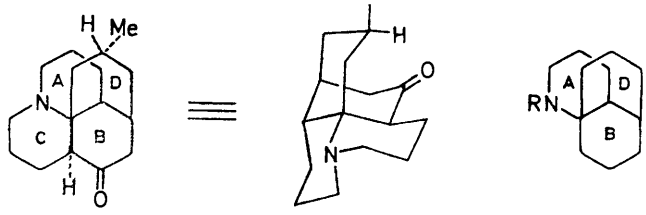
Bridged Ring Systems. Part XVI.[1] A Synthetic Approach to Lycopodium Alkaloids [2]

By **E. W. Colvin, J. Martin, W. Parker, R. A. Raphael,* B. Shroot,** and (in part) **M. Doyle,** Department of Chemistry, The University of Glasgow, Glasgow, G12 8QQ

A novel ring annelation technique has been devised to convert 9-oxobicyclo[3,3,1]non-3-ene-1-carboxylic acid (3; R = CO_2H) into *N*-acetyl-2-azatricyclo[5,3,3,$0^{1,6}$]tridecane (2; R = Ac), which comprises three rings of the tetracyclic system of lycopodine (1). Further progress towards the application of this annelation to a stereoselective synthesis of lycopodine is described.

CONSIDERABLE efforts have been made in recent years to provide synthetic routes to the lycopodium alkaloids.[3] In particular Stork [4] and Ayer [5] have achieved the total synthesis of lycopodine (1) while a synthesis of the *epi*-isomer has been described by Wiesner.[6] In devising an alternative, stereoselective, multipurpose route to a variety of these alkaloids, we considered rings A and C as addends to a preformed bicyclo[3,3,1]-nonane, principally because of our previous experience of the chemistry of this bridged-ring system.[7] As a model experiment, our first aim was to construct the hitherto unknown 5,8a-propanoperhydroquinoline system (2) from readily available starting materials.



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The ethyl ester (3; R = CO_2Et), when prepared by the method of Cope and Synerholm,[8] has been shown by us [9] to contain about 20% of the Δ^2-isomer. Since removal of the latter was tedious, and its presence was not expected to affect our conclusions from model experiments, the isomeric mixture was chosen as suitable starting material (for brevity only 3-ene structures are shown). The keto-ester was converted into the acetal ester (4; R = CO_2Et), and then into the acetal acid (4; R = CO_2H) by standard methods. Treatment of the acid with methyl-lithium in ether gave the methyl ketone (4; R = COMe) in high yield. The corresponding oxime (5; R = H), which for obvious steric reasons should have the *syn*-methyl configuration, was prepared in the usual manner, and converted by treatment with sodium hydride, followed by toluene-*p*-sulphonyl chloride, into the oxime toluene-*p*-sulphonate (5; R = $SO_2 \cdot C_6H_4Me$). The unstable toluene-*p*-sulphonate, when heated in aqueous ethanol, underwent simultaneous rearrangement and acetal hydrolysis to give the *N*-acetylamino-ketone (3; R = NHAc), in only 20% yield.

Although the product had the required C-1 nitrogen substitution, the low yield in the Beckmann rearrangement made an alternative method more attractive. The acid [8,9] (3; R = CO_2H) was converted, *via* the mixed anhydride [10] (3; R = $CO \cdot O \cdot CO_2Et$), into the azide (3; R = $CO \cdot N_3$). Curtius rearrangement of the azide in toluene at 100° produced the isocyanate (3; R = NCO), which by direct treatment with benzyl alcohol was converted into the benzyl carbamate (3;

[1] Part XV, W. Parker, R. A. Raphael, and J. S. Roberts, *J. Chem. Soc.* (*C*), 1969, 2634.

[2] Preliminary communication of part of this work, E. W. Colvin, J. Martin, W. Parker, and R. A. Raphael, *Chem. Comm.*, 1966, 596. The methods described have since been utilised by Z. Horii, S. Kim, T. Imanishi, and I. Ninomiya, *Chem. and Pharm. Bull.* (*Japan*), 1968, **16**, 2107.

[3] K. Wiesner, *Fortschr. Chem. org. Naturstoffe*, 1962, **20**, 271.

[4] G. Stork, R. A. Kretchmer, and R. H. Schlessinger, *J. Amer. Chem. Soc.*, 1968, **90**, 1647.

[5] W. A. Ayer, W. Russell Bowman, T. C. Joseph, and P. Smith, *J. Amer. Chem. Soc.*, 1968, **90**, 1648.

[6] H. Dugas, M. E. Hazenberg, Z. Valenta, and K. Wiesner, *Tetrahedron Letters*, 1967, 4937.

[7] *Cf.* previous Parts of this series, in particular, P. Doyle, I. R. Maclean, R. D. H. Murray, W. Parker, and R. A. Raphael, *J. Chem. Soc.*, 1965, 1344; J. Martin, W. Parker, and R. A. Raphael, *J. Chem. Soc.* (*C*), 1967, 348.

[8] A. C. Cope and M. E. Synerholm, *J. Amer. Chem. Soc.*, 1950, **72**, 5228.

[9] E. W. Colvin and W. Parker, *J. Chem. Soc.*, 1965, 5764.

[10] J. Weinstock, *J. Org. Chem.*, 1961, **26**, 3511; A. Burger and W. E. Coyne, *ibid.*, 1964, **29**, 3079.

R = NH·CO_2·CH_2Ph) in 80% yield from the acid (3; R = CO_2H). Catalytic hydrogenation of the benzyl carbamate over palladium–charcoal gave a single crystalline product presumed to be the dimeric diamino-diol (6) on the basis of the i.r. data [$\nu_{max.}$ (Nujol) 3300, 3260, and 3200—3150 cm^{-1}; no absorption around 1700 cm^{-1}]. The mass spectrum of this material showed a parent ion at *m/e* 153, but it is not unlikely that thermal dissociation to the amino-ketone (dihydro-3; R = NH_2) would occur prior to electron impact. In any event, the monomeric amino-ketone could not be isolated after catalytic hydrogenation of the benzyl carbamate, and an alternative method of removal of the benzyloxycarbonyl group was sought.

Treatment of the benzyl carbamate (3; R = NH·CO_2·CH_2Ph) with hydrogen bromide in glacial acetic acid [11] gave the crystalline amine hydrobromide (7) in almost quantitative yield. This salt could be stored indefinitely and the free amine liberated *in situ* during projected acylations, thereby avoiding dimerisation to the diamino-diol (6). No rearrangement had occurred under the strongly acidic conditions used to cleave the benzyl carbamate, since the hydrobromide (7) was converted into the *N*-acetylamino-ketone (3; R = NHAc) described before by treatment with acetic anhydride in pyridine.

The construction of the third ring on structure (7) was envisaged as requiring a three-carbon fragment capable of acylating the amino-group, and of condensing with the 9-carbonyl function. The pyruvyl group was chosen, and the acylation initially accomplished by forming the mixed anhydride [12] of pyruvic acid and ethyl hydrogen carbonate (from the reaction of pyruvic acid and ethyl chloroformate in chloroform solution containing triethylamine), adding to this the hydrobromide (7), and finally adding enough triethylamine to liberate free amino-ketone (3; R = NH_2) *in situ*. In this way, dimerisation of the amino-ketone was avoided, and the desired crystalline pyruvylamino-ketone (3; R = NH·CO·COMe) was obtained in 40% yield. Attack of nitrogen at the alternative mixed anhydride carbonyl centre [13] was seriously competitive however, since a similar amount of the ethyl carbamate (3; R = NH·CO_2Et) was also formed. A marked improvement in yield was observed when pyruvic acid, activated by treatment with phosphoryl chloride,[14] was used in place of the carbonate mixed anhydride. Reaction of the hydrobromide (7) with this active intermediate in the presence of triethylamine afforded the same pyruvylamino-ketone (3; R = NH·CO·COMe) in 90% yield.

The cyclisation to the tricyclic enone-lactam (8) was difficult. The u.v. spectrum of the pyruvylamino-ketone (3; R = NH·CO·COMe) in ethanolic base showed a hyposochromic shift from 275 to 255 nm, with an increase in intensity, during 30 min. Similar treatment with base was applied on a larger scale, but after apparent reaction, only starting material was recovered. These observations could be accommodated by *reversible* aldol cyclisation of (3; R = NH·CO·CO-Me) to the tricyclic dione (9). Other unsuccessful cyclisation procedures included the use of toluene-*p*-sulphonic acid in benzene, triethylamine benzoate in benzene, and methylsulphinyl carbanion in dimethyl sulphoxide.

Ultimately, efficient conversion of (3; R = NH·CO·-COMe) into the crystalline enone-lactam (8) was achieved with sodium hydride in carefully dried tetrahydrofuran. Reproducible yields of *ca.* 70% could be obtained, provided the reaction conditions were strictly controlled. Although the unique polyfunctional heterocyclic ring in (8) had the potential for the construction of variously substituted alkaloids, our immediate aim was to produce the basic propanoperhydroquinoline (2), and to that end various reductive methods were applied.

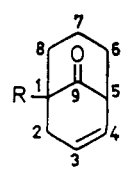
Catalytic hydrogenation of the enone lactam (8) afforded a mixture of the oxo- and hydroxy-lactams, (10) and (11; R = H) respectively, which was further reduced to the pure hydroxy-lactam (11; R = H) by treatment with sodium borohydride. The corresponding acetate (11; R = Ac) was recovered unchanged from zinc–acetic acid, indicating that a lactam carbonyl cannot replace a ketonic carbonyl group in the normal α-acetoxy-ketone reduction with zinc. Of other reductive methods applied to the lactam (8), treatment with lithium aluminium hydride, and reaction with lithium in liquid ammonia both produced complex and intractable mixtures whereas sodium borohydride converted the enone lactam smoothly into the hydroxy-lactam (12; R = H).

A radically different method was devised, *via* the lactim ether (13), obtained in 85% yield by treatment of the enone lactam (8) with triethyloxonium fluoroborate [15] in dichloromethane. By reduction with lithium aluminium hydride, this lactim ether was quantitatively converted into the β-hydroxy-amine (14; $R^1 = R^2 = H$), whose analytical and spectroscopic properties were consistent with the structure assigned. The hydroxy-amine was readily converted into the diacetate (14; $R^1 = R^2 = Ac$).

The remaining task, of reducing the diacetate (14; $R^1 = R^2 = Ac$) to the propanoperhydroquinoline (2; R = Ac), was neatly solved after several exploratory experiments. The necessary combination of allylic *O*-acetate hydrogenolysis and double bond hydrogenation was achieved with palladium–charcoal in ethanol containing perchloric acid, and the diacetate (14; $R^1 = R^2 = Ac$) was converted into the desired, fully hydrogenated *N*-acetylamine (2) in quantitative yield. Thus the enone lactam (8) could be converted into the fully saturated amine (2) in four very efficient and experimentally straightforward steps.

[11] D. Ben-Ishai and A. Berger, *J. Org. Chem.*, 1952, **17**, 1564.
[12] J. R. Vaughan, *J. Amer. Chem. Soc.*, 1951, **73**, 3547.
[13] N. F. Albertson, *Org. Reactions*, 1962, **12**, 183.
[14] B. Heinke and T. Wieland, *Annalen*, 1956, **599**, 70.
[15] G. Hinz, P. Hofman, F. Kroning, H. Meerwein, and E. Pfeil, *J. prakt. Chem.*, 1937, **147**, 257.

A separate check on the course of the hydrogenation to (2) was carried out by specific hydrolysis of the *O*-acetate (14; $R^1 = R^2 = Ac$) to obtain the allylic alcohol (14; $R^1 = Ac$, $R^2 = H$), oxidation of the latter,



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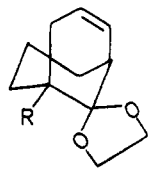

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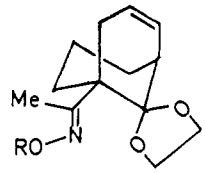

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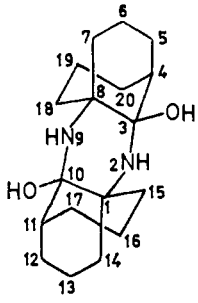

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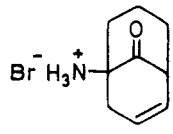

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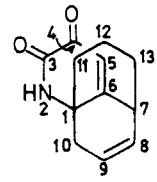

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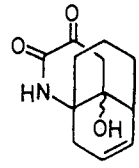

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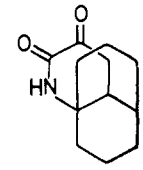

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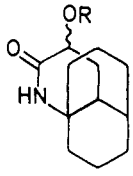

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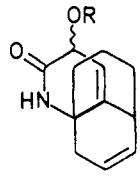

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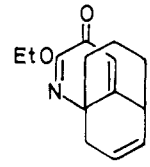

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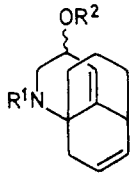

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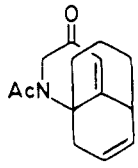

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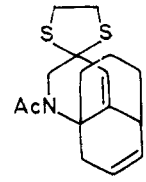


(16)

with chromium trioxide, to the enone (15), thioacetalisation of the newly created carbonyl group to give (16), and Raney nickel desulphurisation of (16), followed by exhaustive catalytic hydrogenation. This series of reactions produced one pure crystalline product, identical with the perhydroquinoline (2; R = Ac) obtained before by the more direct route from (14; $R^1 = R^2 = Ac$).

Through the successful conclusion of the model experiments a feasible route from the simple bicyclo-[3,3,1]nonane derivative (3; $R = CO_2H$) to the *N*-acetate (2) containing three of the four rings of lycopodine (1) had now been established in a non-stereospecific manner. The functionality created in intermediates such as the enone lactam (8), however, should allow both the steric control necessary for a total synthesis of lycopodine and the substituent control desirable in a versatile route with several other lycopodium alkaloids [3] in view.

Attention was then turned to the construction of a more complex analogue of (3; $R = CO_2H$), capable of elaboration to lycopodine itself; the tricyclic keto-acid (25; R = H) was chosen as the immediate synthetic target. The aromatic portion, amenable to reduction with metal–ammonia, could be regarded as a potential source of a propionic acid side chain attached to C-2 (after oxidative cleavage of the 6,7-bond), which would eventually be coupled to a nitrogen substituent at C-1 to provide ring c of lycopodine (1). In addition, this scheme would also create the necessary carbonyl function at C-7. Finally we hoped that the spatial relationship of the aromatic ring to substituents at C-11 might provide an interesting bonus. From examination of stereomodels of (25) and the epimeric (26) it was predicted that the aromatic ring should affect the ^1H n.m.r. chemical shifts of 11-substituents, thus providing an internal probe for diagnosis of stereochemistry at that centre in later synthetic intermediates.

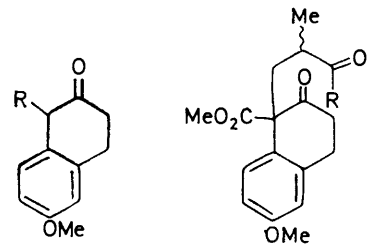
The obvious starting point for the synthesis of the keto-acid (25; R = H) was 6-methoxy-2-tetralone (17; R = H), recently made available in quantity as a result of the work of Darling and Kidwell.[16] This was converted into the methyl 1-carboxylate (17; $R = CO_2Me$) by treatment with sodium hydride in dimethyl carbonate, a method [17] which avoids the usual problem of the production of mixed 1- and 3-alkoxycarbonylations of 2-tetralones. Condensation of the ester (17; $R = CO_2Me$) with methacrylaldehyde, followed by acid-catalysed cyclisation of the resultant keto-aldehydes (18; R = H), afforded a mixture of epimeric ketols (19; R = H) in high yield. G.l.c. of the corresponding acetates (19; R = Ac) revealed the presence of four components in the ratio 1 : 1 : 1·5 : 2·5. At this stage, no one peak could be assigned to any of the four possible isomers, but since the reaction was carried out under equilibrating conditions, it was expected that the most abundant isomer would possess both the 11-methyl and the 10-oxygen functions in the thermodynamically more stable equatorial environments. The four ketols, on oxidation with Jones reagent, furnished a mixture of the diones (22), which consisted of two components as indicated by t.l.c.

It was decided to dehydrate the four epimeric ketols (19; R = H) to the single olefin (23; R = Me), which would provide a means of controlling the stereochemistry at C-11. Pyrolysis on a small scale of the keto-acetates (19; R = Ac) produced small amounts of the olefin (23; R = Me), but in larger scale reactions, the bulk of material proved to be starting material, along with

[16] S. D. Darling and R. L. Kidwell, *Tetrahedron Letters*, 1966, 531.

[17] E. W. Colvin, J. Martin, and B. Shroot, *Chem. and Ind.*, 1966, 2130.

completely degraded fragments. After several modifications of the conditions (temperature, solvent, powdered glass and zinc oxide as additives, *etc.*) decomposition was still extensive. Pyrolysis of the corresponding ethyl carbonates (19; R = CO_2Et) was then studied. The optimum yield of the olefin was obtained, in small scale runs, when the carbonate esters were heated at 350° for 15 min. Here again, however, the optimum results could not be sustained in large scale experiments.



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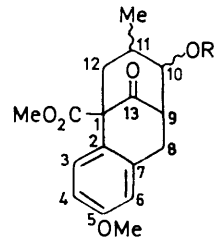

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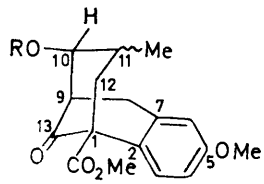

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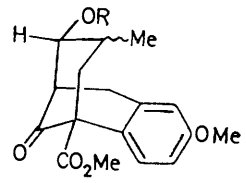

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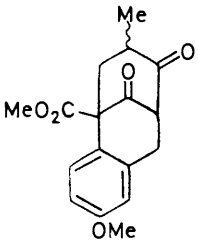

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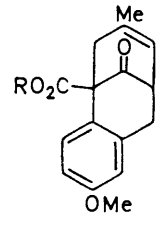

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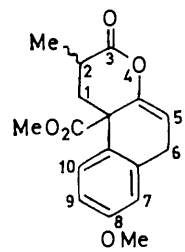

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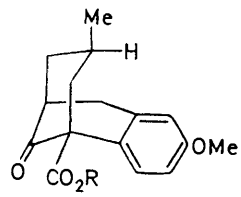

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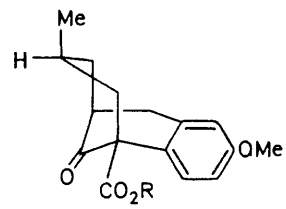

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It became apparent that milder conditions would be necessary to effect the desired elimination in acceptable yields, and the solvolytic behaviour of the four epimeric toluene-*p*-sulphonates (19; R = $SO_2 \cdot C_6H_4Me$) was investigated.

In order to gain some insight into the stereochemical course of toluene-*p*-sulphonic acid eliminations, the separate pairs of axial (20; R = H) and equatorial (21; R = H) ketols were prepared, and their corresponding pairs of toluene-*p*-sulphonate esters examined separately ('axial' and 'equatorial' refer to the 10-hydroxy-configuration).

The preparation of the axial ketols (20; R = H) was carried out by the general procedure previously described,[18] and known to be stereoselective. Reduction with lithium hydridotri-t-butoxyaluminate of the enol lactone (24) of the keto-acid (18; R = OH), obtained by oxidation of the keto-aldehyde (18; R = H), produced a ketol mixture (20; R = H). Analysis of the products (by g.l.c. of the acetates) indicated two components in a 1 : 1 ratio. These ketols were converted into the corresponding toluene-*p*-sulphonates, which were heated under reflux in 10% aqueous acetic acid, to produce, as sole product, an acidic material, which on treatment with diazomethane, gave the olefin (23; R = Me), identical with the material formed in the pyrolysis experiments.

Again by analogy with results obtained with simpler bicyclo[3,3,1]nonanes,[18] the diones (22), on reduction with lithium hydridotri-t-butoxyaluminate, yielded the pair of equatorial ketols (21; R = H) in the ratio of 1 : 1 as indicated by g.l.c. analysis of the acetates. Co-injection experiments established that the ketols formed by dione reduction did not correspond to the pair of ketols formed by reductive rearrangement of the enol lactone (24), but did enhance the intensity of the remaining two peaks observed in the four-component mixture from the original keto-aldehyde cyclisation. The equatorial toluene-*p*-sulphonates (21; R = $SO_2 \cdot C_6H_4Me$) were solvolysed in aqueous 10% acetic acid, and produced mainly ketol 15 along with a small amount of olefin acid (23; R = H). Acetylation of a portion of the crude product (after diazomethane treatment), followed by g.l.c. analysis, indicated the presence of two components (1 : 1). It therefore appears that under these conditions the equatorial toluene-*p*-sulphonate (21; R = $SO_2 \cdot C_6H_4Me$) was solvolysed with retention of configuration to give the corresponding alcohols.

When the mixture of all four toluene-*p*-sulphonates (19; R = $SO_2 \cdot C_6H_4Me$) was treated with aqueous acetic acid, the olefin (23; R = H) was obtained in 30% yield, along with ketols. In dry, buffered acetic acid–sodium acetate, however, the mixture of toluene-*p*-sulphonates gave the desired olefin in 65% yield, after removal of the unwanted acetate by column chromatography (a gratifying solution to this important step, particularly in the light of the unfavourable nature of the pyrolytic procedures).

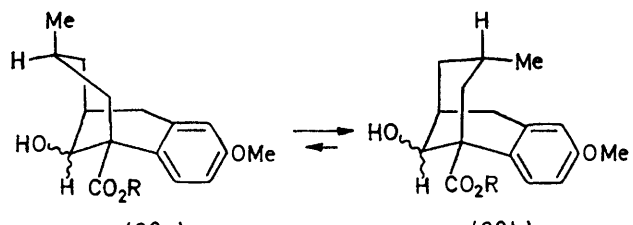
With the olefin (23; R = Me) obtained in good yield, an obvious choice for stereochemical control in creating a tetrahedral centre at C-11 was catalytic hydrogenation. Reduction over 10% palladium–charcoal in 95% ethanol afforded a three-component mixture, which exhibited some hydroxy-absorption in the i.r., indicating partial reduction of the 13-carbonyl group in addition to

[18] J. Martin, W. Parker, B. Shroot, and T. Stewart, *J. Chem. Soc.* (*C*), 1967, 101.

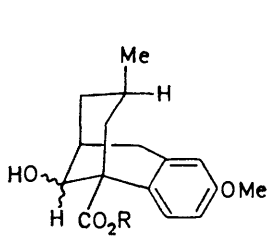
double-bond hydrogenation. Accordingly, the crude product was oxidised with Jones reagent to yield a mixture of the saturated keto-esters (25; R = Me) and (26; R = Me) in approximately equal amounts. [The stereochemical conclusions assumed here, and the reasons for representing the saturated ring in (26) in the boat form, will be discussed later.]

In order to induce some steric specificity in the direction of double-bond hydrogenation, the reduction of the olefin (23) was carried out with a lower catalyst concentration in absolute ethanol as solvent. Use of 5% palladium–charcoal afforded the ketones (25; R = Me) and (26; R = Me) in the ratio 10 : 1 (after oxidation of the crude hydrogenation product with Jones reagent); two crystallisations afforded the pure saturated ketone (25; R = Me). In the ^{1}H n.m.r. spectra (100 MHz) of the ketone and the corresponding alcohols (27; R = Me) (obtained by borohydride reduction), the 11-methyl protons were revealed as a doublet (3H) centred at τ 9·2 (J 6 Hz).

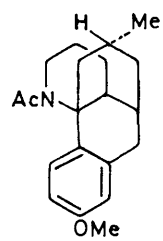
When the olefin (23; R = Me) was catalytically reduced over 5% rhodium–charcoal in ethyl acetate solution, a second single ketone (26; R = Me) was obtained, a striking stereochemical complement to the result of palladium-catalysed reduction. The ^{1}H n.m.r. spectrum (100 MHz) of this epimer revealed the 11-methyl signal as a doublet (3H), again centred at τ 9·2 (J 6 Hz). *However, the corresponding alcohols* (28a, b; R = Me), *obtained by borohydride reduction, showed the* 11-*methyl signal as a doublet* (3*H*) *centred at* τ 9·6. This very striking upfield shift of 0·4 p.p.m. can only be explained by assuming that the ketone (26; R = Me) exists in the boat conformation depicted, in which the 11-methyl group has a normal magnetic environment. Reduction at C-13 to a tetrahedral centre (28a; R = Me) must create a sufficiently serious



(28a) (28b)



(27)



(29)

flagpole H–H or H–OH interaction to force the saturated ring into a chair conformation (28b; R = Me). In turn, the 11-methyl group would then be forced over the aromatic ring, the shielding effect of which is reflected in the abnormally high-field methyl signal in the ^{1}H n.m.r. spectrum. The members (25) and (27) of the epimeric series contain, as expected, the 11-methyl group in an unexceptional magnetic environment throughout, and therefore the methyl doublet signals occur at normal positions.

From a synthetic angle, the above results established that the keto-ester (25; R = Me), having the correct stereochemistry at C-11, *i.e.* equatorial methyl, was readily obtainable by selective catalytic hydrogenation of olefin (23; R = Me). Finally, normal basic hydrolysis of the keto-ester afforded the crystalline keto-acid (25; R = H), the analogue of the model compound (3; R = CO_2H) used in the earlier ring-annelation experiments. Parallel elaboration of the keto-acid (25; R = H) to the tetracyclic analogue of the perhydroquinoline (2), *viz.* (29), is under way. The latter compound should be amenable to conversion into lycopodine (1) as outlined earlier, and progress along these lines will be described in a subsequent publication.

EXPERIMENTAL

M.p.s were recorded on a Kofler hot-stage apparatus and are corrected; b.p.s are uncorrected. T.l.c. plates were prepared from Kieselgel G (Merck); preparative plates were 1 mm thick. Analytical g.l.c. was performed on a Pye Argon Chromatograph. All organic extracts were dried over anhydrous $MgSO_4$.

Mass spectra were determined on an A.E.I. MS9 spectrometer. U.v. absorption spectra refer to ethanolic solutions, and were measured with a Unicam SP800 instrument; 'base' refers to the addition of 3 drops of 4N-sodium hydroxide to both the sample and reference cells. Routine i.r. spectra were measured on a Unicam SP200 instrument, and for high resolution spectra, on a Unicam SP 100 double-beam i.r. spectrophotometer equipped with an SP 130 sodium chloride prism-grating double-monochromator, operated under vacuum. ^{1}H N.m.r. spectra were measured on a Perkin-Elmer 60 MHz instrument, equipped with an integrator. The samples were run in carbon tetrachloride or deuteriochloroform solution, with tetramethylsilane as internal reference.

Ethyl 1-(2-*Formylethyl*)-2-*oxocyclohexane*-1-*carboxylate*.—This compound was prepared by the method of Cope and Synerholm.[8]

Ethyl 9-*Oxobicyclo*[3,3,1]*non*-3- *and* -2-*ene*-1-*carboxylate* (3; R = CO_2Et).—The foregoing keto-aldehyde (48 g) was added, as fine droplets with vigorous stirring, to concentrated sulphuric acid (96 ml), cooled in an ice–salt bath. The mixture was left at room temperature for 4 h, and then poured onto ice; the product separated as a non-filterable semi-solid. The total mixture was extracted twice with ether, the ethereal extracts were combined, washed with saturated sodium hydrogen carbonate solution and brine, and dried. (Acidification of the basic washings afforded solely 2-oxocyclohexanecarboxylic acid.) Removal of solvent under reduced pressure afforded a brown solid (27 g). Chromatography on alumina (Spence H; 150 g) gave pale yellow crystals (26 g), m.p. 46—47·5°. T.l.c. of these (150 mg) with 10% ethyl acetate–light petroleum (b.p. 60—80°) separated the two isomers; the 3-*ene* sub-

limed as needles (99·4 mg), m.p. 45—45·5°, $\nu_{max.}$ (Nujol) 3100, 1740, 1715, 1660, 720, and 695 cm^{-1} (Found: C, 68·9; H, 7·75. $C_{12}H_{16}O_3$ requires C, 69·2; H, 7·75%), and the 2-*ene* sublimed as needles (21·7 mg), m.p. 58·5—59·5°, $\nu_{max.}$ (Nujol) 3100, 1735, 1715, 1660, and 720 cm^{-1} (Found: C, 69·35; H, 7·75%).

The accurate ratio of 3- to 2-ene was determined by evaluation of peak areas on g.l.c. analysis, and was 4·7 : 1.

A solution of the pure 3-ene isomer (100 mg) and hydrazine hydrate (100%, 0·1 ml) in ethanol (5 ml) was heated under reflux for 24 h, and evaporated under reduced pressure to give the crude 3,4-*diazatricyclo*[4,3,3,$0^{1,5}$]-*dodeca*-4,7-*dien*-2-*one* (75 mg). This was recrystallised twice from benzene to give needles, m.p. 217—218° (sealed tube) (Found: C, 68·15; H, 6·65; N, 16·0. $C_{10}H_{12}N_2O$ requires C, 68·15; H, 6·85; N, 15·9%). 3,4-*Diazatricyclo*[4,3,3,$0^{1,5}$]*dodeca*-4,8-*dien*-2-*one* was obtained similarly as needles, m.p. 195—196° (sealed tube) (Found: C, 67·95; H, 6·9; N, 16·05%).

Ethyl 9,9-*Ethylenedioxybicyclo*[3,3,1]*non*-3-*ene*-1-*carboxylate* (4; R = CO_2Et).—Ethyl 9-oxobicyclo[3,3,1]non-3-ene-1-carboxylate (3; R = CO_2Et) (5 g) was heated with ethyl orthoformate (20 ml), ethylene glycol (9 ml), and toluene-*p*-sulphonic acid (50 mg) on an oil-bath at 130—150° until distillation of ethanol ceased. The mixture was cooled, ether was added, and the solution was washed with saturated sodium hydrogen carbonate solution and brine, and then dried. Removal of solvent under reduced pressure, followed by chromatography of the residue on silica gel, afforded the pure *acetal ester* (4; R = CO_2Et) as an oil (5·37 g), b.p. 130° at 0·4 mmHg, n_D^{20} 1·5009, $\nu_{max.}$ (film) 1735, 1090, 1080, 1040, and 960 cm^{-1} (Found: C, 66·35; H, 8·15. $C_{14}H_{20}O_4$ requires C, 66·65; H, 8·0%).

9,9-*Ethylenedioxybicyclo*[3,3,1]*non*-3-*ene*-1-*carboxylic Acid* (4; R = CO_2H).—The foregoing acetal ester (4; R = CO_2Et) (5 g) was stirred at 100° for 30 min in an aqueous solution of sodium hydroxide (3N; 100 ml). The cooled, homogeneous solution was carefully acidified at 0° with dilute 6N-sulphuric acid, then extracted twice with ether. The ethereal extracts were combined, washed with brine and dried. Evaporation of solvent yielded the *acetal acid* (4; R = $^{1,8}H)_2H$) (4·01 g), prisms, m.p. 123—125° (from methylcyclohexane), $\nu_{max.}$ (Nujol) 3200—2700, 1710, 1090, 1080, 1040, and 960 cm^{-1}.

1-*Acetyl*-9,9-*ethylenedioxybicyclo*[3,3,1]*non*-3-*ene* (4; R = Ac).—A solution of methyl-lithium [from lithium (0·7 g) and methyl iodide (7 g)] in ether (50 ml) was added to a stirred solution of the acetal acid (4; R = CO_2H) (2·8 g) in ether (50 ml) during 5 min, in an atmosphere of nitrogen. After initial precipitation of the lithium salt of the acetal acid, the solution clarified then slowly turned opaquely white. The mixture was heated under reflux under nitrogen with stirring for 2 h, then cooled; water was added carefully, and the ethereal solution was washed with brine and dried. Evaporation of solvent under reduced pressure, followed by chromatography of the residue on silica gel, afforded the *methyl ketone* (4; R = Ac) as a low-melting solid (2·4 g), b.p. 135° at 0·2 mmHg, $\nu_{max.}$ (film) 1710, 1090, 1080, 1040, and 960 cm^{-1} (Found: C, 69·9; H, 8·25. $C_{13}H_{18}O_3$ requires C, 70·25; H, 8·15%).

1-*Acetyl*-9,9-*ethylenedioxybicyclo*[3,3,1]*non*-3-*ene* *Oxime* (5; R = H).—A solution of the methyl ketone (4; R = Ac (1 g), hydroxylamine hydrochloride (500 mg), and potassium hydroxide (500 mg) in methanol (90 ml) and water (10 ml) was heated under reflux for 48 h. The methanol was removed under reduced pressure, and the residue partitioned between dichloromethane and water. The aqueous layer was re-extracted with dichloromethane, and the organic layers were combined, washed with brine, and dried. Removal of solvent gave the crude *oxime*; white needles (952 mg), m.p. 157—158° [from benzene–light petroleum (b.p. 40—60°)], $\nu_{max.}$ (Nujol) 3300—3200, 1680, 1090, 1080, 1040, and 960 cm^{-1} (Found: C, 65·8; H, 7·85; N, 5·65. $C_{13}H_{19}NO_3$ requires C, 65·8; H, 8·05; N, 5·9%).

1-*Acetyl*-9,9-*ethylenedioxybicyclo*[3,3,1]*non*-3-*ene* O-*p*-*Tolylsulphonyloxime* (5; R = $SO_2{\cdot}C_6H_4Me$).—The oxime (5; R = H) (650 mg) and sodium hydride [washed with light petroleum (b.p. 40—60°) to remove mineral oil (275 mg)] were stirred in ether (25 ml) for 24 h. The suspension was cooled to 0°, and toluene-*p*-sulphonyl chloride (600 mg) added. Stirring was continued for 3 h at room temperature, then the suspension was filtered through Celite. Removal of solvent under reduced pressure at 0° yielded the crystalline *O*-*p*-tolylsulphonyloxime (5; R = $SO_2{\cdot}C_6H_4Me$) (986 mg), $\nu_{max.}$ (Nujol) 1680, 1600, 1500, 1195, 1180, 1090, 1080, 1040, and 960 cm^{-1}.

N-(9-*Oxobicyclo*[3,3,1]*non*-3-*en*-1-*yl*)*acetamide* (3; R = NHAc).—The above crude *O*-*p*-tolylsulphonyloxime (980 mg) in ethanol (40 ml) and water (10 ml) was heated under reflux for 30 min. The ethanol was removed under reduced pressure, and the residue taken up in dilute 4N-sodium hydroxide. The solution was extracted twice with ether; the extracts were combined, washed with brine, and dried. Removal of solvent under reduced pressure, followed by chromatography of the residue on silica gel, gave the pure *acetamide* (3; R = NHAc) as a low-melting solid (120 mg), b.p. 140° at 0·1 mmHg, $\nu_{max.}$ (film) 3400—3300, 1710, and 1680 cm^{-1} (Found: C, 68·25; H, 7·85; N, 7·4. $C_{11}H_{15}NO_2$ requires C, 68·35; H, 7·8; N, 7·25%).

Benzyl 9-*Oxobicyclo*[3,3,1]*non*-3-*ene*-1-*carbamate* (3; R = $NH{\cdot}CO_2{\cdot}CH_2Ph$).—A solution of 9-oxobicyclo[3,3,1]non-3-ene-1-carboxylic acid (3; R = CO_2H) was prepared by adding sufficient acetone to a suspension of the acid (38 g) in water (250 ml). The solution was cooled to 0°, and triethylamine (40 g) in acetone (30 ml) was added with stirring. A solution of ethyl chloroformate (30 g) in acetone (30 ml) was added slowly at 0°; the mixture was stirred for 30 min at 0° and a solution of sodium azide (30 g) in water (40 ml) was added dropwise. After being stirred at 0° for 1 h, the mixture was poured onto ice, the separated oil was extracted with ether, and the ethereal extract was washed with brine and dried. [Acidification of the aqueous layer gave, on ether extraction, the starting acid (12·4 g).] The oily residue (29 g), obtained by evaporation of solvent, was heated in toluene (100 ml) at 100° for 4 h; evolution of nitrogen had then ceased. Evaporation of a portion of this solution gave the isocyanate (3; R = NCO) as an oil, $\nu_{max.}$ (film) 2250 and 1730 cm^{-1}. Benzyl alcohol (25 g) was added to the main toluene solution, and heating was continued at 100° for 4 h. Evaporation of solvent, followed by chromatography of the residue on silica gel, afforded the benzyl carbamate (3; R = $NH{\cdot}CO_2{\cdot}CH_2Ph$) as a thermally unstable, pale yellow oil (49 g), $\nu_{max.}$ (film) 3450, 1720, and 1510 cm^{-1}.

A by-product obtained by chromatography was 1,1′-*ureylenedibicyclo*[3,3,1]*non*-3-*en*-9-*one* (1 g), which gave white needles, m.p. 244—245° (from acetone), $\nu_{max.}$ (Nujol) 3350, 1720, 1625, and 1550 cm^{-1} (Found: C, 69·25; H,

7·2; N, 8·55. $C_{19}H_{24}N_2O_3$ requires C, 69·5; H, 7·35; N, 8·55%).

Catalytic Hydrogenation of the Benzyl Carbamate (3; R = NH·CO_2·CH_2Ph).—A portion of the foregoing benzyl carbamate (1·24 g) in ethyl acetate (AnalaR; 50 ml) was hydrogenated over 10% palladium–charcoal (50 mg) till uptake of hydrogen ceased. The catalyst was filtered off through Celite, and the solvent removed under reduced pressure, to give 2,9-*diazapentacyclo*[9,3,3,$3^{4,8}$,$0^{1,10}$,$0^{3,8}$]-*eicosane*-3,10-*diol* (6h a ·ich by crystallisation from light petroleum (b.p. 60–7) (3·), gave needles (500 mg), m.p. 174—175°, $\nu_{max.}$ (Nu$_j$ol) 3330, 3260, and 3200—3150 cm^{-1} (Found: C, 70·75; H, 10·05; N, 8·85. $C_{18}H_{30}N_2O_2$ requires C, 70·55; H, 9·85; N, 9·15%), M^+ (hot-box or probe sampling technique), 153 ($C_9H_{15}NO$ requires 153).

1-*Amientra*·*yclo*[3,3,1]*non*-3-*en*-9-*one Hydrobromide* (7).—The benz n thei·bamate (3; R = NH·CO_2·CH_2Ph) (48 g) was added slowly to a solution of hydrogen bromide in acetic acid (50% solution, 100 ml) at 0° with stirring, evolution of carbon dioxide being vigorous. Stirring was continued at 0° for 45 min, and the solution poured slowly into ether (1 l). The resulting solid was separated by filtration and washed well with ether. Drying of the solid gave the amine hydrobromide (7) as a white solid (24·3 g), $\nu_{max.}$ (Nujol) 3200—2700 and 1720 cm^{-1}.

Treatment of the amine hydrobromide (7) with acetic anhydride in pyridine afforded solely *N*-(9-oxobicyclo-[3,3,1]non-3-en-1-yl)acetamide (3; R = NHAc) as shown by t.l.c. and i.r. spectral comparison with an authentic sample.

N-(9-*Oxobicyclo*[3,3,1]*non*-3-*en*-1-*yl*)*pyruvamide* (3; R = NH·CO·COMe).—(a) *Mixed anhydride procedure.* Pyruvic acid (2·6 g) was dissolved in chloroform (AnalaR; 30 ml) and a solution of triethylamine (3 g) in chloroform (AnalaR; 5 ml) added dropwise. Ethyl chloroformate (3·2 g) in chloroform (AnalaR; 5 ml) was added slowly, with stirring, to the cooled solution; stirring was continued for 1 h at 0°, the system being protected from moisture with a silica gel drying tube. The amine hydrobromide (7) (3·8 g) was added, with stirring, as a slurry in chloroform (AnalaR; 10 ml), followed by a final addition of triethylamine (1·4 g), this latter addition clarifying the solution. The solution was stirred at room temperature for 4 h, then washed with saturated sodium hydrogen carbonate and brine, and dried. Evaporation of solvent, followed by chromatography of the residue on silica gel, afforded the crude pyruvamide (3; R = NH·CO·COMe) (1·8 g). T.l.c. of a portion of this product (150 mg) with 50% ethyl acetate–light petroleum (b.p. 60—80°) afforded the pure *pyruvamide*, which crystallised from light petroleum (b.p. 40—60°) as white needles (60 mg), m.p. 84—86°, $\nu_{max.}$ (CCl_4) 3352, 3018, 1733, 1686, 1652, 1507, and 1235 cm^{-1}, $\lambda_{max.}$ (neutral) 241 (ε 2456), $\lambda_{max.}$ (base) 275 nm (2035) (Found: C, 64·85; H, 6·7; N, 6·35. $C_{12}H_{15}NO_3$ requires C, 65·15; H, 6·85; N, 6·35%). A second product was a thermally unstable oil (56 mg), shown to be ethyl 9-oxobicyclo[3,3,1]non-3-ene-1-carbamate (3; R = NH·CO_2Et), $\nu_{max.}$ (film) 3410, 1750, 1735, and 1500 cm^{-1}, by its characteristic ethyl proton absorption pattern in its ^{1}H n.m.r. spectrum [τ 8·9 (3H, t, *J* 7 Hz) and 6·08 (2H, q, *J* 7 Hz)], *M* (mass spec.), 223 (Calc.: *M*, 223).

Increasing the concentration of pyruvic acid, *i.e.* effectively reducing the conc). wh tion of ethyl chloroformate, produced no change —80° ratio of the two products. This observation rules out the possibility of simple acylation of the liberated amine with ethyl chloroformate in the presence of triethylamine.

(b) *Phosphoryl chloride method.* A solution of pyruvic acid (4·03 g), triethylamine (7·2 ml), and the amine hydrobromide (7) (10 g) in tetrahydrofuran (200 ml) was cooled to −15°. Phosphoryl chloride (9·25 g) and triethylamine (16·8 ml) in tetrahydrofuran (50 ml) were added dropwise to the stirred solution at −15°, and stirring was continued for 1 h at room temperature. Water (40 ml) was added, and the tetrahydrofuran removed under reduced pressure. The residue was taken up in ether and the ethereal solution was washed with water, saturated sodium hydrogen carbonate, and brine, and dried. Removal of solvent gave the crude pyruvamide (3; R = NH·CO·COMe), which crystallised from light petroleum (b.p. 40—60°) as white needles (8·5 g), m.p. 84—86°, t.l.c. and i.r. properties identical with those of the product obtained in (a).

2-*Azatricyclo*[5,3,3,$0^{1,6}$]*trideca*-5,8- *and* -5,9-*diene*-3,4-*dione* (8).—The pyruvamide (3; R = NH·CO·COMe) (6·4 g) was dissolved in tetrahydrofuran [freshly distilled from lithium aluminium hydride (1 l)], and sodium hydride (50% dispersion in mineral oil; 3·2 g) added. The suspension was heated under reflux for 12 h, a granular solid having separated from the solution within the first 30 min. The suspension was cooled, excess of tetrahydrofuran was removed under reduced pressure, and water was added carefully to destroy unchanged sodium hydride. The residue was taken up in chloroform, and the chloroform solution washed with 1N-hydrochloric acid and brine and dried. Removal of solvent under reduced pressure gave the enone lactam contaminated with mineral oil. Trituration with ether, followed by centrifugation and decantation, gave the pure *enone lactam* (8), which crystallised from chloroform–light petroleum (b.p. 60—80°) as prisms (4 g), m.p. 228—231°, $\nu_{max.}$ (KCl disc) 3191, 1694, 1685, 1647, 1225, and 722 cm^{-1}, $\nu_{max.}$ ($CHCl_3$) 3360, 3230—1330, 1690, and 1643 cm^{-1}, $\lambda_{max.}$ 258 nm (ε 11,350), *M* (mass spec.), 203 (Calc.: *M*, 203) (Found: C, 70·6; H, 6·2; N, 6·5. $C_{12}H_{13}NO_2$ requires C, 70·9; H, 6·45; N, 6·9%).

4-*Hydroxy*-2-*azatricyclo*[5,3,3,$0^{1,6}$]*tridecan*-3-*one* (11; R = H) *and its Acetate* (11; R = Ac).—A solution of the enone lactam (8) (200 mg) in ethyl acetate (AnalaR; 100 ml) was hydrogenated over 100% palladium–charcoal (25 mg) for 22 h; uptake of hydrogen had then ceased. The catalyst was filtered off through Celite, and the solvent was removed to give the solid product (205 mg), $\nu_{max.}$ (Nujol) 1738, 1695, and 1650 cm^{-1}, considered to be a mixture of the α-keto- and α-hydroxy-lactams, (10) and (11; R = H), respectively. The total product was reduced with sodium borohydride in methanol and water to afford the *α-hydroxy-lactam* (11; R = H), which crystallised from chloroform–ether as needles (170 mg), m.p. 245—246°, $\nu_{max.}$ ($CHCl_3$) 3508, 3366, and 1654 cm^{-1}, *M* (mass spec.), 209 (calc.: *M*, 209) (Found: C, 68·75; H, 9·2; N, 7·0. $C_{12}H_{19}NO_2$ requires C, 68·85; H, 9·15; N, 6·7%).

The above α-hydroxy-lactam (50 mg) was treated with acetic anhydride–pyridine to give the *α-acetoxy-lactam* (11; R = Ac) which, after sublimation, crystallised from light petroleum (b.p. 60—80°) as white needles (45 mg), m.p. 137—139°, $\nu_{max.}$ (Nujol) 3200, 3100, 1740, and 1680 cm^{-1}, *M* (mass spec.), 251 (Calc.: *M*, 251) (Found: C, 66·75; H, 8·45; N, 5·7. $C_{14}H_{21}NO_3$ requires C, 66·9; H, 8·4; N, 5·55%). Attempted reduction of this compound with zinc–acetic acid left it unchanged.

4-*Hydroxy*-2-*azatricyclo*[5,3,3,$0^{1,6}$]*trideca*-5,8- *and* -5,9-*di*-

en-3-one (12; R = H).—The enone lactam (8) (100 mg) was reduced with sodium borohydride in aqueous methanol. Normal work-up yielded the corresponding unsaturated *α-hydroxy-lactam* (12; R = H) as prisms (74 mg), m.p. 221—224° (from ethyl acetate), $\nu_{max.}$ (KCl disc) 3550, 3380, 1660, 1647, and 1614 cm^{-1}, *M* (mass spec.), 205 (Calc.: *M*, 205) (Found: C, 69·85; H, 7·4; N, 6·8. $C_{12}H_{15}NO_2$ requires C, 70·2; H, 7·35; N, 6·8%).

3-*Ethoxy*-2-*azatricyclo*[5,3,3,$0^{1,6}$]*trideca*-2,5,8- *and* -2,5,9-*trien*-4-*one* (13).—A solution of the enone lactam (8) (3 g) and triethyloxonium fluoroborate (10 g) in dichloromethane (50 ml) was stirred for 5 h in an atmosphere of nitrogen. Anhydrous sodium carbonate (AnalaR; 20 g) was added, and stirring continued for a further 4 h. The suspension was filtered, and the filtrate was concentrated *in vacuo*. Chromatography of the residue on silica gel gave the *lactim ether* (13) which sublimed as prisms (2·9 g), m.p. 91—92°, $\nu_{max.}$ (CCl_4) 3016, 1686, and 1632 cm^{-1}, $\lambda_{max.}$ 255 nm (ε 14,050), *M* (mass spec.), 231 (Calc.: *M*, 231) (Found: C, 72·9; H, 7·05; N, 6·3. $C_{14}H_{17}NO_2$ requires C, 72·7; H, 7·4; N, 6·05%), the ^1H n.m.r. spectrum showed a characteristic ethyl proton absorption pattern, τ 5·84 (2H, q, *J* 7 Hz) and 8·85 (3H, t, *J* 7 Hz).

N-*Acetyl*-2-*azatricyclo*[5,3,3,$0^{1,6}$]*trideca*-5,8- *and* -5,9-*dien*-4-*yl Acetate* (14; $R^1 = R^2$ = Ac).—A suspension of the lactim ether (13) (3·5 g) and lithium aluminium hydride (3 g) in ether (200 ml) was heated under reflux for 24 h, with stirring. The suspension was cooled, the excess of lithium aluminium hydride was decomposed with moist ether, and the supernatant ethereal solution was decanted. The residue was washed twice with ether; the ethereal extracts were combined, washed with brine, and dried. Evaporation of solvent afforded the crude hydroxyamine (14; $R^1 = R^2$ = H) as a gum (2·5 g), $\nu_{max.}$ (film) 3500—3200 cm^{-1}, *M* (mass spec.), 191 (Calc.: *M*, 191). This crude product (2·4 g) was treated with acetic anhydride–pyridine to afford, after chromatography on silica gel, the *acetamido-acetate* (14; $R^1 = R^2$ = Ac) which, after sublimation, crystallised from light petroleum (b.p. 40—60°) as needles (2·83 g), m.p. 96·5—98°, $\nu_{max.}$ (CCl_4) 3012, 1739, and 1662 cm^{-1}, *M* (mass spec.), 275 (Calc.: *M*, 275), τ 7·98 (6H, s; 2 × Ac); the ethyl proton absorption pattern was completely absent (Found: C, 69·65; H, 7·85; N, 5·3. $C_{16}H_{21}NO_3$ requires C, 69·8; H, 7·7; N, 5·1%).

N-*Acetyl*-2-*azatricyclo*[5,3,3,$0^{1,6}$]*tridecane* (2; R = Ac).—A solution of the acetamido-acetate (14; $R^1 = R^2$ = Ac) (500 mg) in ethanol (50 ml) containing perchloric acid (0·5 ml) was hydrogenated over 10% palladium–charcoal for 24 h. The catalyst was filtered off through Celite, and saturated sodium hydrogen carbonate (10 ml) was added to neutralise the perchloric acid. The ethanol was removed under reduced pressure, and the residue was taken up in ether, washed with brine, and dried. Evaporation of solvent under reduced pressure gave the propanoperhydroquinoline (2; R = Ac) (402 mg), which, after sublimation, solidified as prisms m.p. 48—49°, $\nu_{max.}$ (CCl_4) 1743 cm^{-1}, τ 8·14 (3H, s, Ac), *M* (mass spec.), 221 (Calc.: *M*, 221) (Found: C, 75·65; H, 10·4; N, 6·1. $C_{14}H_{23}NO$ requires C, 75·95; H, 10·45; N, 6·35%).

N-*Acetyl*-2-*azatricyclo*[5,3,3,$0^{1,6}$]*trideca*-5,8- *and* -5,9-*dien*-4-*ol* (14; R^1 = Ac, R^2 = H).—The acetamido-acetate (14; $R^1 = R^2$ = Ac) (500 mg) was stirred at 70° for 2 h with 2N-sodium hydroxide (45 ml). The solution was cooled and extracted with ethyl acetate; the organic solution was washed with brine and dried. Removal of solvent under reduced pressure gave the *acetamido-alcohol* (14; R^1 = Ac, R^2 = H), which crystallised from ether as plates (415 mg), m.p. 134—135°, $\nu_{max.}$ (CCl_4) 3590, 3018, and 1660 cm^{-1} (Found: C, 72·3; H, 8·1; N, 6·15. $C_{14}H_{19}NO_2$ requires C, 72·05; H, 8·2; N, 6·0%).

N-*Acetyl*-2-*azatricyclo*[5,3,3,$0^{1,6}$]*trideca*-5,8- (15) *and* -5,9-*dien*-4-*one*.—The above acetamido-alcohol (422 mg) in acetone (10 ml) was treated with excess of Jones reagent at 0° for 30 min. Water (100 ml) was added, and the solution was extracted with ethyl acetate. The extract was washed with saturated sodium hydrogen carbonate and brine, and dried. Removal of solvent under reduced pressure, followed by chromatography on silica gel, afforded the *enone* (15), which crystallised from light petroleum (b.p. 60—80°) as needles (353 mg), m.p. 109—110·5°, $\nu_{max.}$ (CCl_4) 1683, 1668, and 1639 cm^{-1}, $\lambda_{max.}$ 228·5 nm (ε 11,550), *M* (mass spec.), 231 (Calc.: *M*, 231) (Found: C, 72·4; H, 7·3; N, 6·25. $C_{14}H_{17}NO_2$ requires C, 72·7; H, 7·4; N, 6·05%).

N-*Acetyl*-4,4-*ethylenedithio*-2-*azatricyclo*[5,3,3,$0^{1,6}$]*trideca*-5,8- (16) *and* -5,9-*diene*.—A solution of the enone (15) (130 mg), ethanedithiol (0·5 ml), and boron trifluoride–ether ($0·1_{80°}$) in chloroform–ether (1 : 1; 5 ml) was left at room temp$_{651}$ ure for 24 h. Ether (100 ml) was added, and the organic solution was washed twice with 4N-sodium hydroxide solution and with brine and dried. Removal of solvent under reduced pressure gave the crude *thioacetal* (16), which crystallised from light petroleum (b.p. 60—80°) as prisms (98 mg), m.p. 130—131°, $\nu_{max.}$ ($CHCl_3$) 1651 cm^{-1}, *M* (mass spec.), 307 (Calc.: *M*, 307). τ 6·60 (4H, s) (Found: C, 62·6; H, 7·0; N, 4·7. $C_{16}H_{21}NOS_2$ requires C, 62·55; H, 6·9; N, 4·55%).

Action of Raney Nickel on the Thioacetal (16).—A portion of the thioacetal (16) (11·2 mg) in ethanol (25 ml) was heated under reflux with Raney nickel (W2; 50 mg) for 24 h. The mixture was cooled, the solid was removed by filtration through Celite, and the solvent was evaporated under reduced pressure. The product (9·5 mg) was seen by t.l.c. to consist of at least 3 components. The total crude product in ethyl acetate (AnalaR; 25 ml) was hydrogenated over 10% palladium–charcoal for 24 h. The catalyst was filtered off through Celite, and the solvent was removed under reduced pressure. The product (8 mg) was the saturated acetamide (2), as shown by t.l.c. and i.r. comparison with an authentic sample.

6-*Methoxy*-2-*tetralone* (17; R = H).—This compound was prepared from 6-bromo-2-naphthol according to the method of Darling and Kidwell[16] in 35% yield; m.p. 28—30° (lit.,[16] 33—34°), $\nu_{max.}$ (film) 1710 cm^{-1}.

Methyl 1,2,3,4-*Tetrahydro*-6-*methoxy*-2-*oxonaphthalene*-1-*carboxylate* (17; R = CO_2Me).—A solution of the foregoing tetralone (20 g) in dimethyl carbonate (150 ml) was added to a suspension of sodium hydride (50% dispersion in mineral oil; 7·1 g) in dimethyl carbonate (100 ml). Methanol (0·5 ml) was added, and the suspension was heated under reflux for 3 h. The suspension was cooled, poured onto ice-cold 6N-sulphuric acid, and extracted with ether. The organic extract was washed with water, saturated sodium hydrogen sulphite solution, and brine, and dried. Removal of solvent under reduced pressure gave an oil (24 g), which was adsorbed from light petroleum (b.p. 60—80°) on to silica gel; elution with 10% ether–light petroleum (b.p. 60—80°) gave the desired β-*ketoester* (17; R = CO_2Me) as an oil (22 g), b.p. 130° at 0·8 mmHg, $\nu_{max.}$

(film) 1740, 1720, 1640, 1610, 1570, and 1510 cm^{-1}, $\lambda_{max.}$ (neutral) 250 (ε 6200), $\lambda_{max.}$ (base) 281 nm (18,200), *M* (mass spec.), 234 (Calc.: *M*, 234) (Found: C, 66·4; H, 5·65. $C_{13}H_{14}O_4$ requires C, 66·65; H, 6·0%). The β-ketoester gave an intense green colour with ethanolic ferric chloride solution.

Methyl 1-(2-*Formylpropyl*)-1,2,3,4-*tetrahydro*-6-*methoxy*-2-*oxonaphthalene*-1-*carboxylate* (18; R = H).—An ice-cold mixture of the β-ketoester (17; R = CO_2Me) (20·5 g) and methacrylaldehyde (12·5 g) was added during 1 h to a stirred solution of sodium methoxide [from sodium (200 mg), and methanol (500 ml)] containing hydroquinone (100 mg) at −70°. The solution was allowed to warm to room temperature, stirring being continued for 1 h. The solution was neutralised with glacial acetic acid, and the solvent was removed under reduced pressure. The residue was dissolved in ether; the ethereal solution was washed with saturated sodium hydrogen carbonate solution and brine and dried. Removal of solvent under reduced pressure gave the crude keto-aldehyde (18; R = H), as a gum (31 g), $\nu_{max.}$ (film) 1740—1720 cm^{-1}, *M* (mass spec.), 304 (Calc.: *M*, 304).

Methyl 10-*Hydroxy*-5-*methoxy*-11-*methyl*-13-*oxotricyclo*-[7,3,1,0^{2,7}]*trideca*-2(7),3,5-*triene*-1-*carboxylate* (19; R = H).—A solution of the above crude keto-aldehyde (31 g) in dioxan (150 ml) was added, with stirring, to an ice-cold mixture of 6N-hydrochloric acid (100 ml) and dioxan (150 ml), in an atmosphere of nitrogen. The solution was stirred at room temperature for 24 h, then poured onto water and extracted with ether. The organic layer was separated, washed with saturated sodium hydrogen carbonate solution and brine, and dried. Removal of solvent afforded the crude ketols (19; R = H) as a gum (27 g), $\nu_{max.}$ (film) 3600—3400 and 1740—1720 cm^{-1}.

Treatment of a portion of the crude ketols (7 g) with acetic anhydride–pyridine afforded the crude acetates (19; R = Ac) as a gum (8 g). This was adsorbed from light petroleum (b.p. 60—80°)–ethyl acetate (2 : 1) onto silica gel; elution with 10% ethyl acetate–light petroleum (b.p. 60—80°) yielded the pure acetates as a gum (5·2 g), $\nu_{max.}$ (film) 1740 and 1720 cm^{-1}, τ 4·8 (1H, m, $W_{\frac{1}{2}}$ 8 Hz, *eq*-10-H), 5·2 (1H, m, $W_{\frac{1}{2}}$ 24 Hz, *ax*-10-H), 6·2 (6H, s, OMe and CO_2Me), 7·9 (3H, s, Ac), and 9·1 (3H, d, *J* 6 Hz, 11-Me). The mixture of acetates on g.l.c. analysis (5% QFl, 225°, 35 ml min^{-1}) showed four peaks in the ratio 1 : 1 : 1·5 : 2·5, (R_t 17·5, 20·5, 22·5, and 26 min, respectively), *M* (mass spec.), 346 (Calc.: *M*, 346).

The corresponding toluene-*p*-sulphonates (19; R = $SO_2{\cdot}C_6H_4Me$) were prepared by treatment of a solution of the ketols (40 g) in dry pyridine (50 ml) with toluene-*p*-sulphonyl chloride (32 g) and the resulting solution was set aside at room temperature for 5 days. Normal work-up afforded a viscous oil (61 g), which was adsorbed on silica gel (1·8 kg) from light petroleum–ethyl acetate (1 : 2). Elution with light petroleum–ethyl acetate (5 : 1) furnished the mixed toluene-*p*-sulphonates (52 g) as a viscous oil, $\nu_{max.}$ (film) 1740, 1720, 1200, 1190, and 700 cm^{-1}.

Treatment of the ketols (19; R = H) (13 g) with ethyl chloroformate (10 ml) and pyridine (20 ml) afforded a dark viscous oil (17 g), which was adsorbed on silica gel (500 g) from light petroleum–ethyl acetate (1 : 2). Elution with light petroleum–ethyl acetate (5 : 1) yielded the corresponding carbonate esters (19; R = CO_2Et) as a pink viscous oil (14 g), $\nu_{max.}$ (film) 1740—1720, 1260, and 800 cm^{-1}. The above product on g.l.c. analysis (1% QFl, 200°, 45 ml min^{-1}) showed four peaks in the ratio 1 : 1 : 1·5 : 2·5, R_t 15·6, 17·8, 19·6, and 23·4 min, respectively.

Epimeric Methyl 5-*Methoxy*-11-*methyl*-10,13-*dioxotricyclo*-[7,3,1,0^{2,7}]*trideca*-2(7),3,5-*triene*-1-*carboxylates* (22).—Jones reagent (2 ml) was slowly added to an ice-cold stirred solution of the ketols (19; R = H) (1·2 g) in acetone AnalaR; 25 ml) and stirring continued for 30 min. Methanol (1 ml) was then added and after 10 min the mixture was poured into brine and extracted with ether. The combined ethereal extracts were washed with brine, saturated sodium hydrogen carbonate solution, and brine again, dried, and evaporated under reduced pressure to furnish a pale yellow solid. Two successive recrystallisations from benzene–light petroleum (b.p. 60—80°) (2 : 1) afforded the *diones* (22) (1·02 g) as small needles, m.p. 163—167°, $\nu_{max.}$ (KCl disc) 1744, 1732, and 1710 cm^{-1}. The analytical sample of this compound showed only one peak on g.l.c. analysis (1% QFl; 200°; 45 ml min^{-1}) and (5% QFl, 225°, 40 ml min^{-1}) whereas analytical t.l.c. showed two poorly resolved spots [with ethyl acetate–light petroleum (2 : 3) as eluant]. These epimeric diones could not be separated by preparative t.l.c. (Found: C, 67·75; H, 6·15. $C_{17}H_{18}O_5$ requires C, 67·55; H, 6·0%), *M* (mass spec.), 302 (Calc.: *M*, 302).

2-*Methyl*-3-(1,2,3,4-*tetrahydro*-6-*methoxy*-1-*methoxycarbonyl*-2-*oxo*-1-*naphthyl*)*propionic Acids* (18; R = OH).—Jones reagent (2 ml) was added with stirring to an ice-cold solution of the keto-aldehydes (18; R = H) (1 g) in acetone (AnalaR; 10 ml) and the mixture stirred for 1 h further at room temperature. Methanol (2 ml) was added and the mixture poured into brine and extracted with ether. The combined organic extracts were washed with saturated sodium hydrogen carbonate solution and the alkaline extract * was then acidified with 6N-sulphuric acid and extracted with ether. The separated organic phase was washed with brine and dried. Removal of the solvent under reduced pressure afforded a yellow oil (0·7 g) which partially solidified on trituration with ether. Fractional recrystallisation from light petroleum–ether (1 : 2) afforded stereochemically pure (18; R = OH) as needles, m.p. 118—120°, $\nu_{max.}$ (KCl disc) 3300—2500, 1740, and 1704 cm^{-1} (Found: C, 63·95; H, 6·2. $C_{17}H_{20}O_6$ requires C, 63·75; H, 6·3%).

Methyl 2,3,6,10b-*Tetrahydro*-8-*methoxy*-2-*methyl*-3-*oxo*-1H-*naphtho*[2,1-b]*pyran*-10b-*carboxylate* (24).—(*a*) A solution of the crystalline keto-acid (18; R = OH) (300 mg) in acetic anhydride (AnalaR; 20 ml) was heated under reflux for 3 h, then fused sodium acetate (50 mg) was added and reflux was continued for a further 4 h. Normal work-up afforded a yellow oil (250 mg) which solidified on trituration with ether. Analytical t.l.c. with ethyl acetate–light petroleum (2 : 5) showed this product to consist of two components in equal proportions which were separated by preparative t.l.c. The faster moving spot proved to be the *enol lactone* (24), which crystallised from ethyl acetate–light petroleum (2 : 1) as needles, m.p. 144—146°, $\nu_{max.}$ (Nujol) 1740, 1720, and 1680 cm^{-1}, τ 4·2 (1H, t, *J* 4 Hz, 5-H) (Found: C, 67·6; H, 6·15. $C_{19}H_{18}O_5$ requires C, 67·55; H, 6·0%).

The slow moving component was identified as the *enol acetate* of (22), from which it was also prepared by treatment with acetic anhydride–perchloric acid. It crystallised from

* The original ether extract was washed with brine and dried. Removal of the solvent gave the diones (22) (0·2 g), m.p. 163—167°, identical (mixed m.p.) with an authentic sample.

ethyl acetate–light petroleum (b.p. 60—80°) as prisms m.p. 165—168°, $\nu_{max.}$ (KCl disc) 1746, 1728, 1262, 1230, and 1212 cm^{-1}, τ 6·22 (3H, s, OMe), 6·25 (3H, s, CO_2Me), 7·86 (3H, s, OAc), and 8·56 (3H, s, 11-Me) (Found: C, 66·35; H, 5·9. $C_{19}H_{20}O_6$ requires C, 66·3; H, 5·85%).

(*b*) A solution of the keto-acid (18; R = OH) (500 mg) in 1M-acetic anhydride–10^{-3}M-perchloric acid–ethyl acetate solution (50 ml) was set aside at room temperature for 10 min. The mixture was then washed with saturated sodium hydrogen carbonate solution and brine, dried, and evaporated *in vacuo* to furnish a white solid (500 mg), which was recrystallised from ethyl acetate–light petroleum (2 : 1) to furnish a single enol lactone (24) (200 mg), identical with the compound prepared as in (*a*).

Reduction of the Enol Lactone (24) *with Lithium Hydrido-t-butoxyaluminate.*—The crystalline enol-lactone (24) (250 mg) was treated with a suspension of lithium hydridotri-t-butoxyaluminate (330 mg) in dry tetrahydrofuran in the usual way.[18] Normal work-up yielded the axial ketols (20; R = H) as a yellow oil (230 mg), $\nu_{max.}$ (film) 3500 and 1740—1720 cm^{-1}. A portion of the crude product was acetylated and subjected to g.l.c. analysis (5% QF1, 225°, 35 ml min^{-1}), which indicated the presence of two components in the ratio 1 : 1, R_t 17·5 and 22·5 min. The corresponding toluene-*p*-sulphonates were obtained as a viscous oil, $\nu_{max.}$ (film) 1740, 1720, 1200, 1190, and 1 cm^{-1}. These derivatives were purified by preparative t.l.c. to remove small quantities of unchanged ketols.

Reduction of the Diones (22) *with Lithium Hydridotri-t-butoxyaluminate.*—A suspension of lithium hydridotri-t-butoxylaluminate (410 mg) in dry tetrahydrofuran (5 ml) was added with stirring to a solution of the diones (22) (370 mg) in dry tetrahydrofuran (5 ml) and the solution heated under reflux for 2 h. 6N-Hydrochloric acid was added to the cooled solution and the mixture was extracted with ether. The combined organic extracts were washed with brine, saturated sodium hydrogen carbonate solution, and brine again, and dried. Removal of the solvent *in vacuo* gave a yellow oil (350 mg) which partially crystallised from ethyl acetate–light petroleum (1 : 2) to yield the starting diones (100 mg). Evaporation of the mother liquors afforded the equatorial ketols (21; R = H) as an oil (200 mg), $\nu_{max.}$ (film) 3500 and 1740—1710 cm^{-1}. Acetylation of this fraction followed by g.l.c. (conditions as above) revealed the presence of two compounds in the ratio 1 : 1, R_t 20·5 and 26 min.

The corresponding toluene-*p*-sulphonates were obtained as an oil after t.l.c., $\nu_{max.}$ (film) 1740—1720, 1200, 1190, and 700 cm^{-1}.

Methyl 5-Methoxy-11-methyl-13-oxotricyclo[7,3,1,$0^{2,7}$]*trideca-2(7),3,5,10-tetraene-1-carboxylate* (23; R = Me).—(*a*) *Pyrolysis of the mixed carbonates* (19; R = CO_2Et). The mixed carbonates (5 g) were heated in a Woods-alloy bath at 350° for 20 min. The dark brown product was dissolved in ether, washed with saturated sodium carbonate solution and brine and dried. Removal of the solvent under reduced pressure afforded a viscous brown oil (4 g), which was adsorbed on alumina (grade III basic; 120 g) from ether–light petroleum (1 : 2). Elution with light petroleum–ethyl acetate (50 : 1) afforded a pale yellow solid, which was recrystallised from ethyl acetate–light petroleum (1 : 2) to furnish the olefin (23; R = Me) (200 mg) as clusters of needles, m.p. 104·5—105°, (KCl disc) 1740, 1720, 824, 815, 812, and 808 cm^{-1}, $\nu_{max.}$ (CCl_4) 1747 and 1733 cm^{-1}, τ (100 MHz) 4·74 (1H, m, 10-H), 6·30 (3H, s, OMe), 6·34 (3H, s, CO_2Me), and 8·44 (3H, s, 11-Me) (Found: C, 71·35; H, 6·05. $C_{17}H_{18}O_4$ requires C, 71·3; H, 6·35%), *M* (mass spec.), 286 (Calc.: *M*, 286).

The above keto-olefin was hydrolysed with aqueous 2N-sodium hydroxide to furnish the corresponding *keto-acid* (23; R = H), which crystallised from aqueous methanol as clusters of needles, m.p. 210—218°, $\nu_{max.}$ (KCl disc) 3300—2600, 1710, 1690, 840, 820, and 798 cm^{-1} (Found: C, 66·05; H, 6·3. $C_{16}H_{16}O_4$,H_2O requires C, 66·2; H, 6·25%).

Pyrolysis of the corresponding acetates at 350° gave mainly unchanged starting material.

(*b*) A solution of the four *epimeric* toluene-*p*-sulphonates (20 and 21; R = $SO_2{\cdot}C_6H_4Me$) (1·8 g) in dry acetic acid (50 ml) containing fused sodium acetate (350 mg) was heated under reflux for 36 h. Normal work-up followed by column chromatography of the recovered oil (1·1 g) on silica gel (30 g) gave the olefin (23; R = Me) (500 mg) and a white solid (380 mg), which was recrystallised from ethyl acetate–light petroleum (1 : 2) to furnish an axial *acetate* as prisms, m.p. 136—138°, $\nu_{max.}$ (KCl disc) 1736, 1718, 1244, and 812 cm^{-1}, τ 4·75 (1H, m, $W_{\frac{1}{2}}$ 3 Hz, 10-H), 6·2 (3H, s, superimposed OMe and CO_2Me), and 9·1 (3H, d, *J* 6 Hz, 11-Me), R_t 22·5 min (conditions as above) (Found: C, 65·8; H, 6·7. $C_{19}H_{22}O_6$ requires C, 65·9; H, 6·4%).

The foregoing acetate, was reduced with sodium borohydride in the usual manner to furnish the *acetoxy-alcohol*, which was recrystallised from ethyl acetate–light petroleum (1 : 2) to afford an analytical sample as clusters of needles, m.p. 161—163°, $\nu_{max.}$ (Nujol) 3550, 1730—1720, 1240, and 840 cm^{-1}, $\nu_{max.}$ (CCl_4; high dilution) 3592 cm^{-1}, τ 4·9 (1H, m, $W_{\frac{1}{2}}$ 3 Hz, 10-H), 7·6 (3H, s, OAc), and 9·1 (3H, d, 11-Me) (Found: C, 65·65; H, 6·95. $C_{19}H_{24}O_6$ requires C, 65·5; H, 6·95%).

Methyl 5-Methoxy-11-methyl-13-oxotricyclo[7,3,1,$0^{2,7}$]*trideca-2(7),3,5-triene-1-carboxylate* (25; R = Me).—A solution of the olefin (23; R = Me) (800 mg) in ethanol (50 ml) was hydrogenated over 5% palladium–carbon (200 mg) for 16 h. Normal work-up gave an oil (800 mg), $\nu_{max.}$ film) 3500, 1740, 1720, and 820 cm^{-1}, which on treatment with Jones reagent afforded a white solid (800 mg). G.l.c. (conditions as above) indicated the presence of two components in the ratio 1 : 10, R_t 10·25 and 12 min, respectively. This product was recrystallised from ethyl acetate–light petroleum (1 : 2) to yield the pure *ketone* (25; R = Me) as prisms (600 mg), m.p. 125—127°, $\nu_{max.}$ (KCl disc) 1740, 1718, 870, 852, 818, and 806 cm^{-1}, τ (100 MHz) 9·2 (3H, d, *J* 6 Hz, 11-Me), homogeneous by g.l.c. (1% QF1, 175°, 45 ml min^{-1}) R_t 12 min (Found: C, 70·6; H, 7·15. $C_{17}H_{20}O_4$ requires C, 70·8; H, 7·0%).

Alkaline hydrolysis of the keto-ester (25; R = Me) furnished the corresponding *carboxylic acid* (25; R = H), which was recrystallised from aqueous methanol to give an analytical sample as plates, m.p. 257—260°, $\nu_{max.}$ (Nujol) 3300—2600, 1720—1690, and 820 cm^{-1} (Found: C, 66·0; H, 7·05. $C_{16}H_{18}O_4$,$1H_2O$ requires C, 65·75; H, 6·9%).

A portion of the above saturated ketone was reduced with sodium borohydride in the usual manner to furnish the corresponding alcohols (27; R = Me) as an oil, $\nu_{max.}$ (film) 3500 and 1730 cm^{-1}, τ (100 MHz) 9·2 (3H, d, *J* 6 Hz, 11-Me).

The above alcohols were hydrolysed with aqueous base in the usual manner to give the corresponding *hydroxy-acids*

(27; R = H), which crystallised from aqueous methanol as prisms, m.p. 160—167°, $\nu_{max.}$ (Nujol) 3500—2600 and 1700—1690 cm^{-1} (Found: C, 67·7; H, 7·54. $C_{16}H_{20}O_4$,-0·5H_2O requires C, 67·35; H, 7·4%).

Epimeric Methyl 5-Methoxy-11-methyl-13-oxotricyclo-[7,3,1,$0^{2,7}$]*trideca-2(7),3,5-triene-1-carboxylate* (26; R = Me).—A solution of the olefin (25; R = Me) (1 g) in ethyl acetate (AnalaR; 20 ml) was hydrogenated in the presence of 5% rhodium–carbon (300 mg) at atmospheric pressure. After 8 h, 1 mol, equiv. of hydrogen had been absorbed. Normal work-up yielded an oil (1 g) which slowly solidified. Recrystallisation from ethyl acetate–light petroleum (1 : 2) furnished the *ketone* (26; R = Me) as needles (900 mg), m.p. 82—84°, $\nu_{max.}$ (KCl disc) 1742, 1724, 1232, 854, 846, 818, and 810 cm^{-1}, $\nu_{max.}$ (CCl_4) 1746 and 1732 cm^{-1}, τ (100 MHz) 9·18 (3H, d, J 6 Hz, 11-Me), homogeneous by g.l.c. (same conditions as before), R_t 10·25 min (Found: C, 70·5; H, 7·0. $C_{17}H_{20}O_4$ requires C, 70·8; H, 7·0%).

The above ketone was hydrolysed in the usual manner to the corresponding *carboxylic acid* (26; R = H) which crystallised from aqueous methanol as needles, m.p. 240—248°, $\nu_{max.}$ (Nujol) 3300—2600, 1720—1690, and 820 cm^{-1} (Found: C, 65·95; H, 7·15. $C_{16}H_{18}O_4$,H_2O requires C, 65·75; H, 6·9%).

A portion of the ketone was reduced with sodium borohydride in the usual manner to give the corresponding alcohols (28; R = Me) an oil, $\nu_{max.}$ (film) 3500 and 1730 cm^{-1}, τ (100 MHz) 9·6 (3H, d, J 6 Hz, 11-Me).

The corresponding *hydroxy-acids* (28; R = H) crystallised from aqueous methanol as plates, m.p. 170—174°, $\nu_{max.}$ (Nujol) 3500—2600 and 1700 cm^{-1} (Found: C, 67·55; H, 7·6. $C_{16}H_{20}O_4$,0·5H_2O requires C, 67·35; H, 7·4%).

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