Tetrahedron. 1957, Vol. 1, pp. 49–66. Pergamon Press Ltd., London

# STEROIDS AND RELATED COMPOUNDS—I

## SYNTHESIS OF 1:2:3:4:9:10:11"$\beta$":12"$\alpha$"-OCTAHYDRO-7-METHOXY-2"$\alpha$":8:11"$\beta$"-TRIMETHYL-3-OXOPHENANTHRENE

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**Abstract**—Starting with 6-methoxy-5-methyltetralin (I), several routes to the compound (XXI) named in the title have been developed. The tetralin (I) was converted into the hexahydrophenanthrene (X) and some attempts were made to convert the latter into a 2:3-glycol or related compound with a view to changing the potential homo-*D*-ring into a natural *D*-ring before reducing the 4:12-double bond. The ketone (X) was converted into the desired product (XXI) by a three-stage methylation and one-two-, or three-stage reductions, the order of the reactions being varied to achieve structural and steric specificity. When attempting to predict and later to rationalise the steric course of the reductions, it was found that the concept of catalyst hindrance[1] provided a better guide than Hadler's conformational arguments which were originally applied to $\Delta^4$- and $\Delta^5$-steroids.[2]

IN several steroid syntheses a homo-*D*-ring has been built up at an early stage and later converted into a five-membered ring. In this way, advantage can be taken of the better understanding of the stereochemistry of polycyclic *cyclo*hexane derivatives, but this is worth while only if the 6-membered-*D*-ring is easily fabricated and changed into a suitably substituted 5-membered-*D*-ring. In previous syntheses such *homo-D*-rings have come from phenolic aromatic rings (as in 1:6-dihydroxynaphthalene[3] and 2-methylresorcinol[4]) and by diene synthesis,[5] but the use of the "ring extension" method (or an equivalent series of reactions) has been surprisingly neglected. The value of using a naphthalene derivative for the *B*- and *C*-rings has been shown clearly[6,7] and if a 2-methyl-1-tetralone such as (VI) were to be ring-extended, the resulting unsaturated ketone, such as (X), provides (a) several possibilities for reduction to a *C/D-trans*-fused ring system, which is itself a part of the natural steroid structure and leads to stereospecific reduction at a later stage[7] (b) the possibility of introducing a carbon atom at $C_{(2)}$ and (c) the functional group needed for transforming the *homo-D*-ring. Apart from some exploratory experiments,[8] only Stork, Loewenthal, and Mukharji[9] and the present author have used this approach, in almost identical ways.

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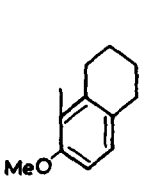
[1] R. P. Linstead, W. E. Doering, S. B. Davis, P. Levine, and R. R. Whetstone *J. Amer. Chem. Soc.* **64**, 1985 (1942).
[2] H. I. Hadler *Experientia* **11**, 175 (1955).
[3] W. S. Johnson, B. Bannister, B. M. Bloom, A. D. Kemp, R. Pappo, E. G. Rogier, and J. Szmuszkovicz *J. Amer. Chem. Soc.* **75**, 2275 (1953).
[4] P. Wieland, H. Ueberwasser, G. Anner, and K. Miescher *Helv. Chim. Acta.* **36**, 376, 1231 (1953); P. Wieland, G. Anner, and K. Miescher *ibid.* 646, 1803.
[5] R. B. Woodward, F. Sondheimer, D. Taub, K. Heussler and W. M. McLamore *J. Amer. Chem. Soc.* **74**, 4223 (1952).
[6] H. M. E. Cardwell, J. W. Cornforth, S. R. Duff, H. Holtermann, and Sir R. Robinson *J. Chem. Soc.* 361 (1953).
[7] J. W. Cornforth, O. Kauder, J. E. Pike, and Sir R. Robinson *ibid.* 3348 (1956).
[8] A. R. Pinder and Sir R. Robinson *ibid.* 3341 (1955).
[9] G. Stork, H. J. E. Loewenthal, and P. L. Mukharji *J. Amer. Chem. Soc.* **78**, 501 (1956).

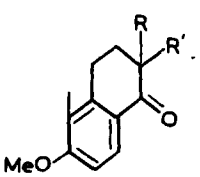
The reactions considered suitable for opening the *D*-ring between $C_{(2)}$ and $C_{(3)}$ depended upon enolisation of a 3-carbonyl group or elimination of a suitable 3-substituent with formation of a 2:3- rather than a 3:4-double bond. This mode of reaction was expected to predominate particularly if the *C*- and *D*-rings were *trans*-fused, but we hope to give a fuller discussion of this point elsewhere.

We had originally intended to use 6-methoxy-1-tetralone as the starting material (cf. ref. 9), since the reduction of polycyclic aromatic ethers related to 6-methoxytetralin had already been accomplished and the $C_{(18)}$* methyl group could be added after the $C_{(1)}$-$C_{(3)}$* part of the *A*-ring, thereby obtaining predominantely axial methylation (this steric control has been realised[10] in a development of Woodward's steroid synthesis). The availability of a supply of 6-methoxy-2-methoxycarbonyl-2:5-dimethyl-1-tetralone (V) and 6-methoxy-5-methyltetralin (I), and the misleading observation that the latter is readily reduced to 1-methyl-$\Delta^{1(9)}$-octal-2-one (II) led us to study a route parallel to, rather than identical with, that followed by Stork, Loewenthal, and Mukharji. In both series of reactions the intermediate 2-methyl-1-tetralone (such as VI) has only one active hydrogen atom and a single racemic product can result from a "ring extension," and a convenient preparation of the ketone (X) was the first objective.

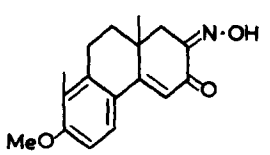
The preparation of the tetralone (VI) from 6-methoxy-5-methyltetralin (I) has been improved and shortened. The methoxycarbonylation and methylation of the tetralone (III) has been carried out without isolation of the intermediate ester (IV), previously prepared by glyoxylation and pyrolytic loss of carbon monoxide.[11] Use was made of filtration through short columns of alumina, using relatively concentrated



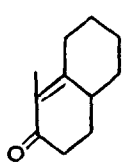

(I)



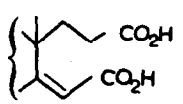

(III) R=R'=H
(IV) R=$CO_2$Me, R'=H
(V) R=$CO_2$Me, R'=Me
(VI) R=Me, R'=H
(VII) R=Me, R'=$(CH_2)_2$.CN
(VIII) R=Me, R'=$(CH_2)_2CO_2H$
(IX) R=Me, R'=$(CH_2)_2CO_2$Me




(XV)




(II)




(XVI)

solutions, instead of distillation in the purification of intermediates. The condensation of the tetralone (VI) with diethylmethyl-(3-oxobutyl)-ammonium iodide was unpromising, and although the ketone (X) was isolated in low yield, this method was not developed. Instead, the tetralone (VI) was cyano-ethylated in *t*-butanol and the resulting nitrile (VII) was hydrolysed to the acid (VIII) and the latter was esterified, giving the methyl ester (IX) (yield *c.* 87% from VI). Under forcing conditions this

* Steroid numbering.

[10] L. B. Barkley, W. J. Knowles, H. Raffelson, and Q. E. Thompson *ibid.* 4111.

[11] R. H. Martin and Sir R. Robinson *J. Chem. Soc.* 491 (1943).

ester reacted with methyl acetate and sodium methoxide and the whole product was boiled with formic acid, giving the phenanthrene derivative (X) (*c.* 70% yield from the tetralone VI). The sodium salts present buffered the mixture sufficiently to prevent decomposition of the ketone (X), which is sensitive to strong acids, including hot concentrated formic acid. The ketone (X) and compounds containing the same chromophore, and the corresponding alcohols, such as (XXVIII), give a variety of colour reactions with acidic reagents which were useful for detecting these compounds, particularly near the end of reductions (see Table 1 and below).

TABLE 1.—COLOUR REACTIONS GIVEN BY SOME OF THE COMPOUNDS PREPARED IN THIS WORK. THE SOLUTION USED FOR THE MODIFIED LIEBERMANN TEST WAS A FRESHLY PREPARED MIXTURE OF ACETIC ANHYDRIDE AND SULPHURIC ACID (12:1)

| Compound | Colour in formic acid | Liebermann test | |
|---|---|---|---|
| | | Cold | Heated to boiling and cooled |
| X | yellow, w | yellow, | cherry |
| XIV | (y-green, w)* | (y-green, s) | (green, s) |
| X† | — | yellow, s (green, w) | red-brown |
| XV | — | orange | orange (y-green) |
| XI | y-green (green, s) | orange, s (green) | crimson, s (red) |
| XII | pale yellow | yellow | yellow |
| XIII | (y-green. w) | | |
| XXVIII | yellow, changing to blue at the boiling-point. | orange | red |
| XXX | yellow, changing to blue-green at the boiling-point | orange | red |

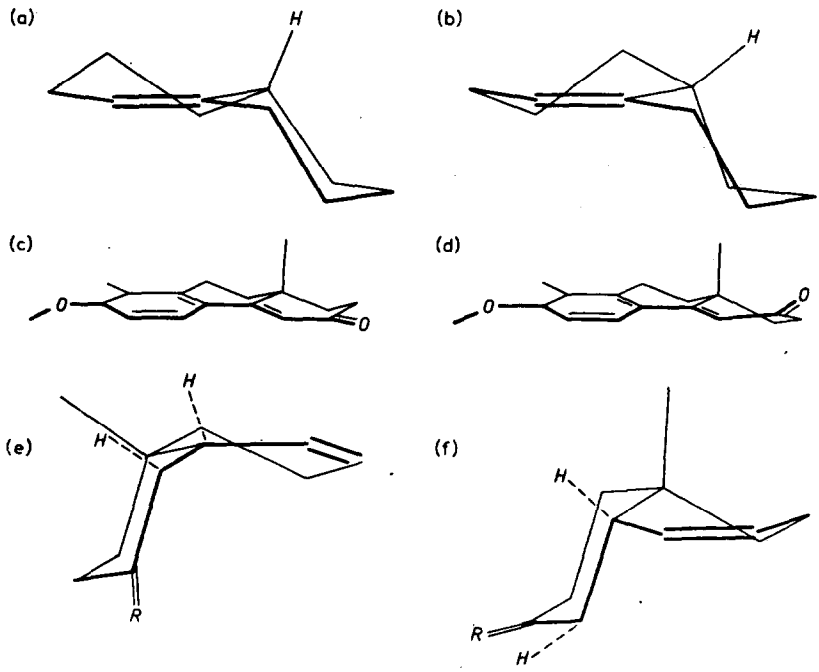
* Colours of fluorescences are enclosed in brackets; intensities are only indicated when they are strong (s) or weak (w).
† Semicarbazone of the ketone (X).
y-green = yellowish green.

Although only racemates were prepared, the 11-methyl group in the ketone (X) will by convention be taken to be "$\beta$"-oriented* (and above the mean plane of the molecule) to facilitate the naming of stereoisomers and to indicate relationships with the natural steroids. It seems very probable that the ketone (X) has the *C*- and *D*-rings in the half-chair conformation,[12] since (a) that is the more stable for *cyclo*hexene (b) allows the molecule to be nearly strain-free, judging from models, and (c) the conjugated system is planar and therefore the resonance stabilisation should be maximal.

*Previous authors, e.g. ref. 7, have used heavy and broken lines in formulae, and Greek letters in inverted commas in names, to denote *relative* configurations of racemic compounds. This convention will be followed in this paper.

[12] C. W. Beckett, N. K. Freeman, and K. S. Pitzer *J. Amer. Chem. Soc.* **70**, 4227 (1948); D. H. R. Barton, R. C. Cookson, W. Klyne, and C. W. Shoppee *Chem. and Ind.* **21**, (1954).

In this conformation (see Xa) only the 11-methyl group is above and the 1- and 10-methylene groups are below the mean plane of the molecule. It seems that the ketone (X) is much more stable in the conformation (Xa) than (Xb), since compounds with two large substituents at $C_{(2)}$ show the same ultra-violet absorption spectra as the unsubstituted ketone (X), in spite of the interference between the axial 11"$\beta$"- and 2"$\beta$"-substituents which would not be present in the conformation (Xb), in which the *D*-ring is in the half-boat form, but this difference in stability is probably reduced considerably in the transition states for reduction of the $\Delta^{4:12}$ double bond or the carbonyl group (see below). Models of the ketone (X) with the *C*-ring in a half-boat form were very strained and were not considered further.




(a) (XXVIIa) (b) (XXVIIb)
(c) (Xa) (d) (Xb)
(e) (XXIIa) R = O (f) (XXIIb) R = O

(XXXIIa) R = H, OH (XXXIIb) R = H, OH

(In (e) and (f) the aromatic ring is omitted except for the (double) bond common to rings *B* and *C*, and only the two hydrogen atoms added during reduction of the 4:12-double bond are shown.)

Fig. 1.—Conformations of $\Delta^{1(9)}$-octalin (XXVII), the ketones (X) and (XXII), and the alcohol (XXXII).

Some attempts were made to introduce an oxygen function at $C_{(2)}$ in the ketone (X) with a view to preparing a 2:3-glycol (cf. ref. 5) before reduction of the double bond. The purpose was to make use of the undirectional enolisation of the ketone (X), although it was recognised that the *trans-C/D* ketones (XVII) and (XXI) should react predominantely at $C_{(2)}$. The ketone (X) gave intractable tars when treated with

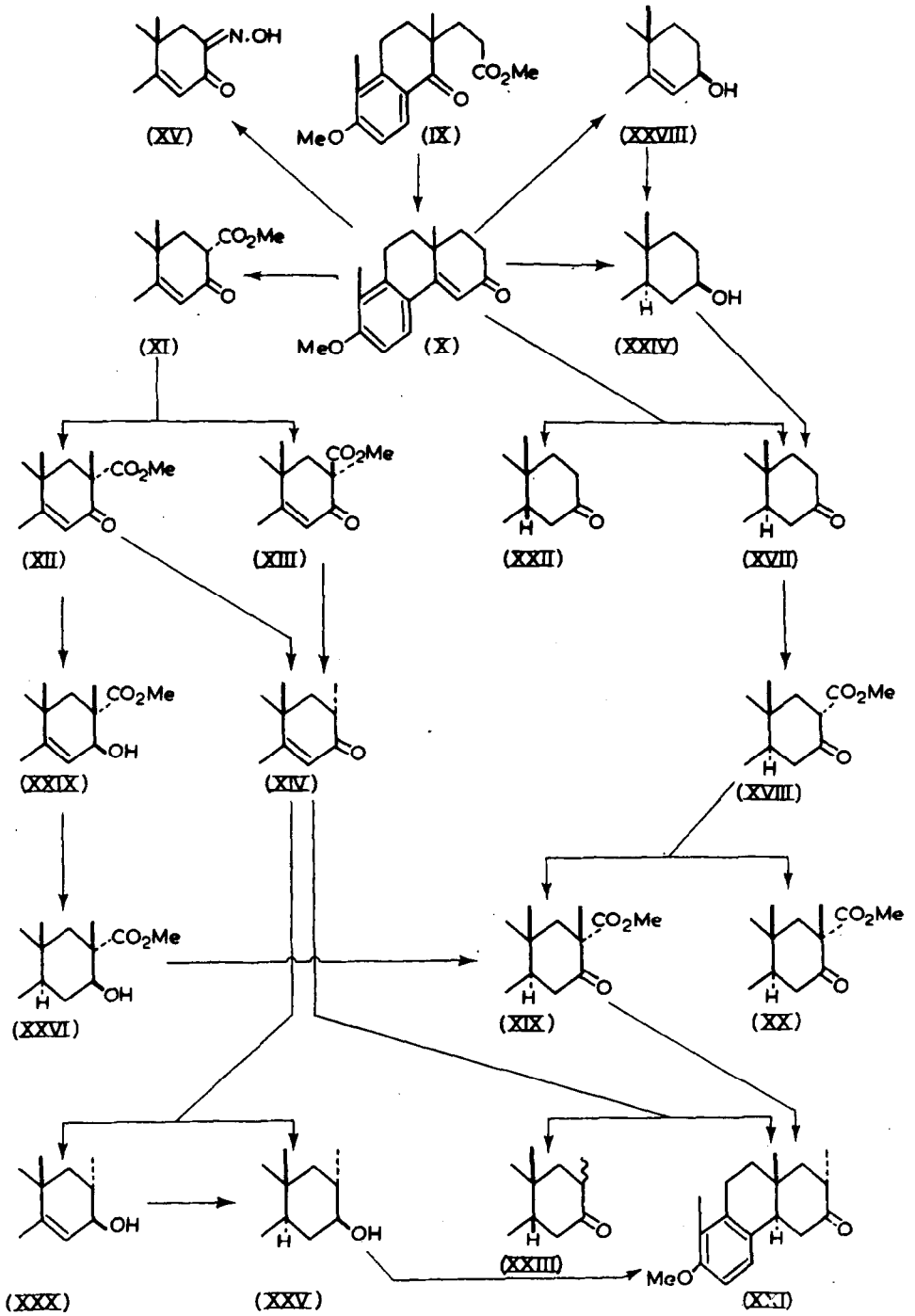
selenium dioxide in ethanol, acetic acid, or acetic anhydride, and with lead tetra-acetate in acetic acid. With bromine in acetic acid the ketone (X) gave green tars, but in the presence of sodium acetate a bromoderivative (probably the 6-bromoketone, because the bromine atom was unreactive and the 6-position is *ortho* to the methoxyl group) was formed. This bromoketone was not sensitive to acids, but further acid-catalysed bromination was not successful. In the presence of sodium acetate, further bromination gave moderate yields of a di- and (impure) tri-bromoketone. Part of the bromine in the latter reacted with sodium acetate, but no acetoxydibromoketone was obtained from this reaction or from the bromination mixture. The most promising approach was nitrosation of the ketone (X) with *t*-butyl nitrite and potassium *t*-butoxide,[13] but the resulting α-oximinoketone (XV) could not be hydrolysed, and the method of reductive hydrolysis applicable to some α-oximino*cyclo*pentanones[14] brought about reduction to a very unstable basic substance, presumably an aminoketone. A similar product was obtained by catalytic reduction, but neither could be purified either as the base or as the hydrochloride.

In the main synthetic route the methylation of the ketone (X) was the next objective. From the methoxycarbonylation of the ketone (X) the β-oxoester (XI) could be isolated in nearly quantitative yield, provided the reaction was forced to completion by removing methanol as it was formed, but the β-oxoester (XI) was conveniently methylated without isolation, forming mainly the 2"β"-methyl derivative (XII) and some of the isomer (XIII). Both the esters (XII) and (XIII) were hydrolysed by alkali to (XIV) (*c.* 80% from X), without any of the expected dibasic acid (XVI). In one experiment, using a shortened reaction time, the sodium salt corresponding to the ester (XII) was isolated as a by-product. The structures of the esters (XII) and (XIII) will be discussed below.

Several methods were tried for the reduction of the ketones (X) and (XIV) to the *trans*octahydrophenanthrenes (XVII) and (XXI). Lithium in liquid ammonia was used first, because this was known to give thermodynamically more stable products[15] in general, and *trans*octahydrophenanthrenes in particular,[7] although the effect of the different positions of the functional groups was not known. The reaction was much slower with the ketones (X) and (XIV) and gave mixtures of *cis* and *trans* ketones, (XVII and XXII) and (XXI and XXIII) respectively, which could not be separated directly by crystallisation, and the mixtures were converted into methyl and ethylene ketals respectively. The ethylene ketals were prepared by a standard method,[17] but the methyl ketals were prepared by crystallising the mixed ketones (XVII) and (XXII) from boiling acidified methanol. Similar preparations of methyl ketals have been reported recently.[18] The ketals from the *trans* ketones (XVII) and (XXI) only were obtained crystalline (*c.* 50% yields), and these were hydrolysed to the pure ketones in acetone.[17] The *cis* ketones (XXII) and (XXIII) were obtained in low yields from the ketal residues.

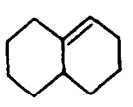
Methoxycarbonylation of the ketone (XVII) gave exclusively the β-oxoester (XVIII), which on methylation gave mainly the derivative (XIX), and a very small

[13] F. Litvan and Sir R. Robinson *J. Chem. Soc.* 1997 (1938).
[14] L. Claisen and E. Manasse *Annalen* **274**, 90 (1893); F. H. Stodola, E. C. Kendall, and B. F. McKenzie, *J. Org. Chem.* **6**, 841 (1941); M. N. Huffman and M. H. Lott *J. Amer. Chem. Soc.* **76**, 4038 (1954).
[15] D. H. R. Barton and C. H. Robinson *J. Chem. Soc.* 3045 (1954).
[16] F. Sondheimer, O. Mancera, G. Rosenkrantz, and C. Djerassi *J. Amer. Chem. Soc.* **75**, 1282 (1942).
[17] G. I. Poos, G. E. Arth, G. E. Beyler, and L. H. Sarett *ibid.* 422.

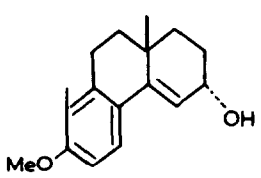

N.OH
O
(XV)
CO2Me
MeO
O
(IX)
OH
(XXVIII)
CO2Me
O
(XI)
MeO
O
(X)
OH
H
(XXIV)
CO2Me
O
(XII)
CO2Me
O
(XIII)
H
O
(XXII)
H
O
(XVII)
CO2Me
OH
(XXIX)
O
(XIV)
CO2Me
H
O
(XVIII)
CO2Me
OH
H
(XXVI)
CO2Me
H
O
(XIX)
CO2Me
H
O
(XX)
OH
(XXX)
OH
H
(XXV)
H
(XXIII)
MeO
H
O
(XXI)

amount of a product thought to be (XX) (the structures are discussed below) and (XIX) was hydrolysed by acid or alkali to the ketone (XXI), identical with the main product from the lithium reduction of the ketone (XIV). This series of reactions (a) shows that the main products from the reductions of (X) and (XIV) belong to the same stereochemical series, (b) strongly supports the assignment of a *trans* configuration to the *C/D*-ring fusion, although the high yield of the β-oxoester (XVIII) may be due to the reversibility of methoxycarbonylation and low solubility of the sodium derivative of (XVIII), and (c) shows that the 2-methyl group in the ketone (XXI) is equatorial (i.e. α-oriented), because the conditions of the hydrolysis should suffice to ensure equilibration. The ketone (X) was also reduced with lithium and ethanol in liquid and from product the *ketones* (XVII) and (XXII) were isolated in low yield through a Girard separation and alcohol (XXIV) in up to 40% yield either directly or from the nonketonic fraction. The alcohol (XXIV) was oxidised by chromium trioxide in pyridine to the trans ketone (XVII) and the hydroxyl group was assigned the equatorial "β"-configuration on the basis of the method of formation.[15] It is interesting to note that the oxidation of the alcohol (XXIV) produced a small quantity of the *unsaturated* ketone (X). The oxidation of a similar alcohol to an unsaturated ketone by chromic acid has been reported,[19] but chromium trioxide in pyridine is usually regarded as very selective and not likely to give the variety of by-products commonly found with chromic acid in acidic solvents.

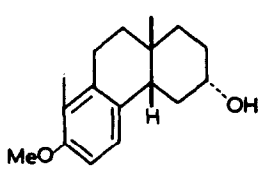
The lithium reductions described above were not suitable on a preparative scale because of the tedious separations and moderate overall yields, and catalytic hydrogenation was considered as an alternative. Although $\Delta^{1(9)}$-octalin (XXVII) and many related compounds give predominantly *cis*decalins[20] when reduced catalytically, some simple exceptions, as well as the more complex examples, such as cholesterol, are now known.[20,21] It has been suggested that catalyst hindrance[1] leads to reduction to a *trans*decalin when there are bulky groups (such as a 10-methoxycarbonyl group) hindering the normal reduction to a *cis*decalin,[20] but the basic cause of the tendency to give a *cis*decalin has only recently been discussed. Hadler[2] considered the steric



(XXVII)




(XXXI)

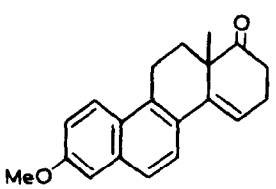



(XXXII)

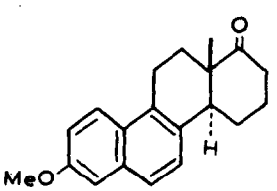
repulsions experienced by the two hydrogen atoms forming part of a 6-membered ring transition complex (two catalyst active sites, the two hydrogen atoms being added and the two carbon atoms of the original double bond), which was assumed to have the shape of the *product*. This approach clearly explains the course of the reduction of cholest-4- and 5-ene, and the influence of 3α- and 3β-substituents in the latter, but the

[18] E. P. Oliveto, C. Gerold, and E. B. Herschberg *ibid.* 76, 6113 (1954); P. A. Robins and J. Walker *J. Chem. Soc.* 3260 (1956).
[19] V. Arkley, F. M. Dean, A. Robertson, and P. Sidisunthorn *ibid.* 2322.
[20] W. G. Dauben, R. C. Tweit, and R. L. MacLean *J. Amer. Chem. Soc.* 77, 48 (1955).
[21] A. S. Dreiding and A. J. Tomasewski *ibid.* 411; M. Yanagita, K. Yamakawa, A. Tahara, and H. Ogura *J. Org. Chem.* 20, 1767 (1955).

effect of a bulky angular group is underemphasised. From the alternative extreme viewpoint, Robinson[22] considered the hindrance offered to the two modes of adsorption of the molecule on the catalyst surface,[1] this being equivalent to assuming that the transition state has the same geometry as the *reactant*. Thus $\Delta^{1(9)}$-octalin is folded in both the possible conformations (XXVIIa) and (XXVIIb), and the adsorption of the open side of the molecule on the catalyst will lead to reduction to *cis*decalin. If a bulky angular group is present, approach to the double bond is less hindered in (XXVIIb), and this will be the favoured one for reduction. But in polycyclic compounds the conformation will be fixed, for example cholesterol corresponds to (XXVIIa), in which the $C_{(18)}$*-methyl group will be most hindering, thereby favouring adsorption of the other side of the molecule. When considering the reduction of the ketone (X) the problem is less simple, because the reduction cannot be stopped at the ketones (XVII) and (XXI) (see below), and there must be some doubt about which stage comes first. Furthermore, when using Hadler's approach both possible conformations (see Fig.) for the *cis*octahydrophenanthrenes, e.g. (XXIIa) and (XXIIb), which are presumably readily interconvertible, must be considered. If the 4:12-double bond is reduced first, catalyst hindrance will lead predominantly to the *trans*-ketone (XVII), because the 11-methyl group should be more effective than the $C_{(1)}$ and $C_{(10)}$ methylene groups, but following Hadler, the predicted yields are in the order (XXIIb)> (XVII)>(XXIIa). The second stage of the reduction should give mainly equatorial hydroxyl groups with the catalyst used. If the carbonyl group is reduced first, product stability and steric hindrance both favour the 3"$\beta$"-alcohol (XXVIII) slightly. This alcohol will be reduced specifically to the *trans*-3"$\beta$"-alcohol (XXIV) through catalyst hindrance, but not otherwise, and the less abundant 3"$\alpha$"-alcohol (XXXI) will be reduced to the *cis*-3"$\alpha$"-alcohol (XXXII) (in the conformation XXXIIb rather than XXXIIa) if Hadler is correct, but not specifically through hindrance. The overall result is that catalyst hindrance should lead mainly to *trans* products and, following Hadler, mainly *cis* products would be expected. Since the reduction of the ketone (X), the 3"$\beta$"-alcohol (XXVIII), and the ester (XII) gives a *trans* product and agrees with the recently reported[24] reduction of the ketone (XXXIII) to (XXXIV) (XXXIV having been converted into equilenin), catalyst hindrance appears to be the better guide.




(XXXIII)




(XXXIV)

When the ketone (X) was reduced catalytically, the alcohol (XXIV) was formed in 60% yield, with no evidence of a break in the slow hydrogen uptake corresponding to the ketone (XVII), and preliminary reduction of the carbonyl group to a 3"$\beta$"-hydroxyl was tried to improve the yield. It has been suggested that the ratio of the amounts of

*Steroid numbering.

[22] M. J. T. Robinson Thesis, Oxford, 1955.

[23] W. G. Dauben, E. J. Blanz, J. Jiu, and R. A. Micheli *J. Amer. Chem. Soc.* **78**, 3752 (1956).

[24] Cheng Chin *Scientia Sinica* **4**, 547 (1955).

epimeric alcohol formed by the metal borohydride reduction of a ketone is determined by a balance between steric hindrance to the approach of the reagent and the relative stabilities of the developing products,[23] the usual result being that the product contains more of the less stable epimer than the equilibrium mixture. Lithium aluminium hydride reduction of cholest-1-en-3-one gave 90% of cholest-1-en-3$\beta$-ol,[25] and 5-methyl*cyclo*hexen-3-one similarly gave 93% of *cis*-5-methyl*cyclo*hexen-3-ol, although the equilibrium amount is only 55% at 100°[26] and there is no marked steric hindrance. The reductions of some 6-alkyl*cyclo*hexen-3-ones to *trans*-6-alkyl*cyclo*hexen-3-ols are qualitatively similar.[27] There is evidence, furthermore, that metal borohydrides are more stereospecific than lithium aluminium hydride,[23] and it seemed that the ketone (X) might be reduced specifically to the 3"$\beta$"-alcohol (XXVIII) by potassium borohydride. The alcohol (XXVIII) was obtained in 83–87% yield, but when it was reduced catalytically the reduction was complete when only 80% of the theoretical amount of hydrogen had been absorbed. The contaminant must have been the saturated alcohol (XXIV), since this was obtained quantitatively and nearly pure from this hydrogenation. The alcohols (XXIV) and (XXVIII) did not depress each other's melting-points very much and probably form a solid solution, since crystallisation of the latter did not raise or sharpen its melting-point, although it must have contained *c.* 20% of the alcohol (XXIV) to account for the hydrogenation. Metal borohydride reduction of double bonds conjugated with carbonyl groups has been reported.[28] The overall reduction was less specific when lithium aluminium hydride was used. Potassium borohydride reduction of the ketone (XIV) gave a mixture from which the alcohol (XXV), contaminated with about 15% of the unsaturated alcohol (XXX), was isolated in 30% yield. When this mixture was reduced catalytically, the pure alcohol (XXV) was obtained and the latter was oxidised to the ketone (XXI). With anhydrous formic acid the alcohols (XXVIII) and (XXX) gave intense orange colorations which changed slowly to blue. A similar slow change in acid solutions of some diarylethylenes has been attributed, somewhat improbably, to a change from a classical to a "$\pi$-complex" carbonium ion.[29]

Because the reduction of the ketone (XIV) was less simple than was the case with the ketone (X), the reduction of the esters (XII) and (XIII) was studied as a route to the ketone (XXI). These esters would be expected to be reduced to *trans* products provided the *homo-D*-ring remains in the half-chair conformation (as in XIIa and XIIIa). However, any reaction which reduces the conjugation in the transition state will decrease this stabilising effect and the reaction may be less specific. The esters (XII) and (XIII) were not hydrogenated under conditions effective with the ketone (X), but were slowly reduced by potassium borohydride. The products, e.g. (XXIX) from (XII), were mixtures which could not be separated by crystallisation and which probably contained some of the saturated alcohols such as (XXVI), obtained in 75% yield after hydrogenation. The overall reaction is less specific than for the ketone (X), but provides the best route to the ketone (XXI), since the oxidation of the ester (XXVI) to the ester (XIX), previously prepared by methylating (XVIII), and the subsequent hydrolysis to (XXI) were both nearly quantitative. As in the oxidation of the alcohol

[25] W. Bergmann, M. Kita, and D. J. Giancola *J. Amer. Chem. Soc.* **76**, 4974 (1954).
[26] H. L. Goering and J. P. Blanchard *ibid.* 5405.
[27] G. Stork and W. N. White *ibid.* **78**, 4604 (1956).
[28] F. Sondheimer, M. Velasco, E. Batres, and G. Rosenkrantz *Chem. and Ind.* 1482 (1954).
[29] A. G. Evans, N. Jones, P. M. S. Jones, and J. H. Thomas *J. Chem. Soc.* 2757 (1956).

(XXIV) some conjugated ketone, presumably (XII), was formed and a relatively long time was required (cf. ref. 17). The mixture of products obtained from the ester (XII) was not studied, because it did not offer a useful route to the ketone (XXI). The sequence I, III, IV, V, VI, VII, VIII, IX, X, XI, XII, XXIX, XXVI, XIX, XXI, was the best route.

The structures given to the methylation products (XII), (XIII), (XIX), and (XX) can now be discussed. Corey[30] has shown that bromination of oxosteroids gives axial products when kinetically controlled, Johnson[31] has suggested that this may be true of cationoid substitutions of enols in general, and Robinson has noted other examples.[22] In addition, the order of decreasing specificity of the reduction of the ketones (X), (XII), and (XIII) was probably due to the differences in the sizes of the axial 2"$\beta$"-hydrogen, methyl and methoxycarbonyl groups, the increasing size of the 2"$\beta$"-substituent causing a progressive decrease in the stability of the (Xa), (XIIa), and (XIIIa) conformations. This evidence all points to the esters (XII) and (XIX), which have been shown to have the same configuration, and are the main products from the methylations of (XI) and (XVIII) respectively, as the *axial* 2"$\beta$"-methyl isomers.

It may be thought that if all the configurations assigned in this work are wrong, an equally consistent set of relationships are possible so far as the hydrogenations are concerned which would then conform with Hadler's approach. For this to be possible, the borohydride reduction of the ketone (X) must give the 3"$\alpha$"-alcohol (XXXI) and then hydrogenation gives the *cis* alcohol (XXXII). But neither product stability (the 3"$\alpha$"-alcohol (XXXI) has a *pseudo*axial hydroxyl group if the *D*-ring is in the half-chair form) nor steric hindrance favour the formation of (XXXI) unless the *D*-ring is in the half-boat form (as in Xb), in which case product stability must outweigh the increased steric hindrance leading to the 3"$\beta$"-alcohol (XXVIII). This in turn requires that the esters (XII) and (XIII), reacting in the same conformation, should be reduced *more* specifically to 3"$\alpha$"-alcohols of the *cis* series. In fact, the reduction was *less* specific than with (X) and thus supports the main body of evidence that *trans*-octahydrophenanthrenes were obtained.

## EXPERIMENTAL

Compounds were frequently purified by passing a concentrated solution in a specified solvent through a short column of alumina (Type A, Messrs. Peter Spence and Co., 0·5–3 g per g of the compound), and evaporating the filtrate and washings before the next operation; for brevity, this will be referred to by the parenthetical phrase "Decolorised in (solvent) with alumina." This simple purification, and a careful choice of reaction conditions, often made wasteful crystallisations and distillations unnecessary before the next reaction. Infra-red spectra were measured for all compounds prepared and were consistent with the structures proposed, but infra-red spectra will only be mentioned specifically in special cases.

*6-Methoxy-5-methyl-1-tetralone* (III). 6-Methoxy-5-methyltetralin (I) (100 g) was oxidised by the method of Martin and Robinson[11] and the product was isolated by diluting the reaction mixture with brine (5 l.). The tetralone was decolorised in benzene with alumina, and needed no further purification (74 g, 66%), m.p. 110–112°

[30] E. J. Corey *J. Amer. Chem. Soc.* **76**, 175 (1954).
[31] W. S. Johnson *Chem. and Ind.* 167 (1956).

(Martin and Robinson claim an average yield 70%, m.p. 103–105°, with m.p. 112–113° after purification).

*6-Methoxy-2-methoxycarbonyl-2:5-dimethyl-1-tetralone* (V). 6-Methoxy-5-methyl-1-tetralone (33·2 g), sodium methoxide (from sodium, 11·5 g) and methyl carbonate (125 c.c., distilled from sodium hydride) were boiled under reflux with stirring in a nitrogen atmosphere (2 hours). Methanol (200 c.c.) and methyl iodide (40 c.c.) were added to the cooled solution, and stirring was continued overnight at room temperature and then at the boiling-point (30 min). The solution was neutralised with 2 N-acetic acid and evaporated, leaving an oil which slowly solidified when shaken with water. The crude ester, in benzene, was decolorised with alumina and then crystallised from light petroleum as large prisms (35 g), m.p. 86–89°. The residues from two runs were recycled and the total yield was raised to 85% (Martin and Robinson obtained an overall yield of 65–69%, m.p. 84–86°, for a three-stage preparation).

*6-Methoxy-2:5-dimethyl-1-tetralone* (VI). A solution of the ester (V) (40·0 g) in 12 N-hydrochloric acid (90 c.c.), acetic acid (150 c.c.), and water (30 c.c.) was boiled (4 hours) and then left overnight at 0°. The tetralone (VI) separated in laths (29·1 g), m.p. 111–113°; the mother liquors, when diluted with an equal volume of brine, deposited a further quantity of the tetralone (1·4 g), m.p. 110–113° (yield and m.p. after crystallisation from methanol) bringing the total yield to 98% (E. B. J. Smith[32] reported a 75% yield, m.p. 112–113°, after crystallisation).

*2-(2'-Cyanoethyl)-6-methoxy-2:5-dimethyl-1-tetralone* (VII). Freshly distilled acrylonitrile (5·0 g, 25% excess), in dry *t*-butanol (5 c.c.), was added during 5 min to a stirred suspension of 6-methoxy-2:5-dimethyl-1-tetralone (15·0 g) in dry *t*-butanol (150 c.c.) containing potassium *t*-butoxide (from potassium, 1·5 g) under nitrogen at 30°. The mixture was stirred (4 hours), acidified with 2 N-acetic acid, and evaporated. The oily residue, decolorised in benzene with alumina, crystallised when diluted with methanol and cooled to 0° giving the *nitrile* (VII) (17·4–18·0 g, 92–95%, 2 crops), m.p. 95·5–97·5°, which separated from methanol in prisms, m.p. 96–98° (Found: C, 74·6; H, 7·3; N, 5·5. $C_{16}H_{19}O_2N$ requires C, 74·6; H, 7·4; N, 5·4%).

*6-Methoxy-2-(2'-methoxycarbonylethyl)-2:5-dimethyl-1-tetralone* (IX). The *nitrile* (VII, previous preparation, 16·25 g) and potassium hydroxide (10 g) in aqueous methanol (1:1, 100 c.c.) were boiled (1 day). The methanol was evaporated under reduced pressure and the cooled residue was added to 4 N-acetic acid (100 c.c.). The precipitated *acid* (VIII) separated from aqueous acetic acid (1:1) in slender needles of the *monohydrate*, m.p. 86–91° (decomp.) (Found: C, 65·0; H, 7·6. $C_{16}H_{20}O_4 \cdot H_2O$ requires C, 65·3; H, 7·5%), which readily lost water at 100°/15 mm and gave the anhydrous acid which solidified in massive prisms, m.p. 92–93° (Found: C, 69·6; H, 7·4. $C_{16}H_{20}O_4$ requires C, 69·5; H, 7·6%). For preparative purposes the crude acid was dried by two evaporations with benzene, and was then boiled (4 hours) with methanol (50 c.c.) and sulphuric acid (1·0 g). From the resulting solution the *methyl ester* (IX) crystallised overnight at 0°, and, after decolorisation in benzene with alumina, separated from methanol in needles (16·9–17·4 g, two crops, 92–95% from the *nitrile*), m.p. 101–102·5° (Found: C, 70·4; H, 7·8. $C_{17}H_{22}O_4$ requires C, 70·3; H, 7·6%).

*1:2:3:9:10:11-Hexahydro-7-methoxy-8:11-dimethyl-3-oxophenanthrene* (X). (a) 6-Methoxy-2:5-dimethyl-1-tetralone (2·0 g) was added to potassamide (from potassium,

[32] E. B. J. Smith Thesis, Oxford, 1949.

0·8 g) in liquid ammonia (100 c.c.), and the mixture was stirred and evaporated to dryness in a stream of nitrogen during 1 hour. 1-Diethylaminobutan-3-one methiodide (2·90 g), dry ether (25 c.c.), and seven steel ball-bearings were then added and stirring was continued at room temperature (1 hour) and then at the boiling-point (30 min). Ethanol (25 c.c.) was then added and the whole again stirred at the boiling-point (30 min). The mixture was shaken with 2 N-sulphuric acid (20 c.c.) and ether, and when the ethereal layer was evaporated, a small amount of the tetralone (VI) separated from the residue under methanol. After several weeks the residue from the methanol mother liquors partly crystallised, and by washing with pyridine and crystalling twice from methanol, 1:2:3:9:10:11-*hexahydro*-7-*methoxy*-8-11-*dimethyl*-3-*oxophenanthrene* (X) was obtained as pale yellow plates (0·02 g, 1%), m.p. 156–158°, $\lambda_{max}^{MeOH}$ 248, 330 m$\mu$ ($\varepsilon$ 13,000, 19,200) (Found: C, 79·5; H, 7·6. $C_{17}H_{20}O_2$ requires C, 79·6; H, 7·8%). The *semicarbazone* precipitated from the pyridine washings when semicarbazide hydrochloride (1·0 g) in water (2 c.c.) was added, and crystallised from acetic acid in pale yellow crystals (0·71 g, 23%), m.p. 262–266° (decomp., rapid heating after immersion at 259°), which turned deep yellow superficially when exposed to air, and was identical with a specimen prepared from the pure ketone (Found: C, 68·7; H, 7·4; N, 13·6. $C_{18}H_{23}O_2N_3$ requires C, 69·0; H, 7·4; N, 13·4%).

(b) 6-Methoxy-2-(2′-methoxycarbonylethyl)-2:5-dimethyl-1-tetralone (IX) (28·7 g), methyl acetate (150 c.c.), sodium methoxide (baked at 150°/15 mm, from sodium, 50 g), ether (50 c.c.), and several glass balls were stirred under nitrogen with slow evaporation (12 hours) of the ether. The resulting pasty solid was baked (2 hours) at 80° and then boiled (18 hours) with formic acid (300 c.c., added slowly). The gummy *product* (isolated with benzene), sodium hydroxide (10 g), water (50 c.c.), and methanol (200 c.c.), were boiled (1 hour), and boiling water (500 c.c.) was added slowly to the mixture. The precipitated solid was collected, washed with hot water (the filtrate and washings contained considerable amounts of the acid (VIII) which was recovered and converted to the methyl ester (IX), 10% after purification), and decolorised in benzene with alumina. The ketone (X) (18·7 g, 82% allowing for recovered ester, 10%), m.p. 154–157°, separated from ethanol in pale yellow needles or, more commonly, plates, m.p. 157–159°, identical with the product from the previous method (Found: C, 79·3; H, 7·8%). The 2:4-*dinitrophenyhydrazone* separated from ethyl acetate in red-brown needles, m.p. 239–241° (decomp.) (Found: C, 63·1; H, 5·7; N, 12·7. $C_{23}H_{24}O_5N_4$ requires C, 63·3; H, 5·6; N, 12·8%). When sodium ethoxide and ethyl acetate were used in the above Claisen condensation, the yield and purity of the product were poorer. When potassium *t*-butoxide and *t*-butyl acetate were used, only ester exchange took place, giving 2-(2′-t-*butoxycarbonylethyl*-6-*methoxy*-2:5-*dimethyl*-1-*tetralone*, which separated from methanol in stout prisms, m.p. 117–119°. (Found: C, 72·1; H, 8·3. $C_{20}H_{28}O_4$ requires C, 72·3; H, 8·5%).

*Bromination of* 1:2:3:9:10:11-*Hexahydro*-7-*methoxy*-8:11-*dimethyl*-3-*oxophenanthrene* (X). (a) Bromine (0·160 g) in acetic acid (1 c.c.) was added to the ketone (0·256 g) and sodium acetate (0·20 g) in acetic acid (2 c.c.). Crystallisation began after 2–3 min, and aqueous acetic acid (1:1, 4 c.c.) was then added dropwise, giving the 6(?)-*bromo derivative* (0·265 g, 80%), m.p. 159–163°, which separated from methanol in slender needles, m.p. 162·6–164° (Found: C, 60·8; H, 5·7; Br, 23·8. $C_{17}H_{19}O_2Br$ requires C, 60·9; H, 5·7; Br, 23·8%). The 2:4-*dinitrophenylhydrazone* separated from ethyl acetate in scarlet needles, m.p. 209–211° (decomp.) (Found: C, 53·8; H, 4·8;

Br, 15·7. $C_{23}H_{23}O_5N_4Br$ requires C, 53·8; H, 4·5; Br, 15·5%). The 6-bromo derivative was recovered (98%, m.p. 162·5–164°) after boiling (12 hours) with sodium acetate in methanol.

(b) The 6(?)-bromo derivative (0·285 g), bromine (0·18 g), sodium acetate (0·30 g), and acetic acid (3 c.c.) were heated at 50° until colourless (*c.* 30 min), and water (20 c.c.) was then added. The gum which separated crystallised from methanol, giving the 6(?):*x-dibromo derivative* as irregular lumps (0·16 g, 45%), m.p. 148–151° (Found: C, 49·1; N, 4·1; Br, 39·0. $C_{17}H_{18}O_2Br_2$ requires C, 49·3; H, 4·4; Br, 38·4%). The 2:4-*dinitrophenylhydrazone* separated from ethyl acetate in clusters of scarlet needles, m.p. 250–252° (Found: C, 46·8; H, 3·7; N, 9·6; Br, 26·4. $C_{23}H_{22}O_5N_4Br_2$ requires C, 46·5; H, 3·7; N, 9·4; Br, 26·9%). The 6:*x*-dibromo derivative did not react with sodium acetate in boiling methanol.

(c) The ketone (1·02 g), sodium acetate (3·0 g), bromine (2·0 g), and acetic acid (15 c.c.) were heated (2 hours) at 85–90° in a stoppered flask. The addition of aqueous methanol (1:1) precipitated a semi-solid mass which was crystallised twice from benzene-light petroleum, giving a 2ζ:6(?):*x-tribromo derivative* (0·1 g, 5%), m.p. 195–197°, for which satisfactory analytical figures were not obtained. (Found: C, 42·8; H, 3·6; Br, 47·3. $C_{17}H_{17}O_2Br_3$ requires C, 41·4; H, 3·5; Br, 48·3%). Part of the bromine in this ketone was displaced by sodium acetate in boiling methanol, but no crystalline product could be isolated.

1:2:3:9:10:11-*Hexahydro*-17-*methoxy*-8:11-*dimethyl*-2-*oximino*-3-*oxophenanthrene* (XV). *t*-Butyl nitrite (5 c.c.), was added with swirling to the ketone (X) (3·07 g) suspended in *t*-butanol (80 c.c.) containing potassium *t*-butoxide (from potassium, 1·0 g) under nitrogen, and the mixture was left (1 day) at 30°. The resulting orange solution was evaporated at room temperature and the residue, in water, was acidified with carbon dioxide, giving the oximinoketone (XV) (3·00 g, 87%), m.p. *c.* 265° (decomp., very dependent upon the rate of heating), which separated from acetic acid in yellow needles, m.p. *c.* 274° (decomp.) (Found: C, 71·3; H, 6·8. $C_{17}H_{19}O_3N$ requires C, 71·5; H, 6·7%). This compound showed absorption bands with $\lambda_{max}^{MeOH}$ 260, 360 mμ, but was too sparingly soluble for accurate measurement of the extinction coefficients.

1:2:3:9:10:11"β"-*Hexahydro*-7-*methoxy*-2"α"-*methoxycarbonyl*-8:11"β"-*dimethyl*-3-*oxophenanthrene* (XI). Methyl carbonate was slowly distilled during 4 hours from a boiling mixture of the ketone (X) (1·02 g), sodium methoxide (from sodium, 0·3 g), and methyl carbonate (freshly distilled from sodium hydride, volume maintained at *c.* 10 c.c. while 20–30 c.c. distilled). The cooled residue was shaken with chloroform and saturated aqueous sodium dihydrogen phosphate, and the chloroform layer was evaporated, leaving the *β-oxoester* (XI) (1·22 g, 97%), m.p. 160–171°, which separated from benzene-light petroleum (1:1) in pale yellow needles (1·15 g, 92%), m.p. 170–173°, $\lambda_{max}^{MeOH}$ 249, 326 mμ (ε 14,300, 21,800) (Found: C, 72·4; H, 7·1. $C_{19}H_{22}O_4$ requires C, 72·6; H, 7·1%). This compound gave a brown coloration after a few seconds with ferric chloride in methanol. The 2:4-*dinitrophenylhydrazone* separated from ethyl acetate in red needles, m.p. 219–221° (Found: C, 60·8; H, 5·6. $C_{25}H_{26}O_7N_4$ requires C, 60·7; H, 5·3%).

1:2:3:9:10:11-*Hexahydro*-7-*methoxy*-2-*methoxycarbonyl*-2:8:11-*trimethyl*-3-*oxophenanthrene* (XII *and* XIII). Methyl carbonate and methanol were slowly distilled through a Vigreux column from a boiling mixture of the ketone (X) (5·12 g), sodium

methoxide (from sodium, 0·6 g), and methyl carbonate (b.p. 89°, 60 c.c., freshly distilled from sodium hydride, with two 20-c.c. portions added after 20 min and 1 hour respectively). The rate of distillation was 20 c.c., b.p. 70–87°, in the first 20 min, 20 c.c., b.p. 87–89°, in the next hour, and 20 c.c., b.p. 89°, in the following 3 hours. The resulting yellow slurry was treated with methyl iodide (10 c.c.), boiled (12 hours), cooled, and shaken with water and chloroform. The organic layer was evaporated, leaving a residue (6·4 g, 98%), m.p. 170–180°, which gave no coloration with ferric chloride in methanol, and which on crystallisation from chloroform-methanol (1:5) gave +1:2:3:9:10:11"β"-*hexahydro*-7-*methoxy*-2"α"-*methoxycarbonyl*-2"β":8:11"β"-*trimethyl*-3-*oxophenanthrene* (XII) as pale yellow plates (4·72 g, 72%), m.p. 192·5–194° (unchanged after crystallisation of this compound from methanol), $\lambda_{max}^{MeOH}$ 249, 330 mμ (ε 12,200, 21,300) (Found: C, 73·1; H, 7·3. $C_{20}H_{24}O_4$ requires C, 73·1; H, 7·4%). This *compound*, when treated with bromine (one molecular equivalent) and sodium acetate in acetic acid at room temperature gave a 6-*bromo derivative*, which separated from ethanol in prismatic needles, m.p. 190–192° (Found: C, 59·0; H, 5·8; Br, 19·6. $C_{20}H_{23}O_4Br$ requires C, 59·0; H, 5·7; Br, 19·6%). The residue from the chloroform mother liquors was crystallised thrice from benzene-light petroleum, giving 1:2:3:9:10:11"β"-*hexahydro*-7-*methoxy*-2"β"-*methoxycarbonyl*-2"α":8:11-"β"-*trimethyl*-3-*oxophenanthrene* (XIII) as pale yellow needles (0·80 g, 12%), m.p. 161–164°, $\lambda_{max}^{MeOH}$ 248,330 mμ (ε 13,200, 23,700) (Found: C, 73·1; H, 7·4. $C_{20}H_{24}O_4$ requires C, 73·1; H, 7·4%).

1:2:3:9:10:11"β"-*Hexahydro*-7-*methoxy*-2"α":8:11"β"-*trimethyl*-3-*oxophenanthrene* (XIV). The β-oxoester (XII) (0·72 g), sodium hydroxide (1·0 g), methanol (25 c.c.), and water (5 c.c.) were boiled (1 day). The solution was concentrated to *c.* 15 c.c. and treated, at the boil, with water (15 c.c.) added dropwise, giving the 2"α"-*methyl ketone* (XIV) (0·56 g, 95%), m.p. 159–162°, which separated from methanol in prisms, m.p. 160·5–162·5°, $\lambda_{max}^{MeOH}$ 248, 328 mμ (ε 13,800, 21,500) (Found: C, 79·7; H, 8·1. $C_{18}H_{22}O_2$ requires C, 80·0; H, 8·2%). The 2:4-*dinitrophenylhydrazone* separated from ethyl acetate in scarlet needles, m.p. 222–224° (Found: C, 63·7; H, 5·8. $C_{24}H_{26}O_5N_4$ requires C, 64·0; H, 5·8%). When the hydrolysis was stopped after 12 hours boiling, *sodium* 1:2:3:9:10:11"β"-*hexahydro*-7-*methoxy*-2"β":8:11"β"-*trimethyl*-3-*oxophenanthrene*-2"α"-*carboxylate trihydrate* (0·08 g, 12%) crystallised from the aqueous filtrate and was recrystallised from moist acetone in needles, m.p. 190–200° (decomp.) (Found: C, 58·6; H, 7·1. $C_{19}H_{21}O_4Na·3H_2O$ requires C, 58·5; H, 7·0%). The ketone (XIV) was obtained from the above sodium salt by warming with 2 N-acetic acid, and by boiling (10 hours) with 2 N-sodium hydroxide, and from the ester (XIII) (previous preparation) by alkaline hydrolysis.

1:2:3:4:9:10:11"β":12"α"-*Octahydro*-3"β"-*hydroxy*-7-*methoxy*:8:11"β"-*dimethylphenanthrene* (XXIV). (a) Lithium (0·2 g) was added during 20 min to the ketone (X) (0·51 g) in dry dioxan (10 c.c.), ether (10 c.c.), ethanol (2 c.c.), and liquid ammonia (150 c.c.). When the blue colour had faded, ammonium chloride (2 g) was added and the ammonia was evaporated. The residue was washed with water and then crystallised twice from methanol, giving the *alcohol* (XXIV) (0·21 g, 40%) as slender needles, m.p. 154–157° (Found: C, 78·7; H, 9·2. $C_{17}H_{24}O_2$ requires C, 78·4; H, 9·3%).

(b) The ketone (X) (0·51 g) in methanol (40 c.c.) was reduced with hydrogen (uptake 3·99 atoms per molecule during 4–8 hours) in the presence of palladium on

strontium carbonate (5%, 0·25 g) at atmospheric pressure and room temperature. The resulting solution was filtered through sodium sulphate and evaporated, leaving a residue (0·51 g, no colour with formic acid) which crystallised from methanol, giving the *alcohol* (XXIV) (0·30 g, 60%) as needles, m.p. 154–157°, undepressed by the specimen prepared above.

(c) Potassium borohydride (0·3 g) in water (1·5 g) was added to the ketone (X) (1·00 g) suspended in methanol (20 c.c.), the mixture was left overnight at 30° and then treated with water (10 c.c.) added dropwise. After 2 hours the precipitated solid was collected and washed with water, giving 1:2:3:9:10:11"$\beta$"-*hexahydro*-3"$\beta$"-*hydroxy*-7-*methoxy*-8:11"$\beta$"-*dimethyphenanthrene* (XXVIII) (0·83–0·87 g, 82–86%), m.p. 157–160°, which separated from methanol in irregular plates, m.p. 159–161°, $\lambda_{max}^{MeOH}$ 267 m$\mu$ ($\varepsilon$ 15,900). The melting-point of this alcohol was depressed only to 151–155° when this unsaturated alcohol was mixed with an equal weight of the saturated alcohol (XXIV), m.p. 154–157°. The alcohol (XXVIII) (0·80 g) in ethanol (20 c.c.) was reduced with hydrogen (uptake 1·6–1·7 atoms per molecule in 1–2 hours) in the presence of palladium on strontium carbonate (5%, 0·8 g) at atmospheric pressure and room temperature. The resulting solution was filtered through sodium sulphate and evaporated, leaving the alcohol (XXIV) (0·80 g, 99%) m.p. 154–157°, undepressed by the specimens prepared above. The *acetate*, prepared with acetic anhydride in pyridine at room temperature, separated from methanol in needles, m.p. 93–94° (Found: C, 75·5; H, 8·8. $C_{19}H_{26}O_3$ requires C, 75·5; H, 8·7%).

1:2:3:4:9:10:11:12-*Octahydro*-7-*methoxy*-8:11-*dimethyl*-3-*oxophenanthrene* (two isomers, XVII and XXII). (a) The ketone (X) (0·51 g) in toluene (5 c.c.) and ether (15 c.c.) was added to lithium (0·040 g) in liquid ammonia (50 c.c.) and the mixture was stirred (4 hours). After the addition of ammonium chloride (1 g) and evaporation, the product (0·50 g) was isolated with ether and dissolved in boiling methanol (5 c.c.) containing 2 N-hydrochloric acid (1 drop), from which 1:2:3:4:9:10:11"$\beta$":12"$\alpha$"-*octahydro*-3:3:7-*trimethoxy*-8:11"$\beta$"-*dimethylphenanthrene* (the dimethyl ketal of the *trans* ketone XVII) separated in prisms (0·30 g, 50%), m.p. 115–117° (Found: C, 74·9; H, 9·3. $C_{19}H_{28}O_3$ requires C, 75·0; H, 9·3%). The dimethyl ketal (0·195 g)-toluene-*p*-sulphonic acid (0·01 g) and acetone (4 c.c.) were boiled (15 min). When the resulting solution was evaporated to about 2 c.c. and diluted with water (4 c.c.), the trans *ketone* (XVII) separated in stout needles (0·14 g, 85%), m.p. 140–141° (Found: C, 79·0; H, 8·9. $C_{17}H_{22}O_2$ requires C, 79·0; H, 8·6%). The 2:4-*dinitrophenylhydrazone* separated from ethyl acetate in yellow prisms, m.p. 221–223° (Found: C, 63·5; H, 5·9. $C_{23}H_{26}O_5N_4$ requires C, 63·2; H, 6·0%). The crude product from the above reduction, after slow crystallisation from methanol, could be separated by hand-picking, giving the *trans* ketone (XVII) as irregular lumps, m.p. 137–140° (undepressed by a pure specimen), and the *cis* ketone (XXII) which separated from methanol after three crystallisations as plates, m.p. 99–101° (Found: C, 79·2; H, 8·4%). Neither isomer gave any coloration in formic acid.

(b) 1:2:3:4:9:10:11"$\beta$":12"$\alpha$"-Octahydro-3"$\beta$"-hydroxy-7-methoxy-8:11"$\beta$"-dimethylphenanthrene (XXIV) (0·5 g) in pyridine (5 c.c.) was added to chromium trioxide (0·5 g) in pyridine (5 c.c.). After 12 hours ether and water were added and the ethereal layer was evaporated on the water-bath. The residue (mainly pyridine) was diluted with water (10 c.c.) and the product (0·40 g, 80%, pale yellow coloration with formic acid), m.p. 138–140°, was crystallised from methanol, giving the *trans* ketone

(XVII), m.p. 140–141°, undepressed by the specimen prepared above. When the aqueous pyridine mother liquors were diluted again with water, a precipitate formed which gave a strong formic acid colorisation, qualitatively similar to that given by the ketone (X), and which formed a red-brown precipitate with 2:4-dinitrophenylhydrazine but too little material was available for purification.

1:2:3:4:9:10:11"$\beta$":12"$\alpha$"-*Octahydro-7-methoxy-2"$\alpha$"-methoxycarbonyl-8:11"$\beta$"-dimethyl-3-oxophenanthrene* (XVIII). The *trans* ketone (XVII) (0·50 g), sodium methoxide (from sodium, 0·2 g), and methyl carbonate (15 c.c.) were boiled (4 hours). After cooling, aqueous sodium dihydrogen phosphate and ether were added and the organic layer was evaporated, leaving the $\beta$-oxoester (XVIII) (0·60 g, 98%), m.p. 147–150°, which separated from methanol in needles, m.p. 150–151° (Found: C, 72·0; H, 7·9. $C_{19}H_{24}O_4$ requires C, 72·1; H, 7·7%). This $\beta$-oxoester gave a violet colour with methanolic ferric chloride.

1:2:3:4:9:10:11"$\beta$":12"$\alpha$"-*Octahydro-3"$\beta$"-hydroxy-7-methoxy-2"$\alpha$"-methoxycarbonyl-2"$\beta$":8:11"$\beta$"-trimethylphenanthrene* (XXVI). The $\beta$-oxoester (XII) (4·73 g) in tetrahydrofuran (80 c.c.) and methanol (100 c.c.) at 50° was treated with potassium borohydride (3·0 g) in water (10 c.c.) and the mixture was left at 50° (30 min) and at room temperature (12 hours). The reduction was complete when an acidified sample, boiled (1 hour) with an excess of alkali, formed no 2:4-dinitrophenylhydrazone after reacidification. The solution was acidified with acetic acid until no more hydrogen was evolved, evaporated to *c.* 30 c.c., and diluted slowly with boiling water (40 c.c.), and the resulting slurry was left at 100° for 10 min. 1:2:3:9:10:11"$\beta$"-*Hexahydro-3"$\beta$"-hydroxy-7-methoxy-2"$\alpha$"-methoxycarbonyl-2"$\beta$":8:11"$\beta$"-trimethylphenanthrene* (XXIX) was collected (4·25 g, 90%), m.p. 180–182° (with presoftening), and crystallised from chloroform-methanol (1:3) in thick plates, m.p. 182–184°, $\lambda_{max}^{MeOH}$ 265 m$\mu$ ($\varepsilon$ 10,500) (Found: C, 72·5; H, 8·2. $C_{20}H_{26}O_4$ requires C, 72·7; H, 7·9%). In one experiment the yield of crude product was nearly theoretical but the purity was much lower and recrystallisation was necessary before the next reaction. The unsaturated hydroxyester (2·60 g) suspended in ethanol (100 c.c.) was reduced with hydrogen (the uptake could not be measured accurately above room temperature in the apparatus used) in the presence of palladium on strontium carbonate (5%, 2·0 g) during 3 hours at atmospheric pressure and at 50–60°. The mixture was diluted with hot chloroform (100 c.c.) to dissolve the product, and filtered through sodium sulphate, evaporated to *c.* 20 c.c., and left overnight at 0°. The *hydroxyester* (XXVI) (2·20 g, 85%), m.p. 200–202° (with softening at 196°) was collected and then crystallised from chloroform-methanol (1:4) in prisms, m.p. 200–202° (Found: C, 72·2; H, 8·5. $C_{20}H_{28}O_4$ requires C, 72·3; H, 8·5%).

1:2:3:4:9:10:11"$\beta$":12"$\alpha$"-*Octahydro-7-methoxy-2"$\alpha$"-methoxy-carbonyl-2-"$\beta$":8:11"$\beta$"-trimethyl-3-oxophenanthrene* (XIX). (a) The $\beta$-oxoester (XVIII) (0·30 g) in methanol (10 c.c.) was treated successively with sodium methoxide (from sodium, 0·3 g) and methyl iodide (2·5 c.c.) and the mixture was left (12 hours) at room temperature. The resulting solution was shaken with ether and water (containing acetic acid, 3 drops) and the ethereal layer was evaporated under reduced pressure. The residue (0·31 g, no coloration with methanolic ferric chloride), m.p. 130–158°, was crystallised from chloroform-methanol (1:4), giving the 2"$\beta$"-methyl derivative (XIX) (0·17 g, 55%) m.p. 170–174, which then separated from methanol in plates, m.p. 173–175° (Found: C, 72·6; H, 8·0. $C_{20}H_{26}O_4$ requires C, 72·7; H, 7·9%). From the

mother liquors was isolated a small quantity of a substance separating from methanol in prisms, m.p. 168–169·5°, which was almost certainly the 2"α"-methyl ester (XX), although satisfactory analytical figures were not obtained. (Found: C, 71·1; H, 7·6%). (b) The hydroxyester (XXVI) (2·65 g) in pyridine (30 c.c.) at *c.* 30° was added to chromium trioxide (2·5 g) in pyridine (25 c.c.), and the mixture was left (36 hours) at 20°. Ether (40 c.c.) and chloroform (20 c.c.), followed after 5 min by water (50 c.c.), were added and the mixture was filtered. The organic layer was washed with water and evaporated to dryness (100°/15 mm). The residue (2·47 g, 94%), m.p. 169–171·5° (with softening at 162°), crystallised from chloroform-methanol (1:3), giving the β-oxoester (XIX), m.p. 172–174°, undepressed by the specimen prepared above. The crude product gave a weak coloration with formic acid, which was presumably due to a trace of the unsaturated β-ketoester (XII). When the oxidation was stopped after only 12 hours, some of the hydroxyester (XXVI) remained unchanged and could not be completely removed by crystallisation, but a pure product was obtained after treatment with succinic anhydride in pyridine (12 hours at room temperature) and dilute alkali.

1:2:3:4:9:10:11"β":12("α" *and* "β")-*Octahydro-7-methoxy-2"β":8:11"β"-trimethyl 3-oxophenanthrene* (two isomers, XXI and XXIII). (a) 1:2:3:9:10:11"β"-Hexahydro-7-methoxy-2"α":8:11"β"-trimethyl-3-oxophenanthrene (XIV) (0·54 g) in toluene (5 c.c.) and ether (10 c.c.) was added to lithium (0·04 g) in liquid ammonia (100 c.c.). After 2 hours lithium (0·02 g), and after a further 4 hours ammonium chloride (1 g), were added, and the solvents were evaporated. The product, isolated with ether, crystallised from methanol as prisms (0·51 g, 94%), m.p. 109–115°, unchanged by further crystallisation from methanol, and the mixture of ketones were converted into ethylene ketals. Benzene (*c.* 400 c.c.) was slowly distilled during 3 hours from a stirred mixture of the mixed ketones (0·50 g), ethylene glycol (2 c.c.), toluene-*p*-sulphonic acid (0·02 g), and dry benzene (volume maintained at *c.* 50 c.c.). The cooled solution was washed with N-sodium hydrogen carbonate (20 c.c.), dried and evaporated. The residue, under ether-methanol, crystallised after several days, giving the *ethylene ketal* of the *trans* ketone (XXI), which separated from methanol containing pyridine (1 drop) as prisms (0·31 g, 50%), m.p. 100–102° (Found: C, 75·9; H, 8·9. $C_{20}H_{28}O_3$ requires C, 75·9; H, 8·9%). This ketal (0·20 g), acetone (3 c.c.), and 10-N hydrochloric acid (0·05 c.c.) were boiled (15 min) and then treated with water (3 c.c.) added dropwise, giving the trans *ketone* (XXI) (0·155 g, 90%), m.p. 120–125°, which separated from methanol in granules (0·14 g, 80%), m.p. 126–128° (Found: C, 79·4; H, 8·8. $C_{18}H_{24}O_2$ requires C, 79·3; H, 8·8%). The 2:4-*dinitrophenylhydrazone* separated from ethyl acetate in orange needles, m.p. 198–202° (Found: C, 63·6; H, 6·3. $C_{24}H_{28}O_5N_4$ requires C, 63·7; H, 6·2%). The residues from the crystallisation of the ketal were hydrolysed in the same way as the crystalline ketal and the product slowly separated as prisms when seeded with the original mixture of ketones. After trituration with methanol, the prisms, m.p. 95–105°, dissolved readily in boiling methanol and sparingly soluble plates immediately separated, and after two more crystallisations from methanol the 2"ζ"-*methyl* cis *ketone* (XXIII) was obtained in irregular plates (0·03 g, 10%), m.p. 137–140° (Found: C, 78·8; H, 8·7. $C_{18}H_{24}O_2$ requires C, 79·3; H, 8·8%). This specimen showed a weak infra-red absorption band at 1650 $cm^{-1}$ which was presumably due to a small amount of the unreduced ketone (XIV).

(b) Potassium borohydride (0·5 g) in water (3 c.c.) was added to the ketone (XIV)

(0·50 g) in tetrahydrofuran (10 c.c.) and methanol (5 c.c.). The solution was left (12 hours) at 30°, concentrated to *c.* 5 c.c. and then left (4 hours) at 0°. The product (0·40 g), m.p. 135–145°, was collected and crystallised twice from methanol, giving long needles (0·15 g, 30%), m.p. 160–163°, which gave an orange coloration with formic acid but by analysis appeared to be mainly a saturated rather than allylic alcohol. This product (0·12 g), in methanol (5 c.c.), was reduced with hydrogen (uptake 0·26 atoms per molecule) in the presence of palladium on strontium carbonate (5%, 0·10 g) at atmospheric pressure and room temperature. The solution was filtered through sodium sulphate and evaporated. The residue (0·12 g) crystallised from chloroform-methanol (1:4), giving the 2"α"-*methyl*-3"β"-*alcohol* (XXV) (0·11 g, 22%), m.p. 162–163° (Found: C, 78·7; H, 9·6. $C_{18}H_{26}O_2$ requires C, 78·8; H, 9·5%). This alcohol was oxidised by the method used for the alcohol (XXIV), and resulting ketone (XXI) (70%), m.p. 126–128°, was identical with the specimen prepared above (in (a)).

(c) The β-oxoester (XIX) (1·0 g), acetic acid (12·5 c.c.), 10-N hydrochloric acid (5 c.c.), and water (2·5 c.c.) were boiled (16 hours) and then water (10 c.c.) was added dropwise. The brown product, decolorised in benzene with alumina, crystallised from methanol, giving the ketone (XXI) (0·70 g, 85%), m.p. 126–128°, which separated from methanol after two more crystallisations as short prisms, m.p. 126–128°, identical with the specimens prepared before. When the hydrolysis was carried out with alkali, using conditions similar to those suitable for the ester (XII), a colourless and more easily purified product was obtained in 90–95% yield.

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