Synthesis of (±)-Homoeburnamenine, (±)-21-*epi*-Homoeburnamenine, (±)-Eburnamine, and (±)-21-*epi*-Eburnamine †

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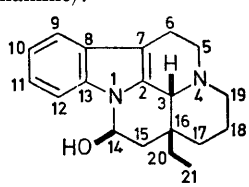
A new synthetic route to eburnamine and 21-*epi*-eburnamine, *via* homoeburnamenine and 21-*epi*-homoeburnamenine, is described.

THE synthesis of alkaloids related to aspidospermine (1) has recently attracted considerable attention; several syntheses of (±)-aspidospermine itself have been reported.[1-3] Other investigations have resulted in the synthesis of (±)- or (+)-aspidospermidine (2),[4,5]

† The numbering system used in this paper is illustrated in formula (30). The alternative system (used by *Chem. Abs.*) is as follows (for eburnamine):



[1] G. Stork and J. E. Dolfini, *J. Amer. Chem. Soc.*, 1963, **85**, 2872.

[2] Y. Ban, Y. Sato, I. Inoue, M. Nagai, T. Oishi, M. Terashima, O. Yonemitsu, and Y. Kanaoka, *Tetrahedron Letters*, 1965, 2261; Y. Ban, M. Akagi, and T. Oishi, *ibid.*, 1969, 2057, 2063; Y. Ban, I. Iijima, I. Inoue, M. Akagi, and T. Oishi, *ibid.*, p. 2067.

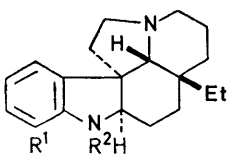
[3] M. E. Kuehne and C. Bayha, *Tetrahedron Letters*, 1966, 1311.

[4] J. Harley-Mason and M. Kaplan, *Chem. Comm.*, 1967, 915.

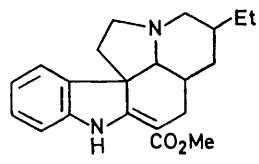
[5] A. Camerman, N. Camerman, J. P. Kutney, E. Piers, and J. Trotter, *Tetrahedron Letters*, 1965, 637; J. P. Kutney, N. Abdurahman, P. Le Quesne, E. Piers, and I. Vlattas, *J. Amer. Chem. Soc.*, 1966, **88**, 3656.

pseudovincadifformine (3),[6] (±)-vincadifformine (4),[7] and (±)-minovine (5).[7] Since the preliminary reports of our work were published [8] a further synthesis of (±)-minovine [9] has been reported, as well as elegant syntheses of (±)-vindorosine (6a) [10] and (±)-tabersonine (7).[11]

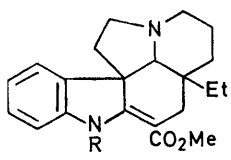
There thus exist several precedents for the construction of the aspidospermine ring system, but at the outset of our work there was still lacking a route that would lead to *Aspidosperma* alkaloids containing additional substituents in the hydroaromatic portion, in particular to those with a double bond at positions 14 and 15, the ultimate example of which is vindoline (6). Our objective, in seeking to develop routes for the synthesis of alkaloids of this type, was the total synthesis of tabersonine (7). In the route adopted we hoped to achieve the double cyclisation of a dialdehyde of the form (8) to give the pentacyclic derivative (9), which we expected would be convertible into tabersonine by unexceptional methods. Alternatively the presence of an appropriate function at the starred position in the dihydro-derivative of the intermediate (8) should allow the introduction of the 14,15-double bond at a later stage, as and when desired. Double condensations of the type adumbrated in the sequence (8) ⟶ (9) have long been known; [12] a recent example involves the construction of the strychnine ring system by an exactly



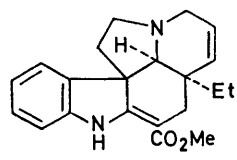
(1) R^1 = OMe, R^2 = Ac
(2) R^1 = R^2 = H



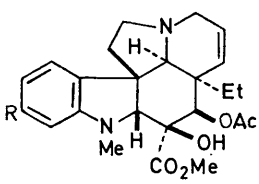
(3)



(4) R = H
(5) R = Me

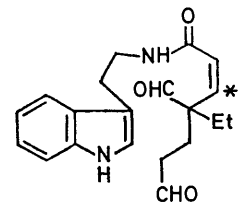


(7)

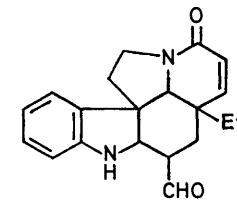


(6) R = OMe
(6a) R = H

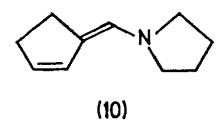
analogous route; full experimental details of this synthesis, however, are still not available.[13] In planning this route we anticipated the possibility that cyclisation of the dialdehyde (8) would proceed on position 2 of the indole ring system with formation of a tetracyclic



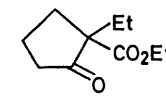
(8)



(9)



(10)



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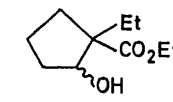

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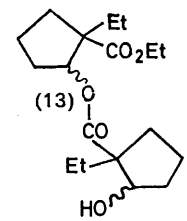

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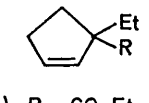
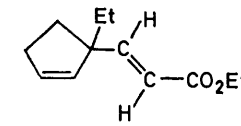
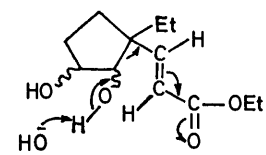


(14) R = CO_2Et
(15) R = CH_2·OH
(16) R = CHO
(17) R = CH_2·O·CH_2·SMe



(18)



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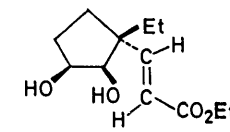
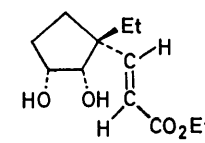


(20a)



(20b)

product related to eburnamine, but it was hoped that with the presence of appropriate functional groups advantage could be taken of the known rearrangement [4,14] of such compounds into products containing the aspidospermine ring system.

The 1,5-dialdehyde grouping present in compounds of the type (8) can in principle be readily obtained from cyclopentene derivatives; accordingly, our first attempt to construct an appropriate intermediate involved the ethylation of the pyrrolidine enamine of cyclopent-2-ene-1-carbaldehyde (10). This approach was encouraged by the report [15] that dienamines are alkylated on the position α to the original carbonyl group; unfortunately,

[6] J. P. Kutney, R. T. Brown, and E. Piers, *J. Amer. Chem. Soc.*, 1964, **86**, 2286.
[7] J. P. Kutney, Ka Kong Chan, A. Failli, J. M. Fromson, C. Gletsos, and V. R. Nelson, *J. Amer. Chem. Soc.*, 1968, **90**, 3891.
[8] K. H. Gibson and J. E. Saxton, *Chem. Comm.*, 1969, 799, 1490.
[9] F. E. Ziegler and E. B. Spitzner, *J. Amer. Chem. Soc.*, 1970, **92**, 3492.
[10] G. Büchi, K. E. Matsumoto, and H. Nishimura, *J. Amer. Chem. Soc.*, 1971, **93**, 3299.
[11] F. E. Ziegler and G. B. Bennett, *J. Amer. Chem. Soc.*, 1971, **93**, 5930.
[12] Sir Robert Robinson and J. E. Saxton, *J. Chem. Soc.*, 1953, 2596.
[13] E. E. van Tamelen, L. J. Dolby, and R. G. Lawton, *Tetrahedron Letters*, 1960, No. 19, 30.
[14] J. E. D. Barton and J. Harley-Mason, *Chem. Comm.*, 1965, 298; J. E. D. Barton, J. Harley-Mason, and K. C. Yates, *Tetrahedron Letters*, 1965, 3669.
[15] G. Stork and G. Birnbaum, *Tetrahedron Letters*, 1961, 313.

all attempts to alkylate the enamine (10) resulted in polymerisation and an alternative approach had to be adopted. The first stage in this route involved the reduction of ethyl 1-ethyl-2-oxocyclopentane-1-carboxylate (11) with sodium borohydride, which generally proceeded in high yield (87%). Occasionally, however, a much lower yield of the product (12) was obtained, together with a considerable amount of an involatile, viscous oil. This material ($\nu_{max.}$ 1720 cm^{-1}) was neutral and could be saponified to an acidic compound which on re-esterification with ethanol gave the required hydroxy-ester (12). The formation of this involatile by-product was particularly extensive when the temperature of the reaction mixture was allowed to rise above 5°, and also when subsequent removal of the solvent was carried out at elevated temperatures. We therefore suggest that base-catalysed transesterification of the hydroxy-ester (12) occurs under these conditions, leading to a complex ester which we formulate as (13).

The dehydration of the hydroxy-ester (12) was initially accomplished by Tschugaev pyrolysis of the xanthate derivative to give the unsaturated ester (14) in 53% yield. The isolation of the product necessitated the use of chromatography, since fractional distillation did not allow the separation of a sulphur-containing impurity. Since xanthate pyrolysis proceeds *via* a cyclic transition state [16] and does not involve carbonium-ion intermediates it was considered to be the most reliable method for the formation of the ester (14). Subsequently it was shown that dehydration by phosphorus pentoxide in benzene gave the same product, and in superior yield (78%). This method was therefore preferred, even though the n.m.r. spectrum and g.l.c. behaviour of the product indicated that it contained *ca.* 10% of impurity of an undetermined nature. This impurity was removed by crystallisation at a later stage.

The unsaturated alcohol (15), prepared from the ester (14) by reduction with lithium aluminium hydride, was oxidised to the aldehyde (16) in moderate yield by means of dimethyl sulphoxide and acetic anhydride.[17] The by-product was the expected methylthiomethyl ether (17), which was readily identified from its n.m.r. spectrum. Separation of these two products proved difficult, and a preferred method of oxidation was the modified Oppenauer procedure (aluminium t-butoxide and *p*-benzoquinone). Subsequent Wittig reaction of the aldehyde (16) with ethoxycarbonylmethylenetriphenylphosphorane afforded an almost quantitative yield of the desired unsaturated ester (18).

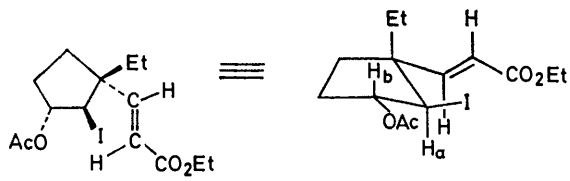
The next stage involved the preferential hydroxylation of the isolated double bond in the diene-ester (18) by osmium tetroxide, which proceeded in ethereal solution in the presence of pyridine with formation of the cyclic osmate ester. However, attempts to decompose the osmate with alkaline mannitol gave, after chromatography, only low yields of the expected glycol (19). It was later realised that this glycol is unstable to alkali, and ring cleavage by a reverse aldol reaction [arrows in (19)] is possible [18] since (19) is a vinylogous β-hydroxy-ester; in addition it has a quaternary position γ to the ester group which increases the ease of reverse aldol cleavage. Consequently the hydroxylation was carried out under the modified conditions described by Baran; [19] this involves the decomposition of the intermediate osmate ester with sodium hydrogen sulphite in aqueous pyridine, a procedure which afforded an inseparable mixture of *cis*-hydroxylated isomers (20a and b) in 79% yield. The slight preponderance of the former isomer (ratio *ca.* 55 : 45) results presumably from the lower steric requirement of the ethyl group compared to that of the ethoxycarbonylvinyl group. The assignment of configuration was made possible when the pure isomer (20b) was prepared by a different procedure (see later) and an estimate of the proportions of the isomers was then made from the integration of the proton resonance signals of the mixture.

Oxidation of the diene-ester (18) by the conventional Woodward–Prévost procedure [20] was also attempted, but no useful product was isolated. This method involves as final stage an alkaline hydrolysis, and in view of the sensitivity of the glycol-ester (19) to alkali, the failure to isolate the desired product is not surprising. Accordingly, this reaction was investigated in a stepwise manner. Treatment of compound (18) with acetyl hypoiodite (prepared *in situ*) gave an oily mixture of the iodoacetates (21a and b). The solution of the iodoacetate mixture in light petroleum when stored at −25° slowly deposited crystals of isomer (21a). This was the predominant isomer and could be obtained in *ca.* 40% yield from the ester (18); it crystallised as two polymorphic forms, m.p. 51—52° and 64·5—65°. The three large substituents on the cyclopentane ring suffer least steric interference in isomer (21a) and the conformation (21a′) necessitates a large dihedral angle between H_a and H_b which is manifested in the large coupling (J 8·5 Hz) between these protons. Integration of the n.m.r. spectrum of the iodoacetate mixture indicated that there was approximately twice as much isomer (21a) as isomer (21b), which suggests that with the diene-ester (18) the reaction with acetyl hypoiodite is more stereoselective than the reaction with osmium tetroxide.

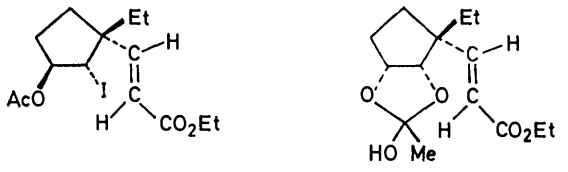
When heated with silver acetate in wet acetic acid, the crystalline iodoacetate (21a) was converted into a mixture of glycol monoacetates (23a and b), presumably *via* the intermediate (22) of the type proposed by Winstein.[21] In accord with previous observations the attempted alkaline hydrolysis of the monoacetate mixture proved unsuccessful; the acetate group was therefore removed by acid-catalysed ethanolysis to give the glycol-ester (20b).

The successful cyclisation of a dialdehyde of the type (8) necessarily requires a *cis*-disposition of the two large substituents attached to the olefinic double bond.

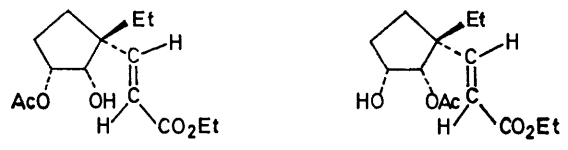
[16] H. R. Nace, *Org. Reactions*, 1962, **12**, 57.
[17] J. D. Albright and L. Goldman, *J. Amer. Chem. Soc.*, 1965, **87**, 4214; 1967, **89**, 2416.
[18] C. S. Rondestvedt and M. E. Rowley, *J. Amer. Chem. Soc.*, 1956, **78**, 3804.
[19] J. S. Baran, *J. Org. Chem.*, 1960, **25**, 257.
[20] R. B. Woodward and F. V. Brutcher, *J. Amer. Chem. Soc.*, 1958, **80**, 209.
[21] S. Winstein and R. E. Buckles, *J. Amer. Chem. Soc.*, 1942, **64**, 2787.



(21a) (21a')



(21b) (22)

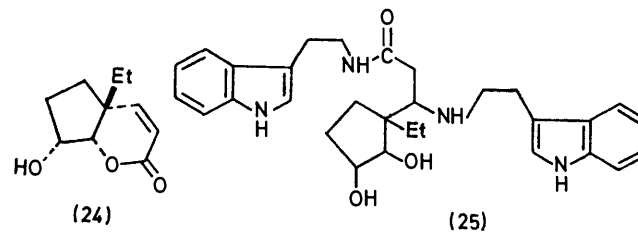


(23a) (23b)

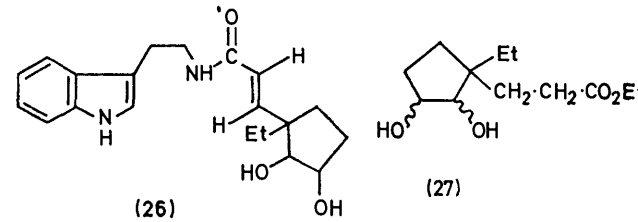
Hence it was vital at some appropriate stage in the synthesis to isomerise the *trans*-disubstituted double bond present in the esters (18)—(20) to the corresponding *cis*-form. With the glycol-ester (20b) in hand a convenient route was immediately available, since conversion of (20b) into the bicyclic δ-lactone (24) could only be completed following isomerisation about the double bond. Accordingly, the ester (20b) was photolysed in the presence of iodine and toluene-*p*-sulphonic acid in a Hanovia photochemical reactor with the emission from a medium-pressure mercury discharge lamp. Owing to side reactions it was found necessary to interrupt the photolysis before all the glycol-ester (20b) had been consumed. By this means the lactone (24), m.p. 112·5—113°, was obtained in an optimum yield of 61% (based on starting material consumed). The carbonyl stretching frequency was only slightly affected by the conversion of the ester (20b) (1715 cm^{-1}) into the lactone (24) (1720 cm^{-1}), but the double-bond stretching frequency was now found at 1600 cm^{-1} [*cf.* 1645 cm^{-1} in (20b)] and the absorption was much weaker. The n.m.r. spectrum of the lactone was diagnostic for the proposed structure (24) and exhibited the α- and β-vinyl proton signals at τ 4·05 and 2·85, respectively, both as doublets with *J* 9 Hz indicative of the *cis*-configuration. The signals for the methine protons adjacent to oxygen were no longer superimposed on the ester methylene resonance; a doublet (*J* 5 Hz) at τ 5·98 and a broad triplet at τ 5·6 were attributed to these protons.

Having obtained the desired δ-lactone (24) we were now in a position to attempt the preparation of the glycol precursor of the dialdehyde (8), by treatment of the lactone with tryptamine. It was expected that attack of a molecule as large as tryptamine at the position β to the carbonyl group would be severely hindered by the bulky substituents attached to the γ-carbon atom. Contrary to these expectations, however, the lactone reacted with two molecules of tryptamine to give the amide (25). Since no transient intermediate was detected by t.l.c. during the course of the reaction it seems likely that the first stage is nucleophilic attack by tryptamine at the β-position of the lactone, and is followed rapidly by reaction of the now saturated (and therefore more reactive) lactone with another molecule of tryptamine.

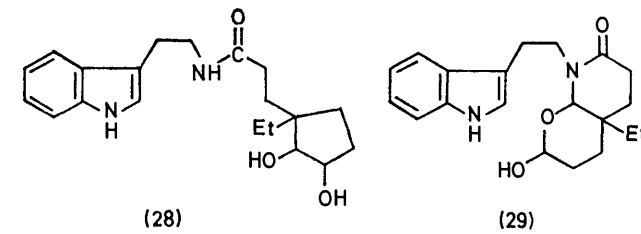
The amide (25) proved difficulty to purify and it was necessary to convert it into its isopropylidene derivative in order to obtain good spectral data. The n.m.r. spectra of the amide (25) and its isopropylidene derivative were notable for the absence of signals in the region τ 3·7—5·5, indicating the absence of olefinic protons in the molecules.



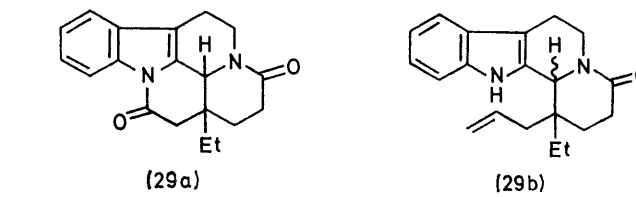
(24) (25)



(26) (27)



(28) (29)



(29a) (29b)

A small amount (9%) of a by-product was also isolated from this reaction. The molecular ion at *m/e* 342·194 indicated the composition $C_{20}H_{26}N_2O_3$, which corresponds to the product of reaction of the lactone with one molecule of tryptamine. I.r. absorptions at 1652, 1622, and 1515 cm^{-1} suggested a *trans*-αβ-unsaturated amide function, and this conclusion was supported by the n.m.r. spectrum, which exhibited a simple AB pattern due to two protons centred at τ 4·15 and 4·43 (*J* 13 Hz).

In addition, the mass spectrum of this by-product exhibited peaks at *m/e* 137, 119, 109, 95, 81, 79, 67, 55, 43, and 41, which are also present in the mass spectrum of the glycol-ester (20b). Consequently we regard the by-product as the unsaturated amide (26); its formation from (25) is merely the β-elimination of a molecule of tryptamine.

In spite of further attempts we have still not been able to isolate the *cis*-isomer of the amide (26), and so this aspect of our synthetic work has been temporarily abandoned. However, we intend to reinvestigate the reaction of the lactone (24) with tryptamine, since in principle the *trans*-amide (26) can also be utilised in our synthetic approach.

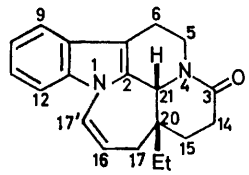
The unpromising results obtained from the reaction of the lactone (24) with tryptamine prompted us to test the viability of our overall approach to the *Aspidosperma–Hunteria* bases by examining the reaction of the saturated ester-diol (27) with tryptamine. The required ester-diol (27) was prepared by hydrogenation of the unsaturated analogue (19). For the preparation of the unsaturated lactone (24) only the crystalline iodoacetate (21a) could be used since only this isomer furnished an unsaturated ester-diol (20b) which would readily lactonise following isomerisation about the double bond. However, lactone formation is not required in the corresponding saturated series; hence the whole of the iodoacetate product was converted into the mixture of isomeric diols (19), which was then hydrogenated to the corresponding saturated diols (27), thus avoiding a considerable wastage of materials. Condensation of (27) with tryptamine afforded a gum which exhibited the composition and spectrographic properties expected for the glycol amide (28).

Oxidative cleavage of (28) proceeded rapidly with sodium periodate in aqueous ethanol to give a partially crystalline mixture of stereoisomeric products. Recrystallisation of this mixture allowed the purification of one of these products as its chloroform solvate, from which the last traces of chloroform could not be removed, even after collapse of the crystal structure just below the m.p. Chromatography of the non-crystalline residue then gave the second product which, although apparently homogeneous (t.l.c.), could not be induced to crystallise. In view of the lack of resolution of the n.m.r. spectrum of this material it seems likely that it is a mixture of stereoisomers.

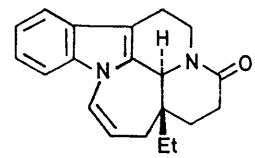
Neither the i.r. nor the n.m.r. spectra of these two products gave any indication of an aldehyde function. In the n.m.r. spectrum of the crystalline isomer (in $[^2H_6]$dimethyl sulphoxide) a one-proton doublet (J 6·5 Hz) at τ 3·53 which disappeared on addition of deuterium oxide was ascribed to a secondary hydroxy-proton.[22] A one-proton singlet at τ 5·62 was consistent with the part-structure ·O·CH(N<)·C<, and a broad one-proton triplet at τ 5·35 with the unit: HO·C*H*(O–)·CH_2·. In addition to these signals and a distorted three-proton triplet at τ 9·25, the non-aromatic portion of the spectrum showed the presence of fourteen other protons. These data, and the accurate molecular weight determined by high resolution mass spectrometry, established that the product of periodate cleavage of the amide (28) had the expected molecular formula ($C_{20}H_{26}N_2O_3$). On the basis of this evidence the cleavage product was assigned the carbinolamide-lactol constitution (29).

The i.r. and n.m.r. spectra of the non-crystalline isomer resembled those of the crystalline product, except that its n.m.r. spectrum exhibited no signal near τ 3·5. Instead, it contained a three-proton multiplet in the region τ 4·5—5·8, due to the part-structure: HO–C*H*–O–C*H*–N<.

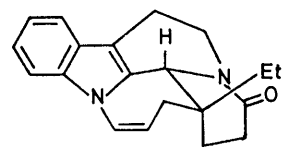
That these two products are stereoisomers was apparent not only from their spectrographic properties but also from their behaviour with glacial acetic acid. Both isomers gave the same mixture of products, which were



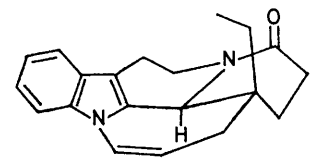
(30)



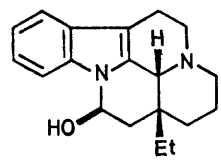
(31)



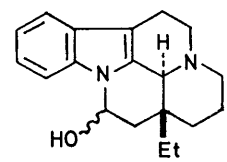
(30a)



(31a)



(32)



(33)

identified as 12aβ-ethyl-1,2,4,5,12a,12bβ-hexahydro-3*H*,12*H*-3a,9b-diazabenzo[*a*]naphth[2,1,8-*cde*]azulen-3-one (homoeburnamenine lactam) (30) and its 12bα-epimer, epihomoeburnamenine lactam (31); * these two isomers were formed in the ratio of *ca.* 9 : 10 in a total yield of 65%. The stereochemical assignments for (30) and (31) were established by their conversion into eburnamine (32) and 21-*epi*-eburnamine (33), respectively (see later), but they can also be deduced with some confidence from their u.v. and n.m.r. spectra, in conjunction with the study of Dreiding models. Both isomers exhibit the u.v. absorption of an *N*-vinylindole chromophore, but there are small differences in the $\lambda_{max.}$ and ε values, which reflect a difference in the geometry of the chromophore in the two isomers. The most stable conformations of these lactams are illustrated in formulae (30a) and (31a). While the 16,17'-double

* The numbering system adopted for (30) and (31) is based on that proposed for the *Hunteria* alkaloids.[23]

[22] O. L. Chapman and R. W. King, *J. Amer. Chem. Soc.*, 1964, **86**, 1256.

[23] J. Le Men and W. I. Taylor, *Experientia*, 1965, **21**, 508.

bond in the D/E-*trans*-isomer (31a) is almost coplanar with the indole ring system, the corresponding double bond in (30a) is inclined at an angle of 20—25° to the plane of the indole system. This twisting from coplanarity results in a reduced extinction coefficient in the 225 nm region for the *cis*-D/E-isomer (ε 31,300) compared with that observed for the *trans*-D/E-isomer (ε 36,600). In the *cis*-isomer the long-wavelength maximum is at 304 nm (ε 8640), which in the *trans*-isomer is replaced by two maxima at 298 and 307 nm (ε 8680 and 9400).

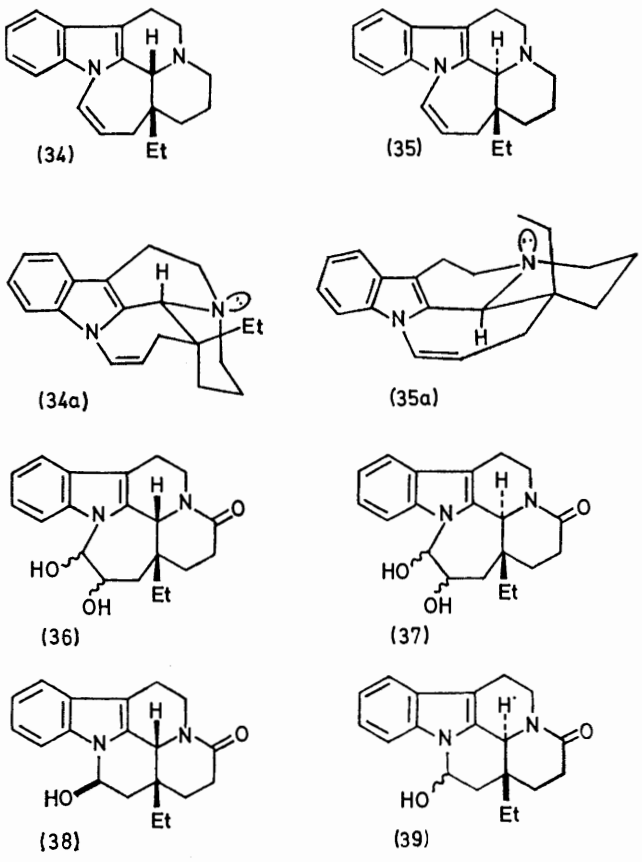
The n.m.r. spectra of these two isomers are also of interest. The C-17′ proton resonates at such a low field in both compounds (τ 3·05) that its signal is partially obscured by those of the aromatic protons. However, the *cis* vinyl coupling constants in (30) ($J_{16,17'}$ 8·5 Hz) and (31) ($J_{16,17'}$ 10 Hz) could be measured and this helped considerably in the interpretation of the C-16 proton resonances. In the *cis*-isomer (30) the multiplet due to this proton is centred at τ 4·65, such that $J_{16,17'} = 8{\cdot}5$, $J_{16,17\alpha} = 6{\cdot}5$, and $J_{16,17\beta} = 6{\cdot}5$ Hz. In the *trans*-isomer (31) the corresponding absorption, centred at τ 5·12, is superimposed on signals due to the C-21 proton and one of the protons on C-5; however, the coupling constants were elucidated as $J_{16,17'}$ 10, $J_{16,17\alpha}$ 3·5, and $J_{16,17\beta}$ 6·5 Hz. These values are reasonably in agreement with those expected for (30) and (31) on the basis of the known relationship between the dihedral angle and the coupling constants.

The chemical shift of the terminal methyl group also differs for compounds (30) and (31). As can be seen from the diagrams (30a) and (31a), in the D/E-*cis*-isomer the angular ethyl group is directed away from the aromatic system whereas in the D/E-*trans*-isomer (31a) the ethyl group is directed into a position in which the methyl group is close to the indole nucleus. This results in shielding of the methyl group in compound (31a), which therefore resonates at higher field (τ 9·25) than the methyl group in (30a) (τ 9·02).

In order to determine whether the product ratio [(30) : (31) *ca.* 9 : 10] was a manifestation of transition state stability (kinetic control) or the result of a secondary equilibration (thermodynamic control) a sample of the lactam (31) was heated at 60—70° in glacial acetic acid for 100 h. No epimerisation occurred, and therefore the possibility of secondary equilibration is excluded. The slight preponderance of the *trans*-compound (31) in this condensation is of some interest; in the report [24] of the preparation of eburnamonine lactam (29a) no mention is made of the formation of the *trans*-D/E-fused isomer, and in the preparation [14] of the lactams (29b) the isomer in which the ethyl group is *trans* with respect to the C-21 hydrogen atom predominated [25] over the corresponding *cis*-isomer in the ratio 6 : 1.

Although other methods for the cyclisation of compound (29) were investigated, no evidence was ever obtained for the formation, even transiently, of a compound related to (9), containing the aspidospermine ring system. Hydrogenation of epihomoeburnamenine lactam (31) in the presence of platinum catalyst gave the dihydro-derivative, which, as expected, exhibited a simple indole u.v. spectrum.

Lithium aluminium hydride reduction of the two lactams (30) and (31) proceeded smoothly to give the corresponding amines, homoeburnamenine (34) and 21-*epi*-homoeburnamenine (35). Both epimers exhibited the 16,17′-double bond stretching vibration at 1682—1685 cm^{-1} and, in addition, the i.r. spectrum of 21-*epi*-homoeburnamenine (35) contained Bohlmann bands [26] characteristic of *trans*-fused quinolizidine derivatives. The nature of the C/D ring fusion in (34) and (35) was



also indicated by their n.m.r. spectra. In homoeburnamenine (34) the C-21 proton resonates at τ 6·02 whereas in the 21-*epi*-isomer (35) the corresponding proton resonates at τ 6·79. The greater chemical shift of this proton in (34) is diagnostic of *cis*-fused quinolizidines, and is the result of deshielding of this proton by the lone pair of electrons on the adjacent nitrogen atom.[27] The chemical shifts of these protons may be compared with those of the analogous protons in their lactam precursors (30) and (31). The C-21 proton in (30) actually resonates at higher field (τ 5·6) than the C-21 proton in (31) (τ 5·26); in these lactams the position of

[24] M. F. Bartlett and W. I. Taylor, *J. Amer. Chem. Soc.*, 1960, **82**, 5941.
[25] L. Castedo, J. Harley-Mason, and T. J. Leeney, *Chem. Comm.*, 1968, 1186.
[26] F. Bohlmann, *Chem. Ber.*, 1958, **91**, 2157; *Angew. Chem.*, 1957, **69**, 641.
[27] M. Uskokovic, H. Bruderer, C. von Planta, T. Williams, and A. Brossi, *J. Amer. Chem. Soc.*, 1964, **86**, 3364.

the C-21 proton resonance is dominated by the relationship of this proton to the aromatic system, and in (30) is shielded to a greater extent than in (31).

Whereas analysis of the C-16 proton multiplet in the spectra of the lactams (30) and (31) was complicated by the presence in this region of a resonance due to one of the C-5 protons, in the amines (34) and (35) only the C-16 proton absorbed in this region. The signals observed for compounds (34) and (35) were similar to those exhibited by the lactams. The C-16 proton multiplet in the spectrum of (34) was centred at τ 5·05, with $J_{16,17'}$ 10, $J_{16,17\alpha}$ 5, and $J_{16,17\beta}$ 7 Hz, whereas the corresponding signal in the spectrum of (35) was centred at τ 5·15, with $J_{16,17'}$ 10, $J_{16,17\alpha}$ 4, and $J_{16,17\beta}$ 6 Hz. As was observed with the lactams, the terminal methyl group in the *cis*-isomer, homoeburnamenine (34), resonates at lower field (τ 9·12) than the analogous methyl group in the *trans*-isomer (35), where it is centred at τ 9·3. Both triplets are reasonably well resolved, as expected, since in both isomers [see (34a) and (35a)] the ethyl group and lone pair of electrons on N_b are *cis*-1,3-diaxially oriented.[28]

For the completion of the synthesis of eburnamine and 21-*epi*-eburnamine, oxidative loss of C-17′ is required, and for this purpose oxidation of the stable lactams (30) and (31) was preferred to oxidation of the more sensitive tertiary bases (34) and (35). In fact both homoeburnamenine lactam (30) and epihomoeburnamenine lactam (31) reacted cleanly with osmium tetroxide in pyridine to give the corresponding glycols (36) and (37). Repeated recrystallisations of the glycols failed to give material of consistent and sharp m.p., and it was concluded that the products, although apparently homogeneous (t.l.c. analysis), were probably mixtures of *cis*-glycols formed by attack of osmium tetroxide at both the α- and β-faces of the lactams. Cleavage of the glycols with sodium periodate in aqueous ethanol was extremely slow, and required several days and a large excess of reagent. With periodic acid in methanol cleavage was rapid, but did not proceed cleanly. Lead tetra-acetate in methanol was the reagent of choice and cleavage occurred cleanly and rapidly (*ca.* 5 min according to t.l.c. analysis). The intermediate *N*-formyl aldehydes were not isolated in view of the known ease of fission of *N*-acylindole derivatives, but were immediately treated with potassium carbonate, which smoothly removed the *N*-formyl group after a short period of heating. Spontaneous cyclisation of the intermediate aldehydes occurred, and the products isolated were eburnamine lactam (38) and 21-*epi*-eburnamine lactam (39). Finally, reduction of these lactams by lithium aluminium hydride, as reported by Harley-Mason,[25] afforded (±)-eburnamine (32; only one epimer shown) and (±)-21-*epi*-eburnamine (33), respectively. Synthetic eburnamine, m.p. 136—140°, was identical in i.r. ($CHCl_3$ solution), n.m.r., and mass spectra, and R_F values, with natural eburnamine. The i.r. spectrum of the non-crystalline 21-*epi*-eburnamine exhibited Bohlmann bands at 2745 and 2800 cm^{-1} indicative of the *trans*-C/D-ring junction. This was consistent with the absence of n.m.r. absorptions between τ 4·8 and 6·8; the C-21 proton must resonate above τ 6·8, and is obscured by the $>N-CH_2-$ signal. This is consistent only with a *trans*-C/D-ring junction. The position of the terminal methyl resonance of 21-*epi*-eburnamine (τ 9·35) is again consistent with this deduction (*cf.* the corresponding absorption at τ 9·16 in the spectrum of eburnamine).

EXPERIMENTAL

M.p.s were measured on a Kofler hot-stage apparatus. I.r. spectra were recorded on a Unicam SP200 spectrophotometer, or on a Perkin-Elmer P.E. 125 instrument; u.v. spectra were recorded on a Unicam SP 800 or SP 800A spectrophotometer (95% ethanol as solvent). N.m.r. spectra were measured on Varian A60 or A60A instruments, with tetramethylsilane as internal standard, and mass spectra were recorded on an A.E.I. MS 902 spectrometer. Mass spectral data for compounds (20b), (24), (25) and its acetonide, (26), (28)—(30), (31) and its dihydro-derivative, and (33)—(39) are given in Supplementary Publication No. SUP 20515 (22 pages, 1 microfiche).*

3-(*Pyrrolidin*-1-*ylmethylene*)*cyclopentene* (10).—A solution of cyclopent-1-enecarbaldehyde (9·6 g, 0·1 mol) and pyrrolidine (8·6 g, 0·12 mol) in anhydrous benzene (150 ml) was refluxed under a Dean–Stark head until no more water was collected (2 h). The benzene was removed *in vacuo* and the residue was fractionally distilled under reduced pressure in a dry nitrogen atmosphere. After a forerun of impure cyclopent-1-enecarbaldehyde (1·85 g), the *enamine* (10) was obtained as a pale yellow oil, b.p. 98—103° at 8 mmHg (9·01 g, 60·5% based on total aldehyde used), $\nu_{max.}$ (film) 1645 (C=C–N), 3042, and 708 (*cis*-CH=CH) cm^{-1}, $\lambda_{max.}$ (cyclohexane) 293 nm (ε 13,700).

Ethyl 1-*Ethyl*-2-*hydroxycyclopentanecarboxylate* (12).—Ethyl 1-ethyl-2-oxocyclopentanecarboxylate (18·4 g, 0·1 mol) dissolved in absolute ethanol (250 ml) was cooled to 0°. Sodium borohydride (1·9 g, 0·05 mol) was added in portions at such a rate that the temperature did not rise above 5°; the solution was then stirred for a further 3·5 h. After acidification (Congo Red) with dilute hydrochloric acid, the solution was filtered. Ethanol was removed *in vacuo* and the residue was extracted with ether. The combined extracts were dried ($MgSO_4$) and evaporated, and the residue was distilled under reduced pressure. The *hydroxy-ester* (12) (16·17 g, 87%) was obtained as an oil, b.p. 66·5—69·5° at 0·45 mmHg, $n_D^{25.5}$ 1·4550, $\nu_{max.}$ (film) 3480 (OH), 1724 (ester), 1233, and 1101 (sec. OH) cm^{-1}, τ (neat) 9·18 (3H, t, *J* 7 Hz, $CH_2 \cdot CH_3$), 8·75 [3H, dt, *J* 7 Hz, separation 1 Hz, $O \cdot CH_2 \cdot CH_3$ (isomers)], 7·6—8·7 (8H, m), 6·28 (1H, s, OH), and 5·6—6·1 [3H: 2H, dq, *J* 7 Hz, separation 2 Hz, $O \cdot CH_2 \cdot CH_3$ (isomers); 1H, $CH \cdot OH$]. The 3,5-*dinitrobenzoate* was obtained from benzene–light petroleum (b.p. 60—80°) as needles, m.p. 130—131° (Found: C, 53·75; H, 5·25; N, 7·35. $C_{17}H_{20}N_2O_8$ requires C, 53·7; H, 5·3; N, 7·35%).

When the temperature of the reaction mixture was allowed to rise above 5°, and particularly when the preparation was carried out on a very large scale, a considerable amount of a by-product, much less volatile than the desired hydroxy-ester, was obtained. This involatile residue (157 g) [after removal of the hydroxy-ester (73·6 g)] was refluxed with a solution of sodium hydroxide (47 g) in water (400 ml) until no organic layer remained. The solution

* For details of Supplementary Publications see Notice to Authors No. 7 in *J. Chem. Soc.* (*A*), 1970, Issue No. 20.

[28] W. F. Trager, C. M. Lee, and A. H. Beckett, *Tetrahedron*, 1967, **23**, 365, 375.

was extracted with ether and these extracts were discarded. The solution was then acidified (Congo Red) with concentrated sulphuric acid and extracted with ether, and the combined extracts were dried ($MgSO_4$) and evaporated. A solution of the residue (155 g) in absolute ethanol (200 ml) and benzene (700 ml), together with concentrated sulphuric acid (10 ml), was refluxed under a Dean–Stark head until no more water was collected. The volume of solution was reduced to *ca.* 400 ml and then the solution was washed with aqueous sodium hydrogen carbonate, dried (K_2CO_3), and evaporated. The residue was distilled under reduced pressure to give ethyl 1-ethyl-2-hydroxycyclopentanecarboxylate (128·3 g) as an oil, b.p. 67—70° at 0·2 mmHg, identical (i.r. spectrum) with the previously described hydroxy-ester (total yield 202 g, 84·5%).

Ethyl 1-*Ethylcyclopent*-2-*enecarboxylate* (14).—(*a*) Ethyl 1-ethyl-2-hydroxycyclopentanecarboxylate (27·9 g, 0·15 mol) was added slowly to freshly cut sodium (5 g, 0·22 mol) in dry ether (75 ml) and rinsed in with dry ether (10 ml). The mixture was stirred for 6 h and then the excess of sodium was removed mechanically. Carbon disulphide (17 ml) was added slowly with stirring, and after 90 min methyl iodide (21 ml) was added. The mixture was stirred overnight at room temperature and the precipitated sodium iodide was removed at the centrifuge. Ether and excess of carbon disulphide and methyl iodide were evaporated off and the crude xanthate (36·5 g) was pyrolysed for 30 min at 200—210°; the bath temperature was then increased to 220—230° and a yellow liquid distilled over at 192°. After 15 min at 220—230° the pressure was reduced slightly to complete the distillation. The product (18·4 g) was dissolved in benzene and chromatographed on Kieselgel G (400 g) with benzene as eluant. A pale-yellow, evil-smelling compound was eluted first, followed by the *unsaturated ester* (14) (13·4 g, 53%), b.p. 69—71·5° at 10 mmHg, $n_D^{22.5}$ 1·4455 (Found: C, 71·7; H, 9·5. $C_{10}H_{16}O_2$ requires C, 71·4; H, 9·6%); $\nu_{max.}$ (film) 1728 (ester) cm^{-1}, τ (neat) 9·17 (3H, t, *J* 7 Hz, $CH_2{\cdot}CH_3$), 8·81 (3H, t, *J* 7 Hz, $O{\cdot}CH_2{\cdot}CH_3$), 7·4—8·6 (6H, m), 5·95 (2H, q, *J* 7 Hz, $O{\cdot}CH_2{\cdot}CH_3$), and 4·3 (2H: 1H, s, $C{=}CH{-}C\lessgtr$; 1H, br,t, *J* 7 Hz, $CH{=}CH{\cdot}CH_2$).

(*b*) The hydroxy-ester (12) (37·2 g, 0·2 mol) dissolved in benzene (80 ml) was cooled in a water-bath. Phosphorus pentoxide (24 g, 0·17 mol) was added and the mixture was heated in an oil-bath at 110—120°. After 45 min at reflux, slight cooling was necessary because of frothing; moderate heating was then continued for a further 15 min. When cold, the supernatant liquid was decanted and the residue washed thoroughly with benzene. The solvent was evaporated off and the residue distilled under reduced pressure to give the ester (14) (26·3 g, 78%), b.p. 69—72·5° at 9 mmHg. G.l.c. analysis showed this material to contain *ca.* 10% impurity; the i.r. spectrum was identical with that of material prepared by method (*a*); the n.m.r. spectrum showed small impurity peaks.

1-*Ethylcyclopent*-2-*enylmethanol* (15).—The ester (14) (37·2 g, 0·22 mol) in dry ether (900 ml) was added to a stirred solution of lithium aluminium hydride (13 g, 0·33 mol) in dry ether (1500 ml) during 20 min. The solution was stirred for a further 2·5 h and then water was added to destroy the excess of lithium aluminium hydride. The precipitated lithium aluminate was filtered off and washed thoroughly with ether. The ethereal solution was dried (K_2CO_3) and evaporated, and the residue was distilled under reduced pressure to give the *alcohol* (15) (24·1 g, 86·5%) as an oil, b.p. 84—87·5° at 22 mmHg, n_D^{21} 1·4710, $\nu_{max.}$ (film) 3370 (OH) and 1038 (primary OH) cm^{-1}, τ (neat) 9·18 (3H, t, *J* 7 Hz, $CH_2{\cdot}CH_3$), 8·1—8·8 (4H, m), 7·7 (2H, br,t, *J* 6·5 Hz, $=C{\cdot}CH_2{\cdot}CH_2$), 6·62 (2H, s, $\gtrless C{\cdot}CH_2{\cdot}OH$), 5·65 (1H, s, O*H*), and 4·53 and 4·27 (2H with AB pattern, *J* 5·5 Hz, each of the four peaks being an incompletely resolved t, *J′ ca.* 1 Hz, *cis*-$CH_2{-}CH{=}CH{-}C\lessgtr$). The 3,5-*dinitrobenzoate* was obtained from ethanol as needles, m.p. 69—71° (Found: C, 56·15; H, 5·15; N, 8·7. $C_{15}H_{16}N_2O_6$ requires C, 56·25; H, 5·05; N, 8·75%).

1-*Ethylcyclopent*-2-*enecarbaldehyde* (16).—(*a*) A mixture of the alcohol (15) (0·504 g), dimethyl sulphoxide (12 ml), and acetic anhydride (8 ml) was stored at room temperature for 24 h, then poured into water. The aqueous solution was extracted with ether and the extract was washed first with aqueous sodium hydrogen carbonate until effervescence ceased, then with water, and then dried (Na_2SO_4) and evaporated. The residue (1·13 g) was divided into two equal portions. One portion was dissolved in benzene and chromatographed on Kieselgel G (25 g). Elution with benzene gave 1-*ethylcyclopent*-2-*enylmethyl methylthiomethyl ether* (17) (0·171 g, 46%) as an oil, $\nu_{max.}$ (film) 1073 (C–O–C) and 687 (C–S) cm^{-1}, τ (neat) 9·16 (3H, t, *J* 7 Hz, $CH_2{\cdot}CH_3$), 8·1—8·8 (4H, m), 7·95 (3H, s, $S{\cdot}CH_3$), 7·7 (2H, m, $C{=}C{-}CH_2$), 6·68 (2H, s, $\gtrless C{\cdot}CH_2{\cdot}O$), 5·45 (2H, s, $O{\cdot}CH_2{\cdot}S$), and 4·5 and 4·3 (2H with AB pattern, *J* 5·5 Hz, each of the four peaks being a partially resolved triplet, *J′* 2 Hz, *cis*-$CH_2{-}CH{=}CH{-}C\lessgtr$); and further elution with benzene gave the *aldehyde* (16) (47 mg, 19%) as an oil which rapidly turned brown on exposure to air; $\nu_{max.}$ (film) 2720 and 1720 (CHO) cm^{-1}. The 2,4-*dinitrophenylhydrazone* derivative was obtained from aqueous ethanol as orange-coloured needles, m.p. 137·5—138° (Found: C, 55·15; H, 5·5; N, 18·15. $C_{14}H_{16}N_4O_4$ requires C, 55·25; H, 5·3; N, 18·4%). The second portion of the crude product was chromatographed on Kieselgel G (25 g), but elution with light petroleum (b.p. 40—60°)–ether (99 : 1) did not give a useful separation of the products. When the experiment was repeated, careful evaporation of the solvent after the chromatography (elution with benzene) gave 44·4% of the aldehyde.

(*b*) A mixture of the alcohol (15) (1 g, 0·008 mol), *p*-benzoquinone (3·2 g, 0·03 mol), aluminium t-butoxide (4 g, 0·016 mol), and dry benzene (40 ml) was refluxed under dry nitrogen for 1 h, then cooled. The volume of solvent was reduced slightly, and the mixture was then filtered. The volume was further reduced, the precipitated *p*-benzoquinone was filtered off, and the filtrate was chromatographed on Kieselgel G (75 g). Elution with light petroleum (b.p. 40—60°)–ether (95 : 5), evaporation of solvent from the eluate, and reduced pressure distillation of the residue gave the aldehyde (16) (0·624 g, 63·5%), b.p. 73° at 37 mmHg, 66° at 27 mmHg, $\nu_{max.}$ (film) 2720 and 1720 (CHO) cm^{-1}, τ (neat) 9·18 (3H, t, *J* 7 Hz, $CH_2{\cdot}CH_3$), 7·4—8·6 (6H, m), 4·5 and 4·1 (2H with AB pattern, *J* 5·5 Hz, each of the four peaks showing unresolved fine structure), and 0·56 (1H, s, C–C*H*O). The 2,4-dinitrophenylhydrazone was identical with that described under (*a*) (i.r. spectrum, m.p., mixed m.p.).

Ethyl trans-β-(1-*Ethylcyclopent*-2-*enyl*)*acrylate* (18).—A solution of the aldehyde (16) (3·57 g, 0·0288 mol) and ethoxycarbonylmethylenetriphenylphosphorane (15 g, 0·0432 mol) in dry benzene (125 ml) was refluxed for 18 h in a dry nitrogen atmosphere, cooled, and then concentrated *in vacuo*. It was then added to a Kieselgel G (250 g) column and this was eluted with benzene. Concentration of the eluate *in vacuo*, followed by distillation of the residue under reduced pressure, gave the *acrylate* (18) (4·68 g, 84%), b.p. 113—116° at 9 mmHg, n_D^{21} 1·4779 (Found: C, 74·2; H, 9·45. $C_{12}H_{18}O_2$ requires C, 74·2; H, 9·35%), $\nu_{max.}$ (film)

1722 and 1647 (C=C–CO_2Et) cm^{-1}, $\lambda_{max.}$ (EtOH) 221 nm (ε 7630), τ (neat) 9·15 (3H, t, *J* 7 Hz, CH_2·CH_3), 8·77 (3H, t, *J* 7 Hz, O·CH_2·CH_3), 8·0—8·7 (4H, m), 7·7 (2H, m, CH_2·C=C), 5·88 (2H, q, *J* 7 Hz, O·CH_2·CH_3), 4·1—4·6 (3H, m: d, *J* 16 Hz clearly distinguishable, *trans*-C–CH=C*H*–CO_2Et; and *cis*-C*H*=C*H*), and 3·05 (1H, d, *J* 16 Hz, *trans*-C–C*H*=CH–CO_2Et).

In larger scale procedures, the oxidation product from the alcohol (15) was purified by chromatography on silica gel M.F.C. [elution with light petroleum (b.p. 40—60°)–ether (95 : 5)]. The eluate was concentrated *in vacuo*, and the residue treated directly with the phosphorane as just described. When the reaction was complete, the benzene was evaporated off and the residue extracted with ether to separate the product from triphenylphosphine oxide. The ether was evaporated and the residue distilled under reduced pressure (yield 57—63% from the alcohol).

Reaction of the Acrylate (18) *with Osmium Tetroxide.*—Osmium tetroxide (100 mg, 0·39 mmol) was dissolved in purified ether (6 ml) and cooled to −78°. A solution of the acrylate (76 mg, 0·39 mmol) in pyridine (0·5 ml) and ether (2 ml) was added; after a few minutes, the deposition of a buff precipitate began. The mixture was set aside at −40° overnight and then evaporated under reduced pressure. A mixture of sodium disulphite (175 mg, 0·92 mmol), water (3 ml), and pyridine (3 ml) was cooled to 0° and added to the osmate ester. The mixture was stirred at 0° for 90 min and then extracted four times with an equal volume of chloroform. The combined chloroform extracts were dried ($MgSO_4$) and evaporated, and the residue (83 mg) was chromatographed on Kieselgel G (20 g). Elution with chloroform and then chloroform–ethanol (95 : 5) gave the mixture of *cis*-hydroxylated isomers, ethyl *trans*-β-(1-ethyl-*t*-2,*t*-3-dihydroxy-*r*-1-cyclopentyl)acrylate and ethyl *trans*-β-(1-ethyl-*c*-2,*c*-3-dihydroxy-*r*-1-cyclopentyl)acrylate (70·3 mg, 78·7%) as an oil, $\nu_{max.}$ (film) 3420 (OH), 1715, 1647 (C=C–CO_2Et), 1312, and 1096 (sec. OH) cm^{-1}, τ ($CDCl_3$) 9·18 (3H, t, *J* 7 Hz, CH_2·CH_3), 8·7 (3H, t, *J* 7 Hz, O·CH_2·CH_3), 7·8—8·7 (6H, m), 5·5—6·4 (6H, m; q, *J* 7 Hz, clearly distinguishable, O·CH_2·CH_3, C*H*OH·C*H*OH), 4·17 (1H, *J* 16 Hz, *trans*-C–CH=C*H*–CO_2Et), and 2·83 and 3·1 [1H, two d's, *J* 16 Hz, *trans*-C–C*H*=CH–CO_2Et (isomers)], τ (Me_2CO) 4·17 [1H, two d's, *J* 16 Hz, separation 2 Hz, *trans*-CH=C*H*–CO_2Et (isomers)], and 2·83 and 3·1 as in $CDCl_3$.

Reaction of the Acrylate (18) *with Acetyl Hypoiodite.*—A mixture of the acrylate (18) (0·582 g, 0·003 mol), iodine (0·85 g, 0·0033 mol), and silver acetate (0·627 g, 0·00375 mol) in glacial acetic acid (22·5 ml) was stirred at room temperature for 4 h. The mixture was filtered (Celite) and the precipitate washed thoroughly with chloroform. The chloroform and most of the acetic acid were evaporated off under reduced pressure and the residue, dissolved in ether, was washed successively with aqueous sodium hydrogen carbonate solution (twice), sodium thiosulphate solution, and water. The ethereal solution was then dried ($MgSO_4$) and evaporated, and the residue (1·24 g), dissolved in benzene, was chromatographed on Kieselgel G (60 g). Elution with benzene–ether (96 : 4) gave an oil (1·04 g, 91·3%), t.l.c. analysis and the n.m.r. spectrum of which clearly indicated the presence of two isomers (Found: C, 44·25; H, 5·6 Calc. for $C_{14}H_{21}IO_4$: C, 44·2; H, 5·55%). The oil partially crystallised; three recrystallisations from light petroleum (40—60°) with cooling to −25° gave the pure predominant isomer, *ethyl* trans-β-(c-3-*acetoxy*-1-*ethyl*-t-2-*iodo*-r-1-*cyclopentyl*)*acrylate* (21a), m.p. 51—52° (Found: C, 44·25; H, 5·6; I, 33·6. $C_{14}H_{21}IO_4$ requires C, 44·2; H, 5·55; I, 33·4%), $\nu_{max.}$ (KCl) 1715 and 1645 (C=C–CO_2Et), 1738 and 1240 (OAc) cm^{-1}, τ ($CDCl_3$) 9·15 (3H, t, *J* 7 Hz, CH_2·CH_3), 8·7 (3H, t, *J* 7 Hz, O·CH_2·CH_3), 7·93 (3H, s, CH_3·CO_2), 7·5—8·7 (6H, m), 5·85 (3H: 2H, q, *J* 7 Hz, O·CH_2·CH_3; 1H, obscured by q, C*H*I), 4·9 (1H, m, C*H*·OAc), 4·2 (1H, d, *J* 16 Hz, *trans*-CH=C*H*–CO_2Et), and 3·15 (1H, d, *J* 16 Hz, *trans*-C–C*H*=CH–CO_2Et).

In large-scale experiments, the crude iodo-acetate (27·3 g) from the acrylate (18) (14·3 g) was crystallised from light petroleum (b.p. 40—60°) to give the pure, crystalline isomer (10·94 g, 39·1% from two crops; further small amounts were obtained on prolonged storage), m.p. 64·5—65°. This material had an i.r. spectrum identical with that of the material of m.p. 51—52°; the n.m.r. spectrum showed slightly better resolution and enabled the identification of a doublet, *J* 8·5 Hz, for CH·C*H*I at τ 5·97. On one occasion, a sample melted almost completely at 51—53°, then recrystallised and remelted at 63—65°.

Conversion of the Iodo-acetate (21a) *into ethyl* trans-β-(1-*ethyl*-c-2,c-3-*dihydroxy*-r-1-*cyclopentyl*)*acrylate* (20b).—A mixture of the iodo-acetate (1·14 g, 0·003 mol; m.p. 64·5—65°), water (0·108 g, 0·006 mol), and silver acetate (0·625 g, 0·00375 mol) in acetic acid (4 ml) was stirred at 95—100° in a nitrogen atmosphere for 3·5 h. When cold, it was filtered and the precipitate was washed thoroughly with chloroform. The filtrate was evaporated to a small volume, dissolved in chloroform, and washed with aqueous sodium hydrogen carbonate. The chloroform solution was dried ($MgSO_4$) and evaporated, and the residue, dissolved in benzene, was chromatographed on Kieselgel G (75 g). Elution with benzene–ether mixtures (85 : 15 to 60 : 40) gave the monoacetate, *ethyl* trans-β-(c-3-*acetoxy*-1-*ethyl*-c-2-*hydroxy*-r-1-*cyclopentyl*)*acrylate* (23a) (0·576 g, 71%), contaminated by another acetate, presumably ethyl *trans*-β-(*c*-2-acetoxy-1-ethyl-*c*-3-hydroxy-*r*-1-cyclopentyl)acrylate, which was ethanolysed without further purification. The monoacetate was dissolved in anhydrous ethanol (60 ml) containing anhydrous toluene-*p*-sulphonic acid (65 mg), and the solution was refluxed for 4 h, after which time the solvent was evaporated off and replaced by a further quantity of anhydrous ethanol (50 ml). The solution was refluxed for a further 4 h, the solvent was evaporated off, and the residue, dissolved in benzene–ethanol (96 : 4), was chromatographed on Kieselgel G (40 g). Elution with benzene–ethanol (96 : 4) and evaporation of the eluate gave the *diol* (20b) (431·4 mg, 94·5% based on monoacetate consumed), and some unchanged monoacetate (35·8 mg). A sample of the diol distilled in a sublimation apparatus (block temp. *ca.* 135° at 0·04 mmHg) was obtained as a viscous oil (Found: C, 63·0; H, 8·65. $C_{12}H_{20}O_4$ requires C, 63·15; H, 8·85%), $\nu_{max.}$ (film) 3440 (OH), 1715 and 1645 (C=C–CO_2Et), 1310 and 1083 (sec. OH) cm^{-1}, τ ($CDCl_3$) 9·18 (3H, t, *J* 7 Hz, CH_2·CH_3), 8·7 (3H, t, *J* 7 Hz, O·CH_2·CH_3), 7·8—8·7 (6H, m), 5·5—6·6 (6H, m, O·CH_2·CH_3, C*H*OH·C*H*OH), 4·17 (1H, *J* 16 Hz, *trans*-C–CH=C*H*–CO_2Et), and 3·1 (1H, *J* 16 Hz, *trans*-C–C*H*=CH·CO_2Et).

In subsequent experiments, the crude monoacetate was ethanolysed directly without prior chromatography. In this way, any diacetate which was present was also converted into the diol, which was purified by reduced pressure distillation in a nitrogen atmosphere.

Photolytic Conversion of the Diol (20b) *into* 4aβ-*Ethyl*-5,6,7,7aβ-*tetrahydro*-7α-*hydroxycyclopenta*[b]*pyran*-2(4aH)-*one* (24).—A solution of the diol (2·007 g), toluene-*p*-sulphonic acid (0·2 g), and a trace of iodine in dry benzene (500 ml), under dry nitrogen, was exposed to the emission from a Hanovia medium-pressure photolyser for 64 h.

The solvent was removed *in vacuo* and the residue was dissolved in benzene–ethanol (39 : 1) and chromatographed on Kieselgel G (125 g). Elution with benzene–ethanol (39 : 1) gave the δ-*lactone* (24) (0·495 g, 60·5% based on diol consumed), and elution with benzene–ethanol (92 : 8) gave unchanged diol (0·987 g). The lactone formed prisms, m.p. 112·5—113° (from benzene) (Found: C, 66·05; H, 7·7. $C_{10}H_{14}O_3$ requires C, 65·9; H, 7·75%), $\nu_{max.}$ (KCl disc) 3395 (OH), 1720 (αβ-unsaturated δ-lactone), 1600 (conj. C=C), 1100 (sec. OH), and 822 (*cis*-CH=CH) cm^{-1}, τ ($CDCl_3$) 9·13 (3H, t, *J* 7 Hz, $CH_2{\cdot}CH_3$), 7·5—8·9 (6H, m), 7·05 (1H, s, O*H*), 5·98 (1H, d, *J* 5 Hz, CH·C*H*O–C⩽), 5·6 (1H, br,t, *J* 6 Hz, $CH_2{\cdot}CH$OH·CH), 4·05 (1H, d, *J* 9 Hz, *cis*-CH=C*H*·CO_2), and 2·85 (1H, d, *J* 9 Hz, *cis*-C*H*=CH·CO_2).

Reaction of the δ-*Lactone* (24) *with Tryptamine*.—A solution of the lactone (0·40 g, 2·2 mmol) and tryptamine (0·42 g, 2·62 mmol) in dry benzene (25 ml) was refluxed under dry nitrogen for 82 h. T.l.c. showed that a large amount of unchanged lactone was still present. More tryptamine (0·42 g) was added and refluxing was continued for a further 60 h. The solvent was removed and the residue dissolved in chloroform–ethanol (4 : 1) was chromatographed on Kieselgel G (100 g). Elution with the same solvent gave some impure lactone (0·127 g) followed by some impure by-product (83 mg). The proportion of ethanol in the eluant was then gradually increased to 60%. Evaporation of the appropriate fractions gave the impure amide, 3-(1-*ethyl*-c-2,c-3-*dihydroxy*-r-1-*cyclopentyl*)-N-[2-(*indol*-3-*yl*)*ethyl*]-3-[2-(*indol*-3-*yl*)*ethylamino*]*propionamide* (25) (0·86 g, 78% based on lactone taken) as an amorphous white solid (softened above 90°, charred above 210°), $\nu_{max.}$ (KCl) 3410 (NH), 3320 (OH), 1650, 1550 (sec. amide), and 1095 (sec. OH) cm^{-1}, $\lambda_{max.}$ (EtOH) 223 (ε 65,800), 276sh (10,800), 282 (11,400), and 290 (9950) nm, τ ($CD_3{\cdot}CO_2H$) 9·15 (3H), 7·5—8·9 (8H), 5·7—7·5 (11H), and 2·3—3·2 (10H), *m/e* 373 (0·4%, *M* − 129) and 372·227 (1·1%, $C_{21}H_{23}N_3O_3$ requires 372·229, *M* − 130).

Attempted crystallisations from a variety of solvents were unsuccessful, and the compound was characterised as the isopropylidene derivative (see later).

The by-product (83 mg) was purified by further chromatography on Kieselgel G (10 g). Elution initially with chloroform–ethyl acetate (4 : 1) and then with eluants of greater ethyl acetate content (eventually 100%) gave pure trans-β-(1-*ethyl*-c-2,c-3-*dihydroxy*-r-1-*cyclopentyl*)-N-[2-(*indol*-3-*yl*)*ethyl*]*acrylamide* (26) (67·7 mg, 9% based on lactone taken) as an amber gum, $\nu_{max.}$ ($CHBr_3$) 3470, 3435 (NH), 3320 (OH), 1652, 1622, 1515 (αβ-unsaturated amide), 1340, 1348, 1080, and 1090 (sec. OH) cm^{-1}, $\lambda_{max.}$ (EtOH) 223 (ε 38,400), 274 (5670), 282 (5720), and 291 nm (4830), τ ($CDCl_3$ with added D_2O) 9·2 (3H, t, *J* 7 Hz, $CH_2{\cdot}CH_3$), 7·7—8·9 (6H, m), 7·08 (2H, t, *J* 6 Hz, $CH_2{\cdot}CH_2{\cdot}$C=), 6·45 (2H, q, *J* 6 Hz, NH·$CH_2{\cdot}CH_2$), 6·15 (1H, d, *J* 6 Hz, ⩾C·C*H*OD·CH), 5·88 (1H, m, $CH_2{\cdot}CH$OD·CH), 4·43 (1H, d, *J* 13 Hz, *trans*-C–CH=C*H*–C=O), 4·15 (1H, d, *J* 13 Hz, *trans*-C–C*H*=CH–C=O), and 2·3—3·2 (5H, m, aromatic and indole α-protons), *m/e* 342·194 (6·1%, $C_{20}H_{26}N_2O_3$ requires 342·194, M^+).

3-(1-*Ethyl*-c-2,c-3-*isopropylidenedioxy*-r-1-*cyclopentyl*)-N-[2-(*indol*-3-*yl*)*ethyl*]-3-[2-(*indol*-3-*yl*)*ethylamino*]*propionamide*.—A mixture of the crude amide (25) (150 mg), freshly dried copper sulphate (1·5 g), and toluene-*p*-sulphonic acid (25 mg) in dry acetone (25 ml) was stirred and refluxed under dry nitrogen for 85 h, then cooled. Potassium carbonate (400 mg) was added, and the mixture was stirred for a further 30 min. Solids were filtered off, the solvent was removed *in vacuo*, and the residue was chromatographed on Kieselgel G (20 g). Elution with ethyl acetate–ethanol (95 : 5) gave the acetonide (97·2 mg) contaminated with a small amount of triacetone alcohol. This material was rechromatographed under the same conditions to give the pure *acetonide* (81·7 mg, 50·5%), $\nu_{max.}$ ($CHBr_3$) 3430—3465 (NH), 1658, 1512 (sec. amide), 1370, and 1378 (Me_2C) cm^{-1}, $\lambda_{max.}$ (EtOH) 223 (58,800), 276sh (10,300), 282 (10,900), and 291 (9450) nm, τ ($CDCl_3$) 9·2 (3H, t, *J* 7 Hz, $CH_2{\cdot}CH_3$), 7·65—9·0 (15H, m; ⩾C·CH_3 singlets at 8·84 and 8·62), 6·9—7·65 (7H, m), 6·55br (2H, q, *J* 6 Hz, $CH_2{\cdot}CH_2{\cdot}$NH·CO), 5·83 (1H, d, *J* 6 Hz, $CH_2{\cdot}$-C*H*·C⩽), 5·56br (1H, t, $CH_2{\cdot}CH$·CH), 3·65br (1H, t, *J* 6 Hz, $CH_2{\cdot}$N*H*·CO), 2·3—3·3 (10H, m, aromatic and indole α-protons), and 1·65 (2H, s, indole NH), *m/e* 527·300 (0·2%, $C_{32}H_{39}N_4O_3$ requires 527·302, *M* − CH_3).

Ethyl β-(1-*Ethyl*-2,3-cis-*dihydroxycyclopentyl*)*propionate* (27).—Ethyl *trans*-β-(1-ethyl-2,3-*cis*-dihydroxycyclopent-1-yl)acrylate [4·56 g; mixture of (20a) and (20b) from the mixture of iodoacetates] was hydrogenated in ethanol (100 ml) at room temperature and pressure in the presence of 10% palladised charcoal (0·456 g) until uptake of hydrogen ceased (3 h). After filtration and evaporation, the residue was distilled under reduced pressure to give the *propionate* (27) (3·52 g, 76·5%) as a viscous oil, b.p. 160—167° at 0·5 mmHg (Found: C, 62·6; H, 9·2. $C_{12}H_{22}O_4$ requires C, 62·6; H, 9·6%), $\nu_{max.}$ (film) 3430 (OH) and 1730 (CO_2Et) cm^{-1}, τ ($CDCl_3$) 9·1 [3H, two t, *J* 7 Hz, $CH_2{\cdot}CH_3$ (isomers)], 8·75 (3H, t, *J* 7 Hz, O·$CH_2{\cdot}CH_3$), 7·9—8·8 (8H, m), 7·3—7·9 (2H, m, $CH_2{\cdot}CO_2$), 6·7—7·2 (2H, 2 × O*H*; removed by addition of D_2O), 6·37br (1H, t, *J* 5 Hz, CH·C*H*OH·C⩽; became d, *J* 5 Hz, when D_2O added), 5·9 (2H, q, *J* 7 Hz, O·$CH_2{\cdot}CH_3$), and 5·75 (1H, obscured by q, C*H*OH·CHOH·C⩽).

3-(1-*Ethyl*-2,3-cis-*dihydroxycyclopentyl*)-N-[2-(*indol*-3-*yl*)*ethyl*]*propionamide* (28).—A mixture of the propionate (27) (2·21 g) and tryptamine (1·85 g, 10% excess) was stirred and heated at 150—160° for 11 h under a dry nitrogen atmosphere. The product was dissolved in ethyl acetate–ethanol (94 : 6) and chromatographed on Kieselgel G (250 g). Elution with ethyl acetate–ethanol mixtures (94 : 6 to 90 : 10) and evaporation of the relevant fractions gave the *amide* (28) (2·76 g, 83·5%) as a gum (Found: C, 69·25; H, 8·05; N, 8·05. $C_{20}H_{28}N_2O_3$ requires C, 69·75; H, 8·2; N, 8·15%), $\nu_{max.}$ ($CHCl_3$) 3480, 3440 (NH), 3330 (OH), 1657, 1518 (sec. amide), 1073, and 1087 (sec. OH) cm^{-1}, $\lambda_{max.}$ (EtOH) 223 (ε 34,400), 276sh (5430), 282 (5790), and 291 (4980) nm, τ ($CDCl_3$) 9·25 (3H, distorted t, $CH_2{\cdot}CH_3$), 7·6—9·1 (10H, m), 5·7—7·3 (8H, m), 4·1 (1H, m, NH·CO), 2·3—3·2 (5H, m, aromatic and indole α-protons), and 1·4 (1H, s, indole NH), *m/e* 344·208 (0·78%, $C_{20}H_{28}N_2O_3$ requires 344·209, *M*).

Periodate Cleavage of the Amide (28).—A solution of sodium periodate (1·12 g, 1·5 mol. equiv.) in water (50 ml) was added to a solution of the amide (1·2 g) in ethanol (50 ml) and the mixture was stirred at room temperature for 1 h. A few drops of phenolphthalein solution were added, followed by hot aqueous barium hydroxide solution until the solution was permanently pink. The solution was evaporated to dryness and the residue partitioned between water (100 ml) and chloroform (100 ml). The aqueous phase was extracted with further portions of chloroform (2 × 100, 1 × 50 ml), and the combined, dried (Na_2SO_4) chloroform extracts were evaporated to dryness. The partially crystalline residue was recrystallised from chloroform to give 4a-*ethyl*-2-*hydroxy*-8-(2-*indol*-3-*ylethyl*)*perhydropyrano*[2,3-b]*pyridin*-7-*one* (29) (0·726 g, 46·7%; two crops) as solvated crystals,

m.p. 105—112° (bubbling) (Found: C, 55·9; H, 6·15; Cl, 20·4; N, 6·55. $C_{20}H_{26}N_2O_3$,0·87$CHCl_3$ requires C, 56·15; H, 6·05; Cl, 20·75; N, 6·3%), $\nu_{max.}$ (KCl) 3340 (OH) and 1630 (amide) cm^{-1}, $\lambda_{max.}$ (EtOH) 223 (ε 43,800), 277sh (7050), 283 (7550), and 291 (6530) nm, τ [$(CD_3)_2SO$] 9·25 (3H, distorted t, CH_2·CH_3), 8·2—9·1 (7H, m), 7·6—8·0 (3H, s), 5·9—7·3 (4H, m), 5·62 [1H, s, O·CH(N<)·C<], 5·35br [1H, t, *J ca.* 6 Hz, HO·CH(O−)·CH_2), 3·53 (1H, d, *J* 6·5 Hz, CHO*H*; removed by addition of D_2O), 2·3—3·2 (5H, m, aromatic and indole α-protons), and −0·75 (1H, s, indole NH), *m/e* 342·192 (1·7%, $C_{20}H_{26}N_2O_3$ requires 342·194).

The non-crystalline residue left after removal of the crystalline isomer was chromatographed on Kieselgel G (25 g). Elution with ethyl acetate–ethanol (96 : 4) and evaporation of the relevant fractions gave the non-crystalline *isomer* of compound (29) (0·469 g, 39·4%), $\nu_{max.}$ (powdered foam in KCl disc) 3360 (OH) and 1625 (amide) cm^{-1}, $\lambda_{max.}$ (EtOH) 223 (ε 34,200), 277sh (5340), 283 (5750), and 291 (5000), nm; n.m.r. poorly resolved but CHO*H* signal occurred at or above τ 4·75, *m/e* 342·192.

Homoeburnamenine Lactam (30) *and* epi-*Homoeburnamenine Lactam* (31).—The amide (28) (1·31 g) was cleaved as previously described and the product, without separation of the crystalline and non-crystalline isomers, was dissolved in glacial acetic acid (12 ml) and heated at 55—60° for 65 h in a dry nitrogen atmosphere. When cold, the product was dissolved in chloroform (100 ml) and washed with 2N-sodium hydrogen carbonate solution until effervescence ceased. The dried (Na_2SO_4) chloroform solution was evaporated and the residue, in chloroform, was chromatographed on Kieselgel G (50 g). Elution with ethyl acetate gave *homoeburnamenine lactam* (0·317 g, 27·2% from glycol), obtained from ethyl acetate as prisms, m.p. 149—151·5° (Found: C, 78·1; H, 7·1; N, 9·15. $C_{20}H_{22}N_2O$ requires C, 78·4; H, 7·25; N, 9·15%), $\nu_{max.}$ (KCl) 1675 (N−C=C) and 1640 (δ-lactam) cm^{-1}, $\lambda_{max.}$ (EtOH) 223 (ε 29,500), 256 (31,300), 299sh (8500), and 304 (8640) nm, τ ($CDCl_3$) 9·02 (3H, t, *J* 6·5 Hz, CH_2·CH_3), 8·0—8·7 (4H, m), 6·8—8·0 (7H, m), 5·6 (1H, s, 21-H), 5·0 (1H, m, 5-H), 4·65 (1H, dt, *J* 8·5, *J′* 6·5 Hz, 16-H), 3·05 (1H, d, *J* 8·5 Hz, 17′-H), and 2·4—3·0 (4H, m, aromatic protons), *m/e* 306·173 (100%, $C_{20}H_{22}N_2O$ requires 306·172). Continued elution with ethyl acetate gave epi-*homoeburnamenine lactam* (0·35 g, 30·1% from glycol), obtained from ethyl acetate as needles, m.p. 180—183° (Found: C, 78·55; H, 7·05; N, 9·4%), $\nu_{max.}$ (KCl) 1675 (N−C=C) and 1630 (δ-lactam) cm^{-1}, $\lambda_{max.}$ (EtOH) 221 (ε 24,600), 255 (36,600), 298 (8680), and 307 nm (9400), τ ($CDCl_3$) 9·25 (3H, t, *J* 7 Hz, CH_2·CH_3), 8·55—9·05 (2H, m, CH_2·CH_3), 7·9—8·55 (2H, m, 15-H_2), 7·45—7·9 (4H, m, 17-H_2 and 14-H_2), 7·0—7·45 (3H, m, 5-H and 6-H_2), 5·26 (1H, s, 21-H), 4·7—5·25 (2H, m, 5-H and 16-H), 3·05 (1H, partially obscured d with partially resolved fine structure, *J* 10 Hz, 17′-H), and 2·4—3·0 (4H, m, aromatic protons), *m/e* 306·173.

The same products were obtained when the pure, crystalline solvated isomer of compound (29) was used (31·1 and 33·6%, respectively), and also when the non-crystalline isomer was used (22·7 and 26·1%, respectively).

epi-Homoeburnamenine lactam (2·5 mg) in glacial acetic acid (0·5 ml) was unchanged when heated at 60—70° for 100 h in a dry nitrogen atmosphere.

Homoeburnamenine (34) *and* epi-*Homoeburnamenine* (35).—A mixture of homoeburnamenine lactam (50 mg) and lithium aluminium hydride (200 mg) in anhydrous ether (25 ml) was refluxed for 1 h. Wet ether was added cautiously to destroy the excess of reducing agent and the solution was then dried (Na_2SO_4). The ether was evaporated off and the residue was recrystallised from light petroleum (b.p. 60—80°) to give *homoeburnamenine* (35·6 mg, 74·5%) as needles, m.p. 86—88°, or prisms, m.p. 113—114·5° (Found: C, 82·3; H, 8·0; N, 9·45. $C_{20}H_{24}N_2$ requires C, 82·15; H, 8·25; N, 9·6%), $\nu_{max.}$ ($CHCl_3$) 1682 (N−C=C) cm^{-1}, $\lambda_{max.}$ (cyclohexane) 230 (ε 21,000), 262 (29,200), 302 (9780), 309 (9620), and 315 nm (10,000), τ ($CDCl_3$) 9·12 (3H, t, *J* 7·5 Hz, CH_2·CH_3), 6·6—8·9 (14H, m), 6·02 (1H, s, 21-H), 5·05 (1H, four sets of d's, *J* 10, 7, and 5 Hz, 16-H), 3·05 (1H, partially obscured dd, *J* 10 and 1·5 Hz, 17′-H), and 2·4—3·0 (4H, m, aromatic protons), *m/e* 292·194 (98%, $C_{20}H_{24}N_2$ requires 292·194). A second crop (11·4 mg, 23·8%) was obtained by concentration of the mother liquor.

Treatment of *epi*-homoeburnamenine lactam (50 mg) in the same manner gave epi-*homoeburnamenine* (37·4 mg, 78·5%), obtained from light petroleum (b.p. 60—80°) as crystals, m.p. 95—99·5°, $\nu_{max.}$ ($CHCl_3$) 2805, 2750 (*trans*-bands), and 1685 (N−C=C) cm^{-1}, $\lambda_{max.}$ (cyclohexane) 227 (ε 19,300), 261 (30,100), 301 (8280), 309sh (8180), and 313 nm (9350), τ ($CDCl_3$) 9·3 (3H, t, *J* 7·5 Hz, CH_2·CH_3), 6·8—9·15 (14H, m), 6·69 (1H, s, 21-H), 5·15 (1H, AMXY pattern, *J* 10, 6, and 4 Hz, 16-H), 3·08 (1H, partially obscured d with partially resolved fine structure, *J* 10 Hz, 17′-H), and 2·4—3·0 (4H, m, aromatic protons), *m/e* 292·194. When exposed to air this material turned yellow.

Dihydro-epi-*homoeburnamenine Lactam.*—*epi*-Homoeburnamenine lactam (20 mg) in ethanol (15 ml) was hydrogenated at atmospheric temperature and pressure over pre-reduced platinum oxide (20 mg). After filtration and evaporation the residue gave *dihydro*-epi-*homoeburnamenine lactam* (18·3 mg) as prisms, m.p. 110—111° (bubbling) (from aqueous ethanol), $\nu_{max.}$ (KCl) 1610 (δ-lactam) cm^{-1}, $\lambda_{max.}$ (EtOH) 228 (ε 30,700), 278 (5800), 285 (6220), and 293sh nm (5300), τ ($CDCl_3$) 9·32 (3H, distorted t, *J* 7 Hz, CH_2·CH_3), 7·2—9·2 (13H, m), 5·45—6·8 (2H, m, N·CH_2), 5·27 (1H, s, 21-H), 4·7—5·0 (1H, m, 5-H), and 2·35—3·15 (4H, m, aromatic protons), *m/e* 308·188 (50%, $C_{20}H_{24}N_2O$ requires 308·189).

Dihydroxyhomoeburnamenine Lactam (36).—A solution of osmium tetroxide (200 mg) in pyridine (2 ml) was added to homoeburnamenine lactam (240 mg) in pyridine (1 ml) at 0°. The solution was left at room temperature for 24 h, during which time a precipitate separated. Sodium disulphite (380 mg) in water (6 ml) and pyridine (4 ml) was added and the mixture was stirred vigorously for 1·5 h, then extracted with chloroform (4 × 12 ml). The combined extracts were washed with brine, dried (Na_2SO_4), and evaporated to dryness. The residue (284 mg) was recrystallised from ethyl acetate containing a small amount of methanol. *Dihydroxyhomoeburnamenine lactam* (234·3 mg, 87·5%, from three crops) was obtained as fine needles, m.p. 215—222° (the m.p. was variable, and in other preparations values in the range 204—232° were observed), $\nu_{max.}$ (KCl) 3120—3440vbr (OH) and 1612 (δ-lactam) cm^{-1}, $\lambda_{max.}$ (EtOH) 228 (ε 36,000), 277 (8650), 284 (9060), and 292 nm (7530), *m/e* 340·179 (100%, $C_{20}H_{24}N_2O_3$ requires 340·179).

Dihydroxy-epi-*homoeburnamenine Lactam* (37).—*epi*-Homoeburnamenine lactam (240 mg) was hydroxylated in the same manner and gave *dihydroxy*-epi-*homoeburnamenine lactam* (37) (218·5 mg, 81·8%, from two crops), obtained from ethyl acetate as needles, m.p. *ca.* 174° (then resolidification, then m.p. 215—216·5°), $\nu_{max.}$ (KCl) 3160—3500vbr (OH) and 1605 (δ-lactam) cm^{-1}, $\lambda_{max.}$ (EtOH) 227 (ε 38,300), 275 (8700), 282 (8540), and 292 nm (6370), *m/e* 340·179. A sample dried at 180° and 0·1 mmHg exhibited m.p. 218—224° (Found: C, 70·7; H, 7·05; N, 8·15. $C_{20}H_{24}N_2O_3$ requires C, 70·55; H, 7·1; N, 8·25%).

Eburnamine Lactam (38).—Dihydroxyhomoeburnamenine lactam (102 mg) was dissolved in methanol (15 ml) and lead tetra-acetate (330 mg; moist with acetic acid) was added. The solution was stirred for 30 min and then excess of ethylene glycol (8 drops) was added. Stirring was continued for a further 10 min. Potassium carbonate (250 mg) was added and the solution was refluxed for 10 min. Methanol was evaporated off *in vacuo* and the residue was partitioned between water (10 ml) and chloroform (15 ml). The aqueous phase was extracted with more chloroform (3 × 10 ml) and the combined extracts were dried (Na_2SO_4) and evaporated. Eburnamine lactam (75 mg, 81·8%) was obtained as a powder, m.p. 160—214° which after prolonged drying exhibited m.p. 232—240° (lit.,[14] m.p. 210—211°, although this sample was probably not stereochemically homogeneous [25]), $\nu_{max.}$ (KCl) 3280 (OH) and 1615 (δ-lactam) cm^{-1}, $\lambda_{max.}$ (EtOH) 227 (ε 41,700), 276 (8650), 282 (8750), and 291 nm (6750), *m/e* 310·166 (100%, $C_{19}H_{22}N_2O_2$ requires 310·168).

21-epi-*Eburnamine Lactam* (39).—Dihydroxy-*epi*-homoeburnamenine lactam (102 mg) was treated in the same manner and gave epi-*eburnamine lactam* (39) (69·4 mg, 74·5%, two crops from ethanol) as plates, m.p. 145—185° (bubbling), $\nu_{max.}$ (KCl) 3340 (OH) and 1624 (δ-lactam) cm^{-1}, $\lambda_{max.}$ (EtOH) 226 (33,200), 275 (8530), 281 (8180), and 291 nm (5350), *m/e* 310·166.

Eburnamine (32).—Lithium aluminium hydride (200 mg) was added to eburnamine lactam (35 mg) in dry ether (20 ml) and the mixture was refluxed for 1·5 h. Excess of reducing agent was destroyed with wet ether and then water; the dried (K_2CO_3) solution was evaporated to dryness *in vacuo*. Recrystallisation of the residue (34·1 mg) from aqueous ethanol gave (±)-eburnamine (28·5 mg, 85·3%), m.p. 136—140°. A further recrystallisation from aqueous ethanol gave material (25·5 mg) of the same m.p. This synthetic material was identical in R_F value (and colour reaction when the plate was sprayed with H_2SO_4–HNO_3) and n.m.r., i.r. ($CHCl_3$ solution), and mass spectra with the natural alkaloid * (m.p. 178—180°).

epi-*Eburnamine* (33).—*epi*-Eburnamine lactam (35 mg) was reduced in the same manner as eburnamine lactam. The product was isolated by preparative plate chromatography on 1 : 1 Kieselgel G–Kieselgel HF_{254} (20 × 20 cm × 1 mm) with benzene–ethanol (9 : 1) as eluant. The relevant portion of Kieselgel was extracted with methanol, the extract was evaporated and the residue in chloroform solution was filtered through a small pad of grade III, neutral alumina. Removal of chloroform left *epi*-eburnamine (21·5 mg, 64·4%) as an amber gum, $\nu_{max.}$ ($CHCl_3$) 3580 (OH), 2800 and 2745 (*trans*-bands), and 1040 (C·OH) cm^{-1}, $\lambda_{max.}$ (EtOH) 225 (ε 24,500), 276 (6450), 282 (6250), and 291sh nm (5000), τ ($CDCl_3$) 6·8—9·4 (18H, m), 4·2—4·7 (1H, m, 16-H), and 2·2—3·1 (5H, m, aromatic protons and OH).

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