Synthetic Studies on the Construction of the Fundamental Skeleton of Erythroxydiol X. Syntheses of 3a,10a-Dimethyl-(3aβ,4aα,6aβ,10aα,10bβ)-perhydrocyclopropa[*j*]phenanthrene-5,8-dione and 8α-Benzoyloxy-3a,10a-dimethyl-(3aβ,4aα,6aβ,10aα,10bβ)-perhydrocyclopropa[*j*]phenanthren-3-one

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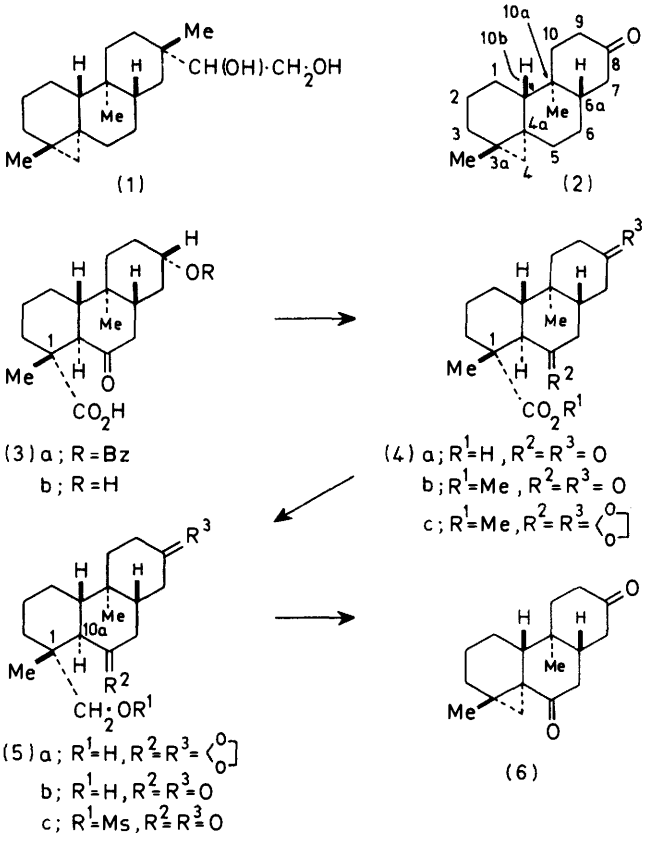
Experiments on the synthesis of the fundamental skeleton (2) of erythroxydiol X (1), a new rosane-type diterpene from *Erythroxylon monogynum*, are described. The cyclopropyl ketones (6) and (9) were synthesised from the tricyclic oxo-acid (3a) and the monomethylated αβ-unsaturated ketone (7), respectively. Contrary to our expectation, reduction of either compound (6) or (9) with lithium aluminium hydride in dioxan did not give the desired compound (2), but the seven-membered ring compound (16), presumably by hydrogenolytic cleavage of the cyclopropane ring.

ERYTHROXYDIOL X[1] (1) is a diterpene which was shown to possess a rosane-type structure containing a cyclopropane ring. In order to elaborate the fundamental skeleton (2) of erythroxydiol X, we first utilised the tricyclic oxo-acid (3a),[2] whose stereochemistry had already been unequivocally established.

On alkaline hydrolysis, compound (3a) † gave the hydroxy-acid (3b), which was then oxidised with Jones reagent [3] to the dioxo-acid (4a). The methyl ester (4b) was transformed into the acetal (4c), which on reduction with lithium aluminium hydride in tetrahydrofuran gave the hydroxy-ketone (5a). Deacetalisation in acetone with hydrochloric acid yielded (5b). In order to construct a cyclopropane ring between C-1 and C-10a, this hydroxy-ketone was converted with methanesulphonyl chloride in pyridine at room temperature into the methanesulphonate (5c), and the latter was refluxed with potassium t-butoxide in t-butyl alcohol. Chromatography over alumina gave the cyclopropyl ketone (6), *m/e* 260 (M^+), in 66% yield. The formation of a cyclopropane ring was clearly demonstrated by the appearance of two carbonyl bands at $\nu_{max.}$ 1 704 (six-membered ring C=O) and 1 646 cm^{-1} (six-membered ring C=O αβ to a cyclopropane ring) [4] in the i.r. spectrum.‡

Since the stereochemistry at C-1 in compound (3a) does not change during the overall sequence (3a) ⟶ (4) ⟶ (5c), the cyclopropane ring in compound (6) should possess the α-configuration, as depicted.

As an alternative approach to compound (2), we considered the monomethylated αβ-unsaturated ketone (7) [5] as a starting material since it is more readily available than compound (3a). On treatment with diethylaluminium cyanide [6] in benzene at room temperature, compound (7) afforded in 80% yield the cyano-ketone (8a). Since these reaction conditions favour a product with the cyano-group axial, the cyano-group in compound (8a) must possess the α (axial)-configuration. In order to protect the carbonyl group at C-2, compound (8a) was further transformed into its acetal (8b). The



† All compounds described here are racemic modifications although only one enantiomer is depicted in the drawings.

‡ In the n.m.r. spectra of those compounds which possess a six-membered ring carbonyl group α to a cyclopropane ring, the cyclopropyl proton signals cannot be observed since they undergo a great downfield shift, due to the anisotropic effect of the carbonyl group, and are hidden in the methylene envelope (see F. Khong-Huu, D. Herlem-Gaulier, MM. Qui Khuong-Huu, E. Stanislas, and R. Goutarel, *Tetrahedron*, 1966, **22**, 3321, and related references).

[1] J. D. Connolly, R. McCrindle, R. D. H. Murray, A. J, Renfrew, K. H. Overton, and A. Melera, *J. Chem. Soc.* (*C*), 1966. 268; G. Ferguson, J. W. B. Fulke, and R. McCrindle, *Chem. Comm.*, 1966, 691.

[2] T. Nakano and A. K. Banerjee, *Tetrahedron*, 1972, **28**, 471.

[3] A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 1953, 2548.

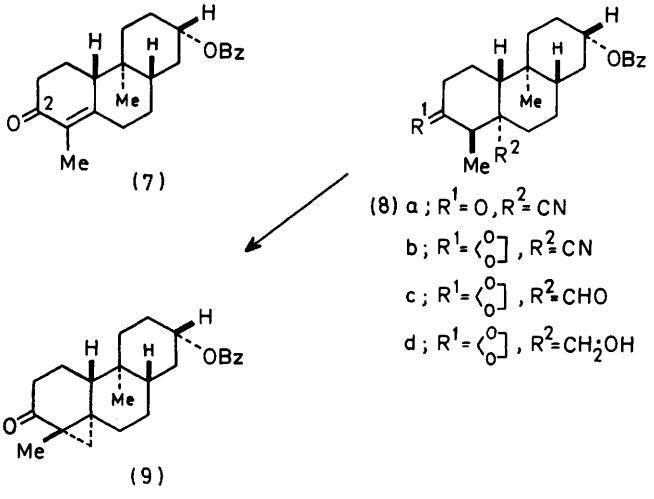
[4] L. J. Bellamy, 'The Infrared Spectra of Complex Molecules,' Methuen, London, 1958, p. 138.

[5] A. K. Banerjee, T. Nakano, and M. C. de Hazos, *Rev. Latinoamericana de Quím.*, 1971, **2**, 135.

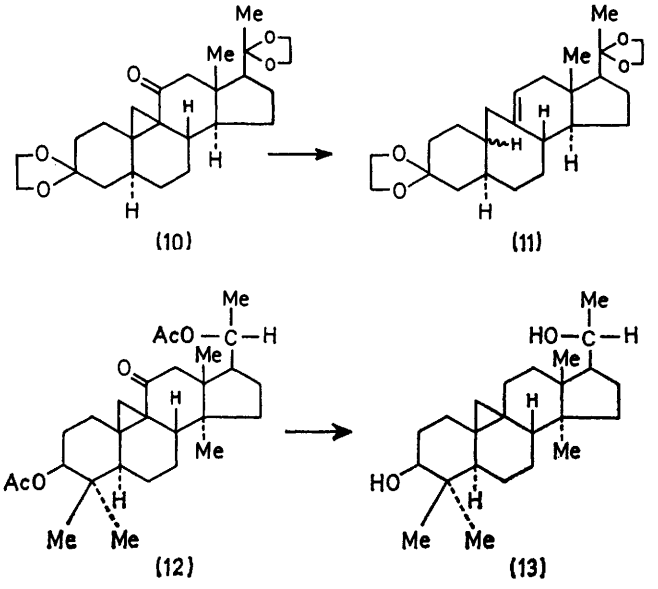
[6] W. Nagata, M. Yoshioka, and S. Hirai, *J. Amer. Chem. Soc.*, 1972, **94**, 4635, and references cited therein. Dr. Nagata kindly provided us with this reagent.

cyano-group in compound (8b) resisted reduction by lithium aluminium hydride, but an imino-alcohol was obtained after refluxing in dioxan with a large excess of reagent for 25 h under nitrogen. The imino-alcohol was not isolated, but was hydrolysed directly with acetic acid–tetrahydrofuran–methanol (1 : 1 : 1) buffered with 5% sodium acetate. After benzoylation of the product, a low-melting aldehyde (8c) was obtained. Subsequent reduction of compound (8c) with sodium borohydride in methanol gave the acetal-alcohol (8d) in 40% overall yield from compound (8a). Compound (8d) was then methylsulphonylated and the product was treated with 3% hydrochloric acid in tetrahydrofuran at room temperature. During this deacetalisation, simultaneous formation of a cyclopropane ring took place,* and the desired cyclopropyl ketone (9), *m/e* 366 (M^+), was obtained, $\nu_{max.}$ 1 712 (benzoate C=O) and 1 672 cm^{-1} (six-membered ring C=O α to a cyclopropane ring).[4]

We were then in a position to attempt to reduce the oxo-group α to the cyclopropane ring in both compounds (6) and (9) without decomposing the three-membered ring. It is known that Wolff–Kishner reduction of a cyclopropyl ketone such as compound (10) causes rupture of the cyclopropane ring to form the olefin (11).[7] As far as we know, the only way to achieve this reduction is by the use of lithium aluminium hydride. This method [8] requires refluxing of the material with a large excess of reagent in dioxan for more than 10 h.



We have previously succeeded in reducing compound (12) to compound (13) [9] by this procedure, and hoped to apply it to the reduction of compounds (9) and (6). Heating compound (9) with a large excess of lithium aluminium hydride in dioxan for 10 h, followed by oxidation of the product with Jones reagent [3] and chromatography over alumina, yielded a ketone, m.p. 119—120°, *m/e* 246 (M^+) in 30% overall yield. The i.r. spectrum



showed a six-membered ring carbonyl band at $\nu_{max.}$ 1 701 cm^{-1}, but no band for C=O α to a cyclopropane ring. The above evidence is in agreement with structure (2). The same ketone was obtained by reducing compound (6) by the same procedure, followed by oxidation with Jones reagent. Identity of the two ketones was established by direct comparison (mixed m.p.; i.r. and mass spectra).† Because of scarcity of material, we did not originally obtain n.m.r. spectra of these ketones, but we have now had an opportunity to examine the spectra. Contrary to expectation, the n.m.r. spectra ‡ did not exhibit any cyclopropyl proton signals, but instead showed one olefinic proton signal at δ 5.76 as a broad multiplet. This indicates that the cyclopropane ring has been ruptured during reduction with lithium aluminium hydride reduction, and a trisubstituted double bond has been formed. Therefore, these ketones do not have structure (2), but may be assigned structure (16). Since Corsano and Nicita [10] have shown that lithium aluminium hydride reduces 11-hydroxycycloartanol acetate in dioxan to cycloartanol, intermediates in this reduction would probably be compounds (14) and (15). It seems that in our case hydrogenolysis of the hydroxy-

* For a similar example, see G. Stork, S. Uyeo, T. Wakamatsu, P. Grieco, and J. Labovitz, *J. Amer. Chem. Soc.*, 1971, **93**, 4945.

† A brief account of this work was presented at the 9th International Symposium on the Chemistry of Natural Products, Ottawa, June 1974.

‡ In the n.m.r. spectra of this type of compound, the cyclopropyl proton signals appear as a characteristic AB quartet between δ 0.0 and 0.6 (see T. Nakano and S. Terao, *J. Chem. Soc.*, 1965, 4512, and related references).

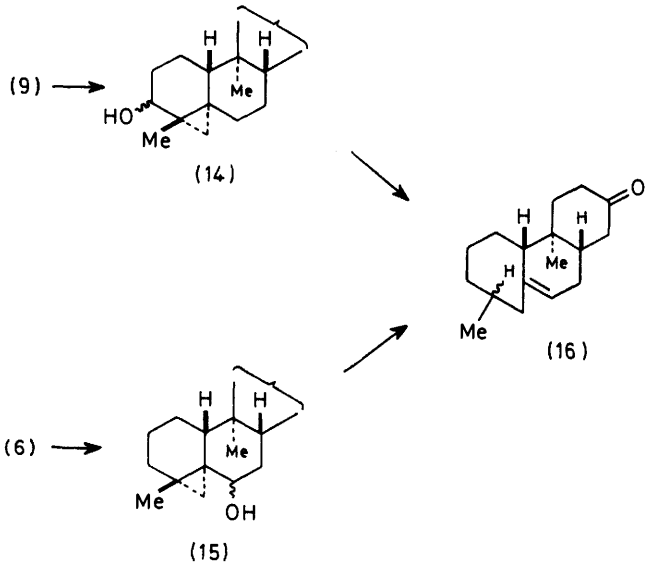
[7] S. M. Kupchan, E. Abushanab, K. T. Shamasundar, and A. W. By, *J. Amer. Chem. Soc.*, 1967, **89**, 6327. Although Overton *et al.* [J. D. Connolly, D. M. Gunn, R. McCrindle, R. D. H. Murray, and K. H. Overton, *J. Chem. Soc.* (*C*), 1967, 668] report that Huang-Minlon reduction of a similar α-cyclopropyl ketone affords the corresponding deoxy-compound, this method would be risky.

[8] D. Herlem-Gaulier, F. Khuong-Huu-Laine, and R. Goutarel, *Bull. Soc. chim. France*, 1966, 3478; S. M. Kupchan, R. M. Kennedy, W. R. Schleigh, and G. Ota, *Tetrahedron*, 1967, **23**, 4563.

[9] T. Nakano, M. Alonso, and A. Martin, *Tetrahedron Letters*, 1970, 4929.

[10] S. Corsano and G. Nicita, *Ricerca Sci.*, 1967, **37**, 351.

group in compounds (14) and (15) would have been accompanied by rupture of the cyclopropane ring. The resulting double bond would then migrate to yield compound (16).*



EXPERIMENTAL

M.p.s were taken with a Kofler hot-stage apparatus. Unless otherwise specified, i.r. spectra were recorded for potassium bromide discs with a Perkin-Elmer 337 spectrometer and n.m.r. spectra with a Varian A-60 spectrometer for solutions in deuteriated chloroform with tetramethylsilane as internal standard. Mass spectra were determined with a Hitachi Perkin-Elmer RMU 6E instrument at 70 eV using a direct inlet system. Microanalyses were carried out by A. Bernhardt Microanalytical Laboratory, 5251 Elbach über Engelskirchen, West Germany.

Alkaline Hydrolysis of the Acid (3a).—The acid (0.54 g) was refluxed with methanolic 10% potassium hydroxide (30 ml) for 5 h. Usual work-up gave *7-hydroxy-1,4b-dimethyl-10-oxoperhydrophenanthrene-1-carboxylic acid* (3b) (0.48 g), m.p. 280—282° (from chloroform), $\nu_{max.}$ 3 430 (OH) and 1 720 cm^{-1} (acid and six-membered ring C=O), *m/e* 294 (M^+) (Found: C, 69.15; H, 8.75. $C_{17}H_{26}O_4$ requires C, 69.35; H, 8.9%).

Oxidation of the Hydroxy-acid (3b).—The hydroxy-acid (0.48 g) in acetone (5 ml) was oxidised with Jones reagent (2 ml) at room temperature for 10 min. After destruction of the excess of oxidant with isopropyl alcohol, the *7,10-dioxo-acid* (4a) (0.42 g), m.p. 283—284° (from chloroform), $\nu_{max.}$ 1 706 (acid C=O) and 1 696 cm^{-1} (six-membered ring C=O), *m/e* 292 (M^+), was obtained (Found: C, 69.65; H, 8.1. $C_{17}H_{24}O_4$ requires C, 69.85; H, 8.25%).

Esterification of the Dioxo-acid (4a).—The dioxo-acid (0.45 g) was treated with ethereal diazomethane to give the *ester* (4b) (0.46 g), m.p. 154—156° (from ether), $\nu_{max.}$ 1 741 (ester C=O) and 1 703 cm^{-1} (six-membered ring C=O), *m/e* 306 (M^+) (Found: C, 70.25; H, 8.4. $C_{18}H_{26}O_4$ requires C, 70.55; H, 8.55%).

Acetalisation of the Ester (4b).—To a solution of the ester (0.41 g) in benzene (150 ml) were added ethylene glycol (10 ml) and toluene-*p*-sulphonic acid (3 mg). The mixture was heated under reflux for 20 h under a water separator. After cooling, the mixture was basified with aqueous 3% sodium hydrogen carbonate and the product was isolated in the usual way. The *diacetal* (4c) (0.39 g) had m.p. 194—195°, *m/e* 394 (M^+) (Found: C, 66.8; H, 8.5. $C_{22}H_{34}O_6$ requires C, 67.0; H, 8.7%).

Reduction of the Acetal (4c).—The acetal (0.35 g) in anhydrous tetrahydrofuran (60 ml) was heated under reflux with lithium aluminium hydride (0.34 g) for 10 h. Water was then added to decompose the excess of reagent, and the complex was treated with aqueous potassium hydroxide. Usual work-up afforded the *acetal-alcohol* (5a) (0.31 g), m.p. 162—163° (from ether–hexane), *m/e* 366 (M^+) (Found: C, 68.55; H, 9.2. $C_{21}H_{34}O_5$ requires C, 68.8; H, 9.35%).

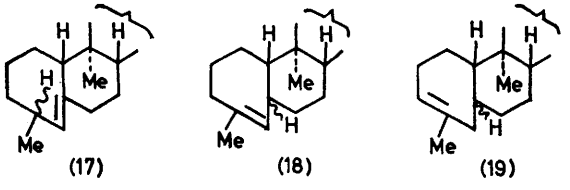
Deacetalisation of the Acetal-alcohol (5a).—The acetal-alcohol (0.31 g) was dissolved in acetone (30 ml) and 10% hydrochloric acid (10 ml) was added. The mixture was stirred at room temperature for 2 h. Usual work-up yielded the hydroxy-ketone (5b) (0.27 g), m.p. 155—156° (from ether–hexane), $\nu_{max.}$ 3 450 (OH) and 1 701 cm^{-1} (six-membered ring C=O), *m/e* 278 (M^+), δ 3.53 and 3.80 (2 H, ABq, *J* 8 Hz, CH_2OH) (Found: C, 73.1; H, 9.25. $C_{17}H_{26}O_3$ requires C, 73.35; H, 9.4%).

Methylsulphonylation of the Hydroxy-ketone (5b).—The hydroxy-ketone (0.20 g) was dissolved in anhydrous pyridine (15 ml) and treated with methanesulphonyl chloride (0.11 g) at room temperature overnight. After the usual work-up, the methanesulphonate (5c) (0.10 g) was obtained; m.p. 197—198° (from dry ether), *m/e* 261 ($M^+ - OSO_2CH_3$).

Synthesis of the Cyclopropyl Ketone (6).—The methanesulphonate (5c) (0.10 g) in anhydrous t-butyl alcohol (15 ml) was treated with potassium t-butoxide (60 mg) in anhydrous t-butyl alcohol (15 ml). The mixture was refluxed for 4 h. Water was then added, and the product was extracted with chloroform. The extract was dried ($MgSO_4$) and evaporated to afford an oily product. Chromatography over Merck standardised alumina (activity II—III) gave *3a,10a-dimethylperhydrocyclopropa[j]phenanthrene-5,8-dione* (6) (40 mg), 270—272° (from ether) (Found: C, 78.3; H, 9.1. $C_{17}H_{24}O_2$ requires C, 78.4; H, 9.3%).

Hydrogenolysis of the Cyclopropyl Ketone (6).—To a solution of the ketone (0.14 g) in dry dioxan (50 ml) was added lithium aluminium hydride (0.1 g), and the mixture

* The evidence on which other plausible structures (17)—(19) are excluded, is as follows. A one proton n.m.r. multiplet at



δ 5.76 is very broad (*ca.* 15 Hz). This indicates that the olefinic proton responsible possesses a maximal number of neighbouring protons three bonds removed, since in general $^3J \gg {}^4J$. In order to satisfy this requirement, only structures (16) and (19) are possible. Furthermore, in the case of structure (19), the methyl group on the double bond would be expected to resonate at rather low field (δ 1.5—1.6). However, such a signal is absent in the spectrum. It is not certain whether the olefin (16) was formed on working up the lithium aluminium hydride reduction product or during subsequent Jones oxidation.

was refluxed for 15 h. The excess of reagent was decomposed with water, and the complex was treated with aqueous potassium hydroxide. The organic extract was dried ($MgSO_4$) and evaporated, yielding a yellowish oil. This was dissolved in acetone (5 ml) and oxidised with Jones reagent (2 ml) at room temperature for 10 min. After the usual work-up, the resulting semi-solid was purified by chromatography over Merck standardised alumina (activity II—III). Elution with benzene–ether (8 : 1) afforded 8,11b-*dimethyl*-$\Delta^{6,6a}$-*dodecahydrocyclohepta*[a]*phenanthren*-3-*one* (16) (22 mg), m.p. 119—120° (from ether), *m/e* 246 (M^+) (Found: C, 82.7; H, 10.45. $C_{17}H_{26}O$ requires C, 82.85; 10.65%).

Hydrocyanation of the Monomethylated αβ-unsaturated Ketone (7).—*With diethylaluminium cyanide.* To a solution of the ketone (0.27 g) in dry benzene (15 ml) was added a solution of diethylaluminium cyanide in dry benzene (1.3M; 3 ml). The solution was stirred at room temperature for 1 h, and then treated with ice-cooled aqueous 8% sodium hydroxide (5 ml). The alkaline solution was extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated. Trituration of the oily residue with ether afforded the *cyano-ketone* (8a) (0.18 g), m.p. 234—235° (from chloroform), *m/e* 379 (M^+), $\nu_{max.}$ 2 240 (C≡N), 1 720 (unresolved ketonic and benzoate C=O), and 1 280 cm^{-1} (benzoate C–O) (Found: C, 75.65; H, 7.55; N, 3.5. $C_{24}H_{29}NO_3$ requires C, 75.95; H, 7.7; N, 3.7%).

With potassium cyanide. The ketone (0.80 g) in ethanol (80 ml) was treated with potassium cyanide (3 g) in water (15 ml). The solution was then refluxed for 20 h. Usual work-up afforded a gummy material which after benzoylation was chromatographed over Merck standardised alumina (activity II—III). Elution with hexane–benzene (7 : 3) gave the ketone (7) (0.78 g). Further elution with ether yielded the cyano-ketone (3 mg), identical with that obtained by the diethylaluminium cyanide method.

Acetalisation of the Cyano-ketone (8a).—To a solution of the cyano-ketone (0.35 g) in benzene (150 ml) were added ethylene glycol (20 ml) and toluene-*p*-sulphonic acid (2 mg). The mixture was heated at reflux temperature for 30 h under a water separator. Then aqueous 2% potassium hydrogen carbonate was added, and the alkaline solution was extracted with chloroform. The usual work-up gave the *acetal* (8b) (0.23 g), m.p. 242—244° (from chloroform), *m/e* 423 (M^+) (Found: C, 73.55; H, 7.65. $C_{26}H_{33}NO_4$ requires C, 73.75; H, 7.85%).

Preparation of the Aldehyde (8c).—The acetal (0.47 g) in dry dioxan (90 ml) was heated under reflux with lithium aluminium hydride (1.14 g) for 25 h under nitrogen. The excess of reagent was destroyed with water, and aqueous potassium hydroxide was added. Usual work-up afforded a yellow oil (0.51 g). This crude imino-alcohol was stirred with acetic acid–tetrahydrofuran–methanol (1 : 1 : 1; 25 ml) buffered with 5% sodium acetate at room temperature overnight. Water (20 ml) was then added, and the product was extracted with chloroform. The extract was dried ($MgSO_4$) and evaporated. The oily material thus obtained was benzoylated to afford the *aldehyde* (8c) (85 mg) as a semi-solid, *m/e* 397 (M^+ — CHO) (Found: C, 72.95; H, 7.85. $C_{26}H_{34}O_5$ requires C, 73.2; H, 8.05%).

Increasing the quantity of lithium aluminium hydride or the time of refluxing did not give a better yield of the imino-alcohol.

Reduction of the Aldehyde (8c).—The aldehyde (50 mg) in methanol (30 ml) was treated with sodium borohydride (20 mg) at room temperature overnight to give the *alcohol* (8d) (30 mg), m.p. 218—220° (from ether), *m/e* 428 (M^+) and 397 (M^+ — CH_2OH) (Found: C, 72.65; H, 8.3. $C_{26}H_{36}O_5$ requires C, 72.85; H, 8.45%).

Synthesis of the Cyclopropyl Ketone (9).—The alcohol (8d) (0.12 g) in pyridine (10 ml) was treated with methanesulphonyl chloride (2 ml) at room temperature overnight. The precipitated pyridine hydrochloride was filtered off and the organic solution was concentrated under reduced pressure. The methanesulphonate was obtained as a semi-solid (0.14 g), which without purification was stirred with 3% hydrochloric acid in tetrahydrofuran (30 ml) at room temperature overnight. Water was then added, and the product was extracted with chloroform. Removal of the solvent left a semi-solid (0.12 g). This was benzoylated with benzoyl chloride–pyridine at room temperature. The usual work-up gave 8-*benzoyloxy*-3a,10a-*dimethylperhydrocyclopropa*[j]*phenanthren*-3-*one* (9) (50 mg), m.p. 188—189° (from ether) (Found: C, 78.4; H, 8.05. $C_{24}H_{30}O_3$ requires C, 78.65; H, 8.25%).

Hydrogenolysis of the Cyclopropyl Ketone (9).—To a solution of the ketone (0.15 g) in dry dioxan (100 ml) was added lithium aluminium hydride (0.63 g), and the mixture was refluxed for 10 h. The excess of reagent was decomposed with water, and aqueous potassium hydroxide was added. The organic layer was dried ($MgSO_4$) and evaporated. The gummy material thus obtained was dissolved in acetone (10 ml) and oxidised with Jones reagent. After the usual work-up, the product was obtained as an oil, which was chromatographed over Merck standardised alumina (activity II—III). Elution with benzene–ether (9 : 1) yielded the ketone (16) (28 mg), m.p. 118—120° (from ether), identical with that obtained previously.

We thank Mrs. M. C. de Hazos for determinations of the i.r., n.m.r., and mass spectra.

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