet apparatus with water and recrystallisation from aqueous ethanol (charcoal); then it was obtained as colourless needles, m. p. 217°.

Formaldehyde (60 c.c. of 40% solution) was added to a mixture of piperidine (90 c.c.) and 5-acetamido-2-naphthol (150 g.) in ethanol (1500 c.c.). Crystallisation began after ½ hr. and was complete after 12 hr. at room temperature. The crude product (185 g., 83%) was collected, washed with a little ethanol, and dried. Purification (which was necessary for the next stage) was effected by crystallisation from pentyl alcohol (charcoal); the base (152 g.) separated as colourless plates, m. p. 198° (Found: C, 72·8; H, 7·3; N, 8·9. $C_{18}H_{22}O_2N_2$ requires C, 72·4; H, 7·4; N, 9·4%).

Substitution of dimethylamine for piperidine in this procedure gave the *dimethylamino-analogue* in 37% yield, colourless prisms (from ethanol), m. p. 193—194° (decomp.) (Found: C, 70·3; H, 7·5; N, 10·2. $C_{15}H_{18}O_2N_2$ requires C, 69·8; H, 7·0; N, 10·8%).

A mixture of the piperidino-base (1 g.) and acetic anhydride (8 c.c.) was heated on the steam-bath for 3 hr. Enough water was added to give a clear solution on warming. On cooling, the product separated as an oil, which later solidified. Crystallisation from 50% aqueous ethanol gave colourless clustered prisms, m. p. 170—171°, consisting of 5-*acetamido*-1-*acetoxymethyl*-2-*naphthyl acetate* (Found: C, 64·6; H, 5·8; N, 4·6. $C_{17}H_{17}O_5N$ requires C, 63·8; H, 5·4; N, 4·4%).

5-*Acetamido*-1-*methyl*-2-*naphthol* (VII).—5-Acetamido-1-piperidinomethyl-2-naphthol (30 g.) in aqueous methanol (600 c.c.; 1 : 1) containing oxalic acid (9·0 g.) was hydrogenated over 1% palladised strontium carbonate (20 g.) at *ca.* 40°/1 atm. Uptake of hydrogen was complete after 3 hr. The catalyst was removed and extracted with methanol (*ca.* 250 c.c.). Methanol was removed from the combined filtrates under reduced pressure, and 2N-hydrochloric acid (50 c.c.) added to the cooled solution. The precipitated solid was collected, washed with water, and dried, giving 5-acetamido-1-methyl-2-naphthol (19·4 g., 90%). It crystallised from aqueous ethanol as colourless needles, m. p. 195—196° (Found: C, 72·1; H, 5·6; N, 6·7. $C_{15}H_{13}O_2N$ requires C, 72·5; H, 6·1; N, 6·9%).

5-*Amino*-1-*methyl*-2-*naphthol* (XVI).—5-Acetamido-1-methyl-2-naphthol (23·7 g.), concentrated hydrochloric acid (100 c.c.), water (20 c.c.), and ethanol (50 c.c.) were refluxed for 3 hr. The solution was cooled and the hydrochloride decomposed with ammonia, to give 5-*amino*-1-*methyl*-2-*naphthol* (17·5 g., 92%), which separated from aqueous ethanol (charcoal) in pale yellow needles, m. p. 186—187° (Found: C, 76·2; H, 6·5; N, 7·8. $C_{11}H_{11}ON$ requires C, 76·3; H, 6·4; N, 8·1%). The *dibenzoyl derivative* crystallised from ethanol in colourless needles, m. p. 231—232° (Found: C, 78·5; H, 5·0. $C_{25}H_{19}O_3N$ requires C, 78·7; H, 5·0%).

1 : 6-*Dihydroxynaphthalene*.—5-Acetamido-2-naphthol (21 g.) was refluxed with concentrated hydrochloric acid (90 c.c.), water (30 c.c.), and ethanol (75 c.c.) for 3 hr. After cooling, an excess of ammonia was added. The product (145 g., 87%), crystallised from aqueous ethanol (charcoal), gave 5-amino-2-naphthol as colourless needles, m. p. 189—190° (Brown, Hebden, and Withrow, *J. Amer. Chem. Soc.*, 1929, **51**, 1767, give m. p. 190°).

5-Amino-2-naphthol (10 g., 1 mol.) was stirred with freshly prepared 40% sodium hydrogen sulphite solution (130 c.c.) at about 95° for 15 hr., by which time a homogeneous solution had been obtained. Sodium hydroxide (50 g.) in water (40 c.c.) was added and the mixture boiled until no more ammonia was evolved (2 hr.). An excess of concentrated hydrochloric acid was cautiously added to the cooled solution, and the whole boiled until no more sulphur dioxide was evolved (1 hr.). 1 : 6-Dihydroxynaphthalene, which separated on cooling, was collected and dried (7·1 g., 70%). Recrystallisation from benzene gave colourless prisms, m. p. 137—138° (Fischer and Bauer, *J. prakt. Chem.*, 1916, **94**, 1, gave m. p. 137—138°). On the addition of ferric chloride to an aqueous solution a pale blue colour was developed, followed by a brownish-red precipitate.

2 : 5-*Dihydroxy*-1-*methylnaphthalene*.—A mixture of 5-amino-1-methyl-2-naphthol (34·7 g.) and freshly prepared 40% sodium hydrogen sulphite solution (500 c.c.) was heated at 95° under reflux with vigorous stirring, for 16 hr. Aqueous sodium hydroxide (150 c.c. of 50%) was then added and the whole heated until the evolution of ammonia had ceased (3 hr.). After cooling, an excess of concentrated hydrochloric acid was cautiously added, and the mixture then boiled

for a further 2 hr. On cooling, 2 : 5-*dihydroxy*-1-*methylnaphthalene* (30 g., 85%) separated; it crystallised from water (charcoal) as colourless needles, m. p. 163—164° (Found : C, 75·5; H, 5·7. $C_{11}H_{10}O_2$ requires C, 75·8; H, 5·7%).

A white precipitate was obtained on the addition of ferric chloride to a solution of this substance. A solution of 2 : 5-dihydroxy-1-methylnaphthalene (28 g.) in 2N-sodium hydroxide (250 c.c.) was shaken with methyl sulphate (25 c.c.) with intermittent gentle heating on the steam-bath. When the initial reaction had subsided, more 2N-sodium hydroxide (100 c.c.) and methyl sulphate (10 c.c.) were added. After further shaking, the mixture was kept for 2 hr., and the excess of methyl sulphate decomposed by heating on the steam-bath for ½ hr. The cooled solution was acidified, and extracted twice with chloroform. The combined extracts were washed with aqueous sodium hydroxide and with water, and then dried, and the solvent was removed, to yield 2 : 5-dimethoxy-1-methylnaphthalene (XVII) (22 g., 68%). After two crystallisations from ethanol it formed colourless, hexagonal plates, m. p. 84—85° (Cornforth and Robinson, *loc. cit.*, gave m. p. 85°). Purification was best effected by passing a solution of the crude product (11·7 g.) in light petroleum (b. p. 60—80°)–benzene (200 c.c.; 2 : 1) through an alumina column; colourless 2 : 5-dimethoxy-1-methylnaphthalene (11·0 g.), m. p. 84—85°, was obtained.

5-*Acetamido*-2-*tetralone* (XIV).—5-Acetamido-2-naphthol was methylated in the usual manner, with 2N-sodium hydroxide and methyl sulphate. Recrystallisation of the resulting methyl ether from ethanol gave 5-acetamido-2-methoxynaphthalene as colourless needles, m. p. 143—144° (Sachs, *Ber.*, 1906, **39**, 3016, gives m. p. 140°). Sodium (5 g.) was rapidly added to a mixture of 5-acetamido-2-methoxynaphthalene (9·6 g.), methanol (30 c.c.), ether (30 c.c.), and liquid ammonia (200 c.c.). Solvents were removed at about 50° and water (200 c.c.) was added, the product being precipitated. Re-acetylation was effected by dissolution of this material in pyridine (10 c.c.) and addition of acetic anhydride (3 c.c.). The whole was kept overnight at room temperature and poured into water, to give 5-*acetamido*-3 : 4-*dihydro*-2-*methoxynaphthalene* (XIII). A portion was crystallised twice from ethanol as white needles, m. p. 190—192° (Found : C, 72·1; H, 6·9. $C_{13}H_{15}O_2N$ requires C, 71·9; H, 6·9%). This enol ether was hydrolysed by warming for 10 min. with 2N-sulphuric acid; the product separated on cooling. Recrystallisation from water (charcoal) gave 5-acetamido-2-tetralone (2·1 g., 25%) as colourless plates, m. p. 179—180° (Found : C, 70·7; H, 6·4. $C_{12}H_{13}O_2N$ requires C, 70·9; H, 6·4%). The *semicarbazone* crystallised from ethanol in colourless needles, m. p. 233° (Found : C, 60·2; H, 6·4. $C_{13}H_{16}O_2N_4$ requires C, 60·0; H, 6·2%).

5-*Acetamido*-2-*methoxy*-1-*methylnaphthalene* (VIII).—Crude 5-acetamido-1-methyl-2-naphthol (102 g.) in aqueous 2N-sodium hydroxide (1·1 equiv.) was shaken with methyl sulphate (1·05 equiv.) for ½ hr. More sodium hydroxide (2N) and methyl sulphate were then added and shaking continued for a further ½ hr. After a further 2 hr., the excess of methyl sulphate was destroyed by gentle heating on the steam-bath. The crude product (98 g.) was recrystallised from ethanol; the *methyl ether* (73 g., 68%) separated as large, colourless laths, m. p. 210—211° (Found : C, 73·2; H, 6·7; N, 5·7. $C_{14}H_{15}O_2N$ requires C, 73·5; H, 6·6; N, 6·1%).

6-*Methoxy*-5-*methyl*-1-*naphthylamine* (IX).—5-Acetamido-2-methoxy-1-methylnaphthalene (64 g.) was refluxed for 3 hr. with concentrated hydrochloric acid (400 c.c.), water (100 c.c.), and ethanol (100 c.c.). The solution was then cooled and made alkaline with ammonia. After ½ hr., the precipitated amine was collected, washed with water, and dried (52 g., 99%). This material was suitable for use in the Bucherer reaction; it had m. p. 124—127°. A portion, recrystallised from benzene (charcoal), gave the *amine* (XI) as colourless needles, m. p. 127—128° (Found : C, 77·1, 77·3; H, 7·1, 7·2; N, 7·1. $C_{12}H_{13}ON$ requires C, 77·0; H, 6·9; N, 7·5%).

6-*Methoxy*-5-*methyl*-1-*naphthol* (X).—A suspension of the foregoing amine (40 g.) in aqueous 40% sodium hydrogen sulphite (1 l.) was stirred vigorously and refluxed for 26 hr. Alternatively the mixture was heated at 100—120° in a rotating autoclave. Aqueous 60% sodium hydroxide (350 c.c.) was then added slowly to the boiling solution with vigorous stirring and the mixture heated until the evolution of ammonia had ceased (*ca.* 4 hr.). After cooling and careful addition of concentrated hydrochloric acid to expel sulphur dioxide the product was allowed to separate overnight. The crude methoxymethylnaphthol (m. p. 137—140°; 36·9 g., 92%) recrystallised from benzene (charcoal) as colourless needles (27·7 g., 70%), m. p. 143—144° (Part XLV, *loc. cit.*, gives m. p. 142—143°) (Found : C, 76·7; H, 6·4. Calc. for $C_{12}H_{12}O_2$: C, 76·6; H, 6·4%).

The *acetate* prepared by use of acetic anhydride and pyridine crystallised from ethanol in plates, m. p. 145—147° (Found : C, 73·2; H, 6·1. $C_{14}H_{14}O_3$ requires C, 73·1; H, 6·1%).

In our earlier work this naphthol was obtained from the amine (*a*) by diazotisation and

heating of the solution, and also (*b*) by heating with N-sulphuric acid in a sealed tube at 180°. These methods gave unsatisfactory results.

5 : 6 : 7 : 8-*Tetrahydro*-5-*methyl*-6-*oxo*-1-*naphthol* (XI) (cf. Part XLV, *loc. cit.*).—6-Methoxy-5-methyl-1-naphthol (62 g.), suspended in liquid ammonia (800 c.c.) and ethanol (64 c.c.), was reduced by gradual addition, during ½ hr., of sodium (24·7 g.). After evaporation the residue was dissolved in water (500 c.c.), and concentrated hydrochloric acid (200 c.c.) was added. After being shaken for 10 min. the mixture was allowed to cool and the solid was collected. Crystallisation from ethanol (*ca.* 40 c.c.) gave the tetralone (32 g.), m. p. 119—124°, raised to 127—129°, on recrystallisation (27·3 g., 47%) (Part XLV, *loc. cit.*, gave m. p. 127—128°). A small further quantity (0·5 g.) was obtained by stirring the mother-liquors for 30 hr. in ethereal solution with sodium hydrogen sulphite solution and decomposing the aqueous layer with sodium carbonate. The *semicarbazone* separated from ethanol in diamond-shaped, solvated needles, m. p. 170—171° (Found: C, 60·2; H, 7·5. $C_{12}H_{15}O_2N_3,C_2H_6O$ requires C, 60·2; H, 7·5%). The *benzoate* crystallised from ethanol in needles, m. p. 140—141° (Found: C, 77·4; H, 5·5. $C_{18}H_{16}O_3$ requires C, 77·1; H, 5·7%).

5 : 6 : 7 : 9 : 10 : 13-*Hexahydro*-1-*hydroxy*-13-*methyl*-7-*oxophenanthrene* (XVIII).—4-Diethylaminobutan-2-one (21·55 g.) and methyl iodide (9·7 c.c.) were combined by the procedure of Part XLVIII (*loc. cit.*, 1949). 5-Hydroxy-1-methyl-2-tetralone (25 g.) in dry ethanol (150 c.c.) was added with ice-cooling to the methiodide under dry nitrogen, followed by a solution of potassium (16·0 g.) in ethanol (150 c.c.) added in one portion. Swirling was continued for about an hour and until all the methiodide had dissolved. After being kept in ice for a further hour the mixture was boiled gently for ½ hr. and then cooled. 2N-Sulphuric acid (250 c.c.) was added, followed by water (500 c.c.). After 2 hr. the solid was collected and recrystallised from ethanol, to give the phenanthrene derivative (16·9 g., 52%), m. p. 210—212° (Part XLV, *loc. cit.*, 1946, m. p. 208—210°). A portion recrystallised from alcohol had m. p. 212—213° (Found: C, 79·1; H, 6·9. Calc. for $C_{15}H_{16}O_2$: C, 78·9; H, 7·0%). The 2 : 4-dinitrophenylhydrazone separated from acetic acid in red, irregular rhombs, m. p. 244° (decomp.) [Part XLV, *loc. cit.*, m. p. 246° (decomp.)]. The phenol on methylation with methyl sulphate and aqueous alkali gave the known methoxy-ketone (XIX), m. p. 118—120° after crystallisation from light petroleum (b. p. 40—60°) (Part XLV, *loc. cit.*, m. p. 119—120°).

7-*Ethylenedioxy*-5 : 6 : 7 : 8 : 10 : 13-*hexahydro*-1-*methoxy*-13-*methylphenanthrene* (XX; R = Me).—A mixture of the methoxy-ketone (XIX) (20 g.), benzene (400 c.c.), and ethylene glycol (30 c.c.) was slowly distilled with stirring for 1 hr. Toluene-*p*-sulphonic acid (300 mg.) was added and distillation was continued for 4 hr., the volume being maintained by addition of benzene. The cooled solution was washed with saturated sodium hydrogen carbonate solution (100 c.c.) and with water, dried, and evaporated. The residue was triturated with light petroleum (b. p. 40—60°) and crystallised twice from methanol. The *methoxy-ketal* (XX; R = Me) was obtained as colourless prisms (15·7 g.), m. p. 110—111° (Found: C, 75·7; H, 7·8. $C_{18}H_{22}O_3$ requires C, 75·5; H, 7·7%). Concentration of the methanolic mother-liquor and hydrolysis with 2N-hydrochloric acid (20 c.c.) at 100° for 1 hr. allowed 2·4 g. of the ketone to be recovered. The net yield of the ketal was therefore 76%.

From the phenolic ketone (XVIII) (2·3 g.), by a similar procedure, 7-*ethylenedioxy*-5 : 6 : 7 : 8 : 10 : 13-*hexahydro*-1-*hydroxy*-13-*methylphenanthrene* (XX; R = H) (2·2 g., 85%) was obtained, forming pale yellow needles (from ethanol), m. p. 213—214° depressed by starting material (Found: C, 75·0; H, 7·6. $C_{17}H_{20}O_3$ requires C, 75·0; H, 7·4%).

7-*Ethylenedioxy*-5 : 6 : 7 : 8 : 9 : 10 : 13 : 14"β"-*octahydro*-1-*methoxy*-13-*methylphenanthrene* (XXI).—The methoxy-ketal (XX; R = Me) (1 g.) in ethyl acetate (20 c.c.) was shaken with hydrogen at 15°/5 atm. over platinum oxide (120 mg.). After 4 hr. the catalyst and solvent were removed. The residue was triturated with methanol and collected. The methoxy-ketal (XXI) separated from methanol in elongated prisms (600 mg.), m. p. 84—85° (Found: C, 74·8; H, 8·4. $C_{18}H_{24}O_3$ requires C, 75·0; H, 8·3%). The ketal (500 mg.) was boiled for 20 min. with ethanol (5 c.c.) and hydrochloric acid (5 c.c.; 2N). On cooling, the ketone separated; recrystallisation from ethanol gave 5 : 6 : 7 : 8 : 9 : 10 : 13 : 14"β"-octahydro-1-methoxy-13-methyl-7-oxophenanthrene (XXII) in colourless prisms, m. p. 121—122° (350 mg.) (Part XLV, *loc. cit.*, m. p. 120—121°). A specimen of ketone prepared by the earlier method was converted into the ketal by the procedure described above. The product had m. p. 84—85° alone or on admixture with the hydrogenation product (XXI).

5 : 6 : 7 : 8 : 9 : 10 : 13 : 12"α"-*Octahydro*-1-*methoxy*-13-*methyl*-7-*oxophenanthrene* (XXIII).—5 : 6 : 7 : 9 : 10 : 13-Hexahydro-1-methoxy-13-methyl-7-oxophenanthrene (21 g.) in dioxan–ether (1 : 1; 420 c.c.) was slowly added to a stirred solution of lithium (1·9 g.) in liquid ammonia

(1 l.). After 15 min. ammonium chloride (30 g.) was cautiously added and the ammonia was evaporated. Water (500 c.c.) was added and the mixture was extracted twice with chloroform, which was then washed successively with dilute hydrochloric acid, water, aqueous sodium carbonate, and water, dried, and evaporated. The residue on crystallisation from ethanol gave the *trans*-methoxy-ketone (XXIII) in colourless needles, m. p. 156—158° (13·55 g., 65%). A portion recrystallised from ethanol had m. p. 158—159° (Renfrow and Cornforth, *loc. cit.*, gave m. p. 158—159°) (Found: C, 78·6; H, 8·0. Calc. for $C_{16}H_{20}O_2$: C, 78·7; H, 8·2%). The *oxime* crystallised from light petroleum (b. p. 60—80°)–benzene in irregular prisms, m. p. 187—188° (Found: C, 73·8; H, 8·3. $C_{16}H_{21}O_2N$ requires C, 74·1; H, 8·1%). Chromatography of the mother-liquors on alumina gave an additional amount of the above ketone (0·83 g.; m. p. *ca.* 155°, eluted with benzene) and a smaller amount (0·43 g.) of the "β"-alcohol (XXV) (described below), m. p. 115·5—116° (eluted with ether).

5 : 6 : 7 : 8 : 9 : 10 : 13 : 14"α"-*Octahydro*-7"β"-*hydroxy*-1-*methoxy*-13-*methylphenanthrene* (XXV).—5 : 6 : 7 : 9 : 10 : 13-Hexahydro-13-methyl-7-oxophenanthrene (1 g.) in ether–dioxan (1 : 1; 40 c.c.) was added slowly with stirring to a mixture of methanol (10 c.c.) and liquid ammonia (250 c.c.). Lithium (400 mg.) was added in small pieces to this solution with stirring during about 15 min. Ammonium chloride (5 g.) was cautiously added and the product was isolated as described in the previous experiment. The product, a brown oil, was dissolved in benzene and chromatographed on acid-washed alumina (*ca.* 30 g.); the portion eluted with ether crystallised on trituration with light petroleum (b. p. 40—60°). The crude product (550 mg.) was recrystallised from this solvent and gave the *methoxy-alcohol* (XXV) as colourless rosettes of needles, m. p. 117·5—118·5° (Found: C, 77·9; H, 8·9. $C_{16}H_{22}O_2$ requires C, 78·1; H, 8·9%). The acetate (acetic anhydride–pyridine) crystallised from light petroleum (b. p. 40—60°) in long, colourless needles, m. p. 107·5—108·5° (Renfrow and Cornforth, *loc. cit.*, gave m. p. 106—107°). The alcohol (XXV) was also obtained when the *trans*-methoxy-ketone (XXIII) (1 g.) was reduced in ether–dioxan with lithium aluminium hydride. After 2 hours' boiling and destruction of excess of hydride with ethyl acetate the product was isolated as usual and crystallised from light petroleum (b. p. 40—60°). Rosettes of colourless needles (800 mg.) were obtained, having m. p. 116—117° alone or mixed with the previous specimen.

5 : 6 : 7 : 8 : 9 : 10 : 13 : 14"α"-*Octahydro*-1-*hydroxy*-13-*methyl*-7-*oxophenanthrene* (XXVI).—The phenolic ketone (XVIII) (14 g.) was dissolved in pyridine (50 c.c.) and acetic anhydride (20 c.c.). After 12 hr. at room temperature the mixture was poured into water and the product extracted with benzene. The benzene solution was washed with dilute hydrochloric acid, sodium carbonate solution, and water, then evaporated. The residue was twice evaporated at low pressure with toluene, dissolved in benzene, and poured on acid-washed alumina (*ca.* 110 g.). Elution with benzene and ether–benzene (1 : 4) gave 1-*acetoxy*-5 : 6 : 7 : 9 : 10 : 13-*hexahydro*-13-*methyl*-7-*oxophenanthrene* (XXIV) (14·9 g., 90%) in colourless irregular rhombs, m. p. 102—104° raised by recrystallisation from aqueous methanol to 104—104·5° (Found: C, 75·3; H, 6·6. $C_{17}H_{18}O_3$ requires C, 75·5; H, 6·7%).

The acetate (15·45 g.) in dioxan–ether (300 c.c.; 1 : 1) was slowly added to a stirred solution of lithium (1·3 g.) in liquid ammonia (1 l.). The blue colour was discharged before the addition was complete and more lithium (*ca.* 0·1 g.) was added in small portions until the blue colour persisted. After a further 15 min. ammonium chloride (30 g.) was added carefully and the ammonia was removed. Water (500 c.c.) was added and the product was extracted with chloroform, which was evaporated after being washed with dilute hydrochloric acid, sodium carbonate solution, and water. The residue on crystallisation from ethanol gave the phenolic trans-*ketone* (XXVI) as a pale yellow crystalline powder (8·57 g., 66%), m. p. 209—211° depressed 2° by the unsaturated ketone (XVIII). From the mother-liquors by acetylation, filtration through alumina, and hydrolysis a further quantity (0·5 g.) of the product was obtained.

The same product (XXVI) was obtained in 33% yield by reduction of the ketone (XVIII) with lithium in ammonia. A sample was obtained in colourless, irregular rhombs, m. p. 209—211°, by shaking in ethanolic solution for 8 hr. with Raney nickel, followed by crystallisation from benzene (Found: C, 78·0; H, 7·8. $C_{17}H_{20}O_3$ requires C, 78·3; H, 7·8%). The acetate crystallised from light petroleum (b. p. 60—80°) and had m. p. 108—110° (Found: C, 75·0; H, 7·3. Calc. for $C_{19}H_{22}O_4$: C, 72·6; H, 7·0%).

A portion of the phenolic ketone (XXVI) on methylation with methyl sulphate and sodium hydroxide gave the methyl ether (XXIII), m. p. and mixed m. p. 158—159° after crystallisation from ethanol.

The saturated and the unsaturated ketone could be conveniently distinguished by colour tests. The material (*ca.* 50 mg.) was dissolved in a mixture of carbon tetrachloride (0·5 c.c.)

and acetic anhydride (0·5 c.c.), and concentrated sulphuric acid (1 drop) was added. On gentle warming the unsaturated ketones (both 1-methoxy and 1-hydroxy) gave deep orange-red colours whereas the saturated ketones gave a transient deep blue colour fading to yellow. Another characteristic test for the unsaturated keto-phenol (XVIII) is the deep red colour developed with aqueous alkali.

7-Ethylenedioxy-5 : 6 : 7 : 8 : 9 : 10 : 13 : 14"α"-octahydro-1-methoxy-13-methylphenanthrene.—The *trans*-methoxy-ketone (XXIII) (8·9 g.) was treated with ethylene glycol in the manner described above for the ketone (XIX). The crude product in 1 : 1 benzene–light petroleum (b. p. 40—60°) was filtered through alumina to give the purified *methoxy-ketal* (9·33 g., 95%), m. p. 132—133°; a sample was crystallised from ethanol and obtained in colourless, irregular plates, m. p. 132—133° (Found: C, 75·2; H, 8·6. $C_{18}H_{24}O_3$ requires C, 75·0; H, 8·3%).

7-Ethylenedioxy-5 : 6 : 7 : 8 : 9 : 10 : 13 : 14"α"-octahydro-1-methoxy-13-methylphenanthrene (XXVII).—(i) A mixture of the above methoxy-ketal (6·5 g.), potassium hydroxide (13 g.), and methanol (70 c.c.) was heated in an autoclave at 180—190° for 5 hr. When cold, water (200 c.c.) was added and the solution extracted with light petroleum. The aqueous layer was separated and saturated with carbon dioxide. The precipitated phenol was collected by means of ether and passed through a short alumina column in benzene–ether (1 : 1). Recrystallisation of the product from methanol gave the phenolic *ketal* (XXVII) (4·1 g., 65%), m. p. 178—179°. A portion, recrystallised from methanol, formed colourless, irregular prisms, m. p. 179—180° (Found: C, 74·8; H, 8·2. $C_{17}H_{22}O_3$ requires C, 74·4; H, 8·0%). On methylation the methoxy-ketal was regenerated, m. p. and mixed m. p. 132—133° after recrystallisation from methanol. The *acetate* separated from methanol in colourless needles, m. p. 154—155° (Found: C, 71·9; H, 7·6. $C_{19}H_{24}O_4$ requires C, 72·1; H, 7·6%). Inferior yields of the phenol were obtained on raising the autoclave temperature to 210—220°. An attempted demethylation in ethylene glycol at 190° under nitrogen left the starting material unchanged.

(ii) The phenolic *trans*-ketone (XXVI) (7 g.) was treated with ethylene glycol as described above for the ketone (XIX). The crude product, m. p. 170—175°, was passed through alumina in benzene–ether (1 : 1) and crystallised from methanol, to give large colourless prisms (6·6 g., 80%), m. p. 178—179° alone or mixed with the product (XXVII) above.

7-Ethylenedioxy-trans-anti-trans-*perhydro*-13-*methyl*-1-*oxophenanthrene* (XXVIII).—The phenolic ketal (XXVII) (5·0 g.) in ethanol (50 c.c.) and aqueous 30% sodium hydroxide (4 drops) was hydrogenated over Raney nickel (W-2; *ca.* 1 g.) at 170°/140 atm. Catalyst and solvent were removed and the residue, dissolved in benzene, was washed four times with 2N-sodium hydroxide and twice with water. After removal of the dried solvent the residue (5·0 g.) was dissolved in pyridine (50 c.c.; purified by treatment with chromic anhydride and subsequent distillation from potassium hydroxide) and added at room temperature to chromium trioxide–pyridine complex [from chromic anhydride (5·0 g.) and pyridine (50 c.c.) according to Sarett *et al., loc. cit.*]. After 12 hr. water (300 c.c.) and benzene–ether (1 : 1; 100 c.c.) were added. The layers were separated after filtration and the aqueous layer was extracted twice more with benzene–ether. The combined extracts were washed twice with water, dried, and evaporated; two distillations at low pressure with toluene then removed traces of pyridine. The crystalline residue was passed through alumina in benzene and recrystallised from methanol, to give the *ketone-ketal* (XXVIII) in clusters of colourless laths, m. p. 113—114·5° (3·7 g., 72%) (Found: C, 73·4; H, 9·2. $C_{17}H_{26}O_3$ requires C, 73·4; H, 9·3%).

trans-anti-trans-*Perhydro*-13-*methyl*-1 : 7-*dioxophenanthrene* (XXIX).—The above ketone-ketal (250 mg.) was boiled gently in acetone (5 c.c.) and 2N-hydrochloric acid (0·1 c.c.) for 20 min. The acetone was removed and water (10 c.c.) added. The crystalline solid was collected and recrystallised from light petroleum (b. p. 60—80°), to give the diketone (XXIX) as thin plates, m. p. 81—82° (Renfrow and Cornforth, *loc. cit.*, gave m. p. 79—81°) (Found: C, 76·7; H, 9·3. Calc. for $C_{15}H_{22}O_2$: C, 76·9; H, 9·4%). The ketone tends to separate in a hydrated form and comparison with an authentic specimen was easier after recrystallisation of each sample from *cyclo*hexane without precautions to exclude water. The m. p. and mixed m. p. of both samples were then 72—74° and the infrared spectra (in potassium bromide; kindly determined by Dr. R. K. Callow) were identical. As a further check the ketone-ketal (XXIX) was converted in the usual manner into the di(ethylene ketal), which crystallised from light petroleum (b. p. 60—80°) in small needles, m. p. 150—152° (Renfrow and Cornforth, *loc. cit.*, gave m. p. 149—150°) (Found: C, 70·8; H, 9·1. Calc. for $C_{19}H_{30}O_4$: C, 70·8; H, 9·3%).

Reaction of the Ketone-ketal (XXVIII) *with Methyl Oxalate.*—Sodium (166 mg.) was dissolved in methanol (2 c.c.), and the solution evaporated at 120° *in vacuo*. The cake of sodium methoxide was broken up, nitrogen was passed in, and methyl oxalate (0·85 g.) and benzene (4 c.c.)

were added. The mixture was refluxed for 10 min., after which a solution of the ketone-ketal (XXVIII) (1 g.) in benzene (6 c.c.) was added. After 4 hr. at room temperature, water (15 c.c.) was added and the benzene layer was separated and extracted twice with 2N-sodium hydroxide. The combined aqueous extracts were saturated with carbon dioxide and extracted with chloroform, which was then washed with water, dried, and evaporated. The residue, after being digested with a little methanol, was collected [300 mg.; m. p. 208—210° (decomp.)]. Crystallisation from methanol gave *7-ethylenedioxy-2 : 3 : 4 : 5 : 6 : 7 : 8 : 9 : 10 : 12"α" : 13 : 14"α"-dodecahydro-1-hydroxy-13-methyl-2-phenanthrylideneglycollic lactone* (XXX) in irregular rhombs, m. p. 220—222° (decomp.) (Found : C, 68·8; H, 7·0. $C_{19}H_{24}O_5$ requires C, 68·7; H, 7·2%). The lactone gave no colour with alcoholic ferric chloride and was soluble in cold aqueous alkali. The infrared absorption spectrum (in Nujol) showed a carbonyl band at 5·75 and a hydroxyl band at 2·8 μ. The ultraviolet absorption (in $CHCl_3$) showed a sharp maximum at 2950 Å (ε 29,500).

The lactone (100 mg.) in ether containing a drop of methanol was methylated with diazomethane (from 1 g. of methylnitrosourea). Removal of the solvent and crystallisation from methanol gave the lactonic *α-methyl ether* in needles, m. p. 170—172° (Found : C, 68·9; H, 7·5. $C_{20}H_{26}O_5$ requires C, 69·3; H, 7·5%). The infrared absorption spectrum (in Nujol) had a carbonyl band at 5·73 μ but no hydroxyl band. Ultraviolet absorption : $\lambda_{max.}$ 2975 Å (ε 22,200 in $CHCl_3$).

Methyl 7-*Ethylenedioxy*-trans-anti-trans-*perhydro*-13-*methyl*-1-*oxophenanthrene*-2-*carboxylate* (XXXI).—The ketone-ketal (XXVIII) (1 g.), methyl carbonate (6·5 c.c.), and methanol (2 drops) were added to a suspension of sodium hydride (0·21 g.) in dry ether (8 c.c.). The mixture was stirred rapidly for 16 hr. with five ¼" ball-bearings and 2 g. of powdered glass. A mixture of water (10 c.c.) and ether (10 c.c.) was then added with rapid stirring and the whole filtered. The residue was suspended in saturated aqueous sodium dihydrogen phosphate and extracted with chloroform; the ethereal filtrate was washed with sodium dihydrogen phosphate solution. The chloroform and ether solutions were washed with water and evaporated and the residues combined. Crystallisation from methanol gave, in two crops, the *keto-ester* (XXXI) as small needles (700 mg., 65%), m. p. 120—124° raised by further crystallisation to 124—126° (Found : C, 67·5; H, 8·1. $C_{19}H_{28}O_5$ requires C, 67·8; H, 8·3%). The keto-ester gave a blue colour with alcoholic ferric chloride.

Methyl 7-*Ethylenedioxy*-trans-anti-trans-*perhydro*-2"ξ":13-*dimethyl*-1-*oxophenanthrene*-2"ξ"-*carboxylate* (XXXII).—The keto-ester (XXXI) (2·2 g.) in dry benzene (18 c.c.) was added to sodium (1·43 g.) in methanol (33 c.c.). The mixture was refluxed with stirring for ½ hr., the sodio-derivative separating. After cooling, methyl iodide (4·5 c.c.) was added and the mixture was stirred at room temperature. After 45 min. more methyl iodide (45 c.c.) was added and after a further 30 min. the reaction was completed by refluxing the clear yellow solution for 45 min. Saturated sodium dihydrogen phosphate solution was added, the organic layer was separated, and the aqueous layer was extracted twice with ether. The combined extracts were washed with 2N-sodium hydroxide and with water, dried, and evaporated. The residue (2·22 g.) was crystallised from a little ether, the methylated *keto-ester* (XXXII) being obtained as irregular prisms, m. p. 140—142° (1·45 g.) raised by further crystallisation to 141—142·5° (Found : C, 68·7; H, 8·4. $C_{20}H_{30}O_5$ requires C, 68·6; H, 8·6%). The substance gave no colour with alcoholic ferric chloride. The mother-liquor, possibly containing an epimer, was carefully chromatographed on alumina but the only crystalline material isolated was more of the above isomeride (150 mg.), making the total yield 70%.

Methyl trans-anti-trans-*Perhydro*-2"ξ":13-*dimethyl*-1:7-*dioxophenanthrene*-2"ξ"-*carboxylate* (XXXIII).—The above keto-ester (XXXII) (150 mg.) in acetone (5 c.c.) and 2N-hydrochloric acid (0·05 c.c.) was refluxed for 15 min. The acetone was removed and water (10 c.c.) was added. The resulting solid was collected, washed with water, and dried (120 mg.; m. p. 125—127°). Crystallisation from light petroleum gave the *diketo-ester* as rhombs, m. p. 127—129° (Found : C, 70·7; H, 8·6. $C_{18}H_{26}O_4$ requires C, 70·6; H, 8·5%).

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