Aust. J. Chem., 1975, **28**, 1843–56

Indole Alkaloids from *Ervatamia orientalis*. III* The Configurations of the Ethyl Side Chains of Dregamine and Tabernaemontanine and Some Further Chemistry of the Vobasine Group

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Abstract

Evidence is presented to show that the configurations of the ethyl side chains of dregamine and tabernaemontanine are the reverse of the original assignments, i.e. the correct structures are (2) and (3) respectively. Dregamine readily forms the 16-epimer (6) from treatment with sodium methoxide; two neutral products from similar treatment of tabernaemontanine are assigned the epimeric structures (7) and (8). Evidence for the mode of formation of the methine products of Hofmann degradation of dregamine and vobasine (1) is presented and the stereochemistry of these products is assigned on the basis of chemical correlations with taberpsychine (23).

Introduction

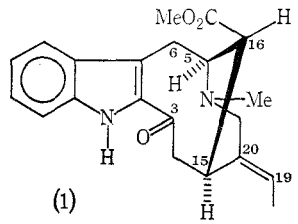
Dregamine and tabernaemontanine are 2-acylindole alkaloids occurring in plants of the Tabernaemontaninae subtribe of the Apocynaceae family.[1] The structures are also units in the dimeric alkaloid structures of 16-demethoxycarbonyldihydrovoacamine (dregamine unit) and 16-demethoxycarbonyl-20′-epidihydrovoacamine (tabernaemontanine unit).[2] The two alkaloids are dihydro derivatives of vobasine (1) from which they have been obtained by catalytic hydrogenation. A mixture of the two with dregamine predominating was reported to be formed with Raney nickel catalyst[3] whereas only tabernaemontanine was isolated with a platinum catalyst.[3] The structure of vobasine (1) has been established by chemical and spectroscopic studies[3] and by an X-ray diffraction study with the methiodide derivative,[4] thus permitting the assignment of the structures (2) and (3) with epimeric configurations of the ethyl side chain for the dihydro derivatives.[3]

The assignment of the side chain configurations of dregamine and tabernaemontanine rests on the alleged comparative facility with which the methoxycarbonyl groups in these compounds undergo epimerization. Tabernaemontanine is reported[3] to undergo a 10% conversion into the compound with the epimeric methoxycarbonyl group on treatment with sodium methoxide in methanol. This epimer was isolated in the pure state only after a tedious manual separation of crystals. A second report[5] claims to have characterized impure tabernaemontanine by conversion into

* Part II, *Aust. J. Chem.*, 1975, **28**, 1825.

[1] Hesse, M., 'Indole Alkaloide in Tabellen' (Springer: Berlin 1964 and supplement 1968).
[2] Knox, J. R., and Slobbe, J., *Aust. J. Chem.*, 1975, **28**, 1813.
[3] Renner, U., Prins, D. A., Burlingame, A. L., and Biemann, K., *Helv. Chim. Acta*, 1963, **46**, 2186.
[4] Jaggi, H., and Renner, U., *Chimia*, 1964, **18**, 173.
[5] Chatterjee, A., Banerji, A., and Majumder, P. L., *Indian J. Chem.*, 1968, **6**, 545.

the epimer and both reports claim that dregamine is recovered unchanged on treatment with sodium methoxide. The resistance of dregamine to epimerization was explained by the severe steric forces it would introduce in the epimer as it would require the ethyl and methoxycarbonyl groups to reside in a *cis*-1,3-diaxial situation.[3] From this evidence dregamine was considered to have the β-ethyl (equatorial) side chain.



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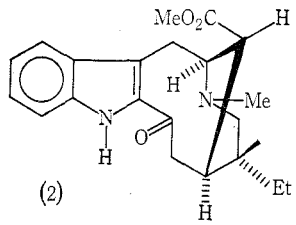

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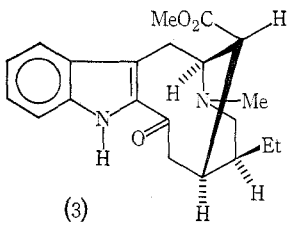

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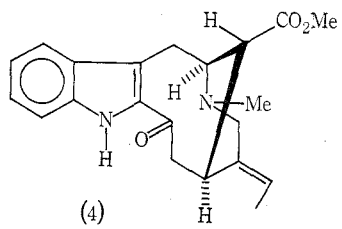

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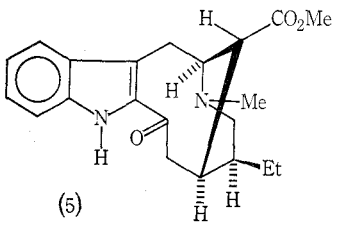

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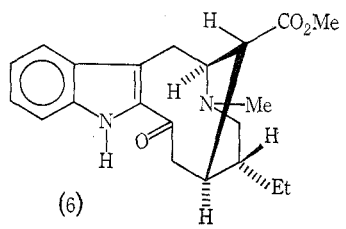

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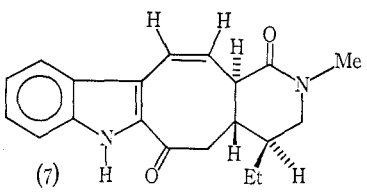

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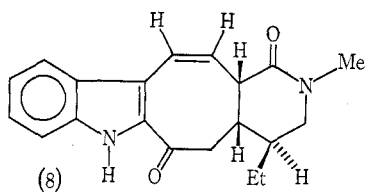


(8)

The results we report in this paper are at variance with the reported course of both the sodium methoxide reactions and the hydrogenation reaction; they have led us to reverse the configuration assignments for dregamine and tabernaemontanine to those shown in (2) and (3) respectively. This reassignment has been verified, subsequent to the completion of our work, by a report of the X-ray diffraction evidence for the structure and relative configuration of ervatamine[6,7] coupled with the formation of

[6] Husson, A., Langlois, Y., Riche, C., Husson, H. P., and Potier, P., *Tetrahedron*, 1973, **29**, 3095.
[7] Riche, C., *Acta Crystallogr., Sect. B*, 1974, **30**, 610.

this compound by the reduction of the product obtained from treating the *N*-oxide of tabernaemontanine with trifluoroacetic anhydride.[6]

Discussion

The reported recovery in small yields of only tabernaemontanine from the hydrogenation of vobasine in the presence of platinum catalyst is at variance with the stereochemical course of other hydrogenations in this area. In the presence of Raney-nickel catalyst, the hydrogenation has afforded good yields of dregamine together with small amounts of tabernaemontanine.[3] Similarly the vobasine unit of voacamine is catalytically hydrogenated to a dregamine unit.[8] Dregamine is also formed from perivine after *N*-methylation of the hydrogenation product.[9]

This caused us to re-examine the hydrogenation of vobasine (1) with a platinum catalyst but, in order to regenerate any reduced ketone functionality, we oxidized the hydrogenation mixture with CrO_3–pyridine[10] before attempting to isolate the products. Separation of the mixture of products by the countercurrent distribution method then gave dregamine (2) as the major product together with only small amounts of tabernaemontanine (3). This brings the stereochemical course of the hydrogenation into line with the other hydrogenations.

The β-face of the piperidine ring in vobasine (1) presents less hindrance to hydrogenation than the α-face and consequently vobasine would be expected to form more readily the dihydro derivative with the α-ethyl (equatorial) configuration. In comparison with vobasine, approach from the β-face of 16-epivobasine[3] should be hindered by the β (axial) methoxycarbonyl group and the hydrogenation of 16-epivobasine would be expected to proceed at a slower rate than for vobasine. The rate of hydrogenation indeed was much slower and the sole product isolated was identified as 17-epitabernaemontanine (5); this shows that hydrogenation, not unexpectedly, proceeded predominantly from the opposite side in this case.

The second reaction that we have reinvestigated is treatment of dregamine and tabernaemontanine with sodium methoxide. In our hands, dregamine gave 50% of the previously unreported epimer 16-epidregamine (6) from reaction with sodium methoxide. This contrasts with the literature reports that dregamine is stable to epimerization.[3,5] The spectral data of 16-epidregamine is typical for the epimeric configuration of the methoxycarbonyl group in this series. The most significant change is in the shift of the methyl ester signal to a normal position (δ 3·58) from the shielded position in vobasine; this is due to the removal of the methoxycarbonyl group from the shielding zone over the indole nucleus.[11] The mass spectrum has the base peak at *m/e* 182 and is very similar to the mass spectrum of dregamine. The u.v. spectrum is typical for 2-acylindoles in contrast to the original report that the epi-series shows small additional 'normal indole' peaks at 280–290 nm.[3] Our observations are that 16-epitabernaemontanine (5) and 16-epivobasine (4) also show typical 2-acylindole absorptions and a more recent report[9] for 16-epivobasine is in accord with this.

[8] Büchi, G., Manning, R. E., and Monti, S. A., *J. Amer. Chem.. Soc.*, 1964, **86**, 4631.
[9] Gorman, M., and Sweeney, J., *Tetrahedron Lett.*, 1964, 3105.
[10] Shioiri, T., and Yamada, S., *Tetrahedron*, 1968, **24**, 4159.
[11] Cava, M. P., Talapatra, S. K., Weisbach, J. A., Douglas, B., and Dudek, G. O., *Tetrahedron Lett.*, 1963, 53.

Re-examination of the reaction of tabernaemontanine with sodium methoxide has also led to an interesting result. The product was found to be a mixture composed of neutral as well as basic substances. The basic fraction consisted of tabernaemontanine and 16-epitabernaemontanine (5) and the ratio of these reached an approximately constant value (5 : 1) relatively quickly. The proportion of neutral products however increased over 5 h. After this time the neutral products constituted 40% of the products and the yield of epitabernaemontanine was comparable to the yield previously reported (10%) for this reaction.[3] The neutral fraction consisted of two substances in approximately equal proportion which were designated lactam A (7) and lactam B (8) in the order of increasing polarity. The evidence for their epimeric structures is presented later in this paper.

The course of the sodium methoxide and hydrogenation reactions thus present a consistent picture with regard to the configuration of the ethyl side chain in dregamine and tabernaemontanine. The epimerization is more favourable for dregamine than for tabernaemontanine and therefore the 16-epimer of tabernaemontanine must have the methoxycarbonyl group in a 1 : 3 diaxial interaction with the ethyl side chain. Furthermore, hydrogenation of vobasine would be expected to give predominantly the dihydro derivative with the ethyl side chain in the α (equatorial) configuration whereas this should be less favoured for 16-epivobasine. This is in accord with the favoured formation of dregamine and 16-epitabernaemontanine from the two hydrogenation reactions.

Further strong evidence for our assignment of the stereochemistry of the ethyl side chains lies in the rates of *N*-methiodide formation of this group of compounds in acetonitrile.[12] The pseudo-first order rates of methiodide formation are as follows:

Vobasine (1)	$6{\cdot}2\times10^{-3}$
Dregamine (2)	$3{\cdot}3\times10^{-3}$
Tabernaemontanine (3)	$2{\cdot}8\times10^{-4}$
16-Epidregamine (6)	$8{\cdot}9\times10^{-4}$
16-Epitabernaemontanine (5)	$1{\cdot}2\times10^{-4}$ (single run only)

The change from an axial ethyl side chain in tabernaemontanine to an equatorial side chain in dregamine is accompanied by a tenfold increase in rate. This increase is further doubled with vobasine (1) which lacks even a hydrogen in this position. Not unexpectedly, the axial methoxycarbonyl groups of the 16-epi compounds seem to have less effect at lowering the rate than do axial ethyl groups. Although these rate differences are less dramatic than have been observed for ethyl side-chain epimers in some instances (e.g. the iboga series[13]), the results are consistent, and the differences are sufficiently large to conclude that the assignments for dregamine and tabernaemontanine should be reversed to the indicated configurations.

The Structures of Lactams A and B

The formation of lactams A (7) and B (8) from tabernaemontanine (3) can be attributed to the initial formation of the isomethine (9) by β-elimination followed

[12] Shamma, M., and Richey, J. M., *J. Amer. Chem. Soc.*, 1963, **85**, 2507.
[13] Shamma, M., and Soyster, H. E., *Experientia*, 1964, **20**, 36.

by migration of the double bond and elimination of methanol to give the epimeric products. Certain β-amino acids, but not the corresponding esters, are analogously transformed to lactams by reaction with acetic anhydride or by heating[14] but it is unlikely that the reaction with NaOMe occurs via a carboxylic acid intermediate. This is because formation of the lactam grouping appears more likely to occur from cyclization of an amino ester intermediate[15] than an amino acid intermediate under the alkaline conditions.

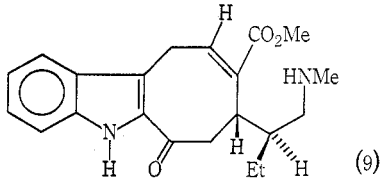
The spectral characteristics of the two lactams give clear evidence for their structures. Thus the mass spectra have strong molecular ions at *m/e* 322 and complex fragmentation patterns. The loss of CO and $CH_2{=}NCH_3$ separately and in combination from the molecular ions is analogous to the fragmentation of *N*-methyl-2-piperidone.[16] The 2-acyl-3-vinylindole chromophores incorporating an eight-membered c-ring have typical u.v. absorptions[3] and the lactam functionalities are revealed by i.r. absorption near 1650 cm^{-1} [17] together with low-field n.m.r. signals (δ *c.* 3·0) for the *N*-methyl groups. The chemical shift difference relative to the *N*-methyl signal of tabernaemontanine for the two compounds is comparable to the difference for *N*-methyl-2-piperidone and *N*-methylpiperidine.[18] The n.m.r. spectra of (7) and (8) also have doublet of doublets due to one proton at δ 6·52 (*J* 11, 8·5 Hz) and 6·10 (*J* 11, 8 Hz) respectively which are characteristic of the β-proton of 3-vinylindoles such as vobasine methine (10).[3] The similarity of the couplings to this hydrogen for the two compounds was unexpected in view of the different configurations of the adjacent allylic hydrogen in the two compounds. However, molecular models indicate that reasonable conformations which are consistent with these couplings[19] are available to the two structures.

The similarity of the spectral characteristics of the two compounds is suggestive of a C 16 epimeric relationship and this is supported by the observation that lactam A (7) is readily converted into an equimolar mixture with lactam B (8) by treatment with sodium methoxide. The C 16 configurations are assigned on the basis of a correlation of lactam A with tabernaemontanine methine[3] which has been achieved in the following way.

The mixture of lactams from sodium methoxide treatment of tabernaemontanine was treated with $LiAlH_4/AlCl_3$ in tetrahydrofuran solution[20] and the product separated into two fractions by preparative t.l.c. The more polar fraction after oxidation with CrO_3–pyridine[10] afforded the readily separated ketones A (11) and B (12) which are named in the order of increasing polarity. The genesis of these compounds was established by similar treatment of pure lactam A (7) which afforded ketone B (12) alone. It is noteworthy that the order of polarity is reversed in the two series. The less polar fraction from the reduction afforded an oxygen-free base (13). This compound and the more polar epimer (14) were

[14] Lee, D. L., Morrow, C. J., and Rapoport, H., *J. Org. Chem.*, 1974, **39**, 893.
[15] Jackson, A. H., and MacDonald, S. F., *Can. J. Chem.*, 1957, **35**, 715.
[16] Duffield, A. M., Budzikiewicz, H., and Djerassi, C., *J. Amer. Chem. Soc.*, 1964, **86**, 5536.
[17] Bellamy, L. J., 'The Infrared Spectra of Complex Molecules' p. 213 (Methuen & Co.: London 1958).
[18] Weitkamp, H., and Korte, F., *Chem. Ber.*, 1962, **95**, 2896.
[19] Jackman, L. M., and Sternhell, S., 'Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry' 2nd Edn (Pergamon: Oxford 1969).
[20] Büchi, G., Kulsa, P., Ogasawara, K., and Rosati, R. L., *J. Amer. Chem. Soc.*, 1970, **92**, 999.

obtained in low yield by $LiAlH_4$ reduction[21] of the same lactam mixture. Of the two products, the former appears to derive from lactam B and the latter from lactam A. This is based on a comparison of optical rotations which have large negative values for compounds in the lactam A configurational series [(7), (12) and (14)] and large positive values for the lactam B configurational series [(8), (11) and (13)].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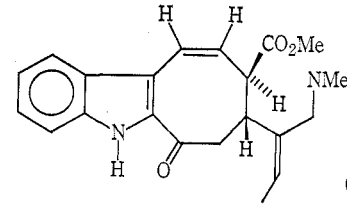
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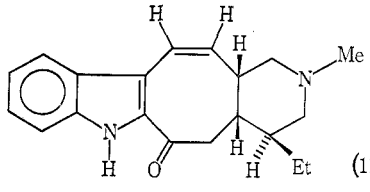
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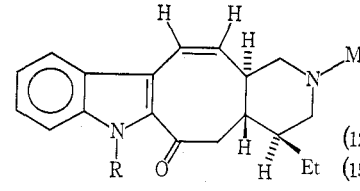
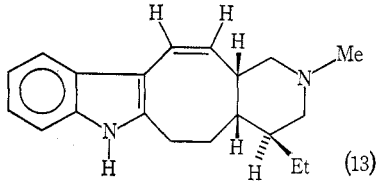

(12) R = H
(15) R = Me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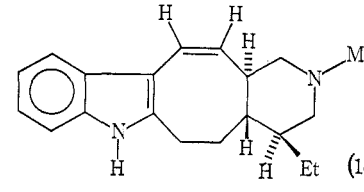
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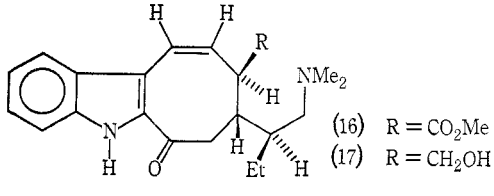
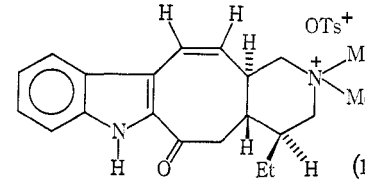

(16) R = CO_2Me
(17) R = CH_2OH


(18)

The u.v. spectra of the basic reduction products [(11), (12) and (13), (14)] are characteristic of the respective 2-alkyl-3-vinylindole[22] and the 2-acyl-3-vinylindole chromophores. The chemical shifts of the *N*-methyl n.m.r. signals are consistent with reduction of the lactam functionalities in the precursors (7) and (8). The n.m.r. signals of both vinyl protons are observable in the spectra of (13) and (14) but, as with lactams A (7) and B (8), the signals for the α-vinyl protons of ketones A (11) and B (12) are hidden by the signals for the aromatic protons.

Ketone B (12) under Hofmann degradation conditions did not undergo elimination but rather formed the *N*-methyl derivative (15). This is revealed in the mass spectrum

[21] Zeigler, F. E., Kloek, J. A., and Zoretic, P. A., *J. Amer. Chem. Soc.*, 1969, **91**, 2342.
[22] Leete, E., *Tetrahedron*, 1961, **14**, 35.

which showed appropriate peaks at 14 units higher mass than for (12). The n.m.r. spectrum has a characteristic N_a-methyl signal at δ 4·01.

Ketone B (12) and the N_a-methyl derivative (15) were then obtained from tabernaemontanine (3) in the following way. The methiodide of (3) was treated with concentrated ammonia to bring about elimination[3] and the product then heated in benzene to isomerize the double bond. By analogy with the transformations of dregamine methiodide (next section), the tabernaemontanine methine product[3] is considered to have the C 16 stereochemistry shown in (16). Reduction of the methine (16) with $LiAlH_4$ followed by oxidation with CrO_3–pyridine to regenerate the 2-acylindole chromophore then gave the alcohol (17). This compound reacted readily with tosyl chloride to form the quaternary tosylate salt (18). The formation of such salts from amino alcohols by way of the tosylate esters has ample analogies in the literature.[23,24] The quaternary tosylate (18) was reduced with $LiAlH_4$[25] to the free amine and, after re-oxidation by CrO_3–pyridine, ketone B (12) was obtained in low overall yield. On the other hand, conversion of the quaternary tosylate (18) into the methohydroxide and pyrolysis of the product afforded the *N*-methyl derivative (15) as the major product together with a small amount of ketone B (12). These correlations demonstrate that lactams A and B have the structures and stereochemistry shown in (7) and (8).

Methines and Isomethines of the Vobasine Group

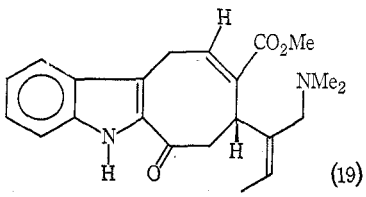
The methiodide of vobasine (1) is reported to undergo Hofmann degradation under mild conditions (concentrated ammonia) to give the methine (10) whereas the methiodide of 16-epivobasine (4) is reported to yield the isomeric isomethine (19) under the same conditions.[3] The two products have been interrelated both by heating the crystals of (19) at 80° for 20 h, which produced (10), and by separately refluxing the two compounds with sodium methoxide, which formed the same mixture of racemic products from the two compounds.[3] With the methiodides of dregamine and tabernaemontanine, the products reported from similar mild treatment are the methine products with the double bond conjugated with the indole nucleus [(20) and (16) respectively]. As we required a model for the 2-acyl-3-vinylindole chromophores in the lactams (7) and (8), we repeated these reactions.

In our hands, vobasine (1) and 16-epivobasine (4) methiodides gave the same gummy but homogeneous product from treatment with ammonia solution. The n.m.r. spectrum showed this to be the isomethine (19). However, the double bond of this product proved to be extremely labile. Attempts to crystallize (19) or passage of a solution of (19) through a column led to appreciable isomerization to the methine (10). This conversion occurred quantitatively in refluxing benzene over 1 h (as compared to 20 h previously[3] used for this conversion). The crystalline vobasine methine had physical properties closely similar to the literature values.[3]

Similarly we have found that the methiodides of dregamine (2) and 16-epidregamine (6) form the same isomethine (21) initially; this is also readily and completely converted into the methine (20) in refluxing benzene or by other mild treatment.

[23] Kupchan, S. M., Cassady, J. M., and Telang, S. A., *Tetrahedron Lett.*, 1966, 1251.
[24] Johns, S. R., Lamberton, J. A., and Occolowitz, J. L., *Aust. J. Chem.*, 1967, **20**, 1463.
[25] Cope, A. C., Ciganek, E., Fleckenstein, L. J., and Meisinger, M. A. P., *J. Amer. Chem. Soc.*, 1960, **82**, 4651.

The most characteristic discernible difference in the n.m.r. spectra of the methine and isomethine for both the vobasine and the dregamine series is that the spectra of the methines have a doublet of doublets near δ 6·3 due to the C 5 hydrogen whereas the corresponding signal for the isomethines is obscured. There are also the differences to be expected in the methyl ester i.r. absorptions and in the u.v. spectra of the isomeric products.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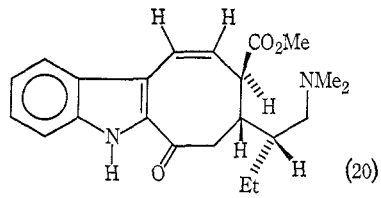
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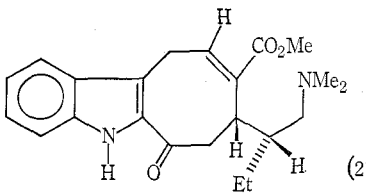
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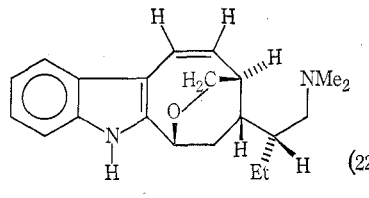
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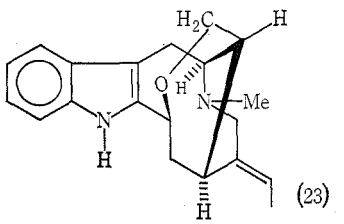
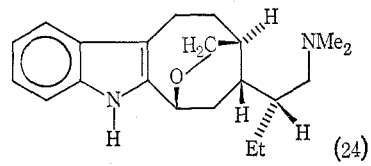
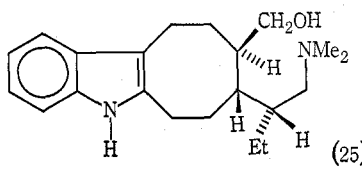

(23)


(24)


(25)

Our results thus show that it is the proton α to the methoxycarbonyl group which is preferentially abstracted under the mild Hofmann conditions so that the α,β-unsaturated ester is the initial product in this series. The facility with which the double bond undergoes isomerization makes these products difficult to purify and obviously is the reason for the confusing results in the literature.[3]

The derivation of the methines (10) and (20) from the respective isomethines (19) and (21) introduces a new asymmetric centre but the properties of the methines point to a single compound in each case. An examination of molecular models suggests

that the configuration with the methoxycarbonyl group *trans* to the adjacent side chain should be more stable on steric grounds.

This stereochemistry is established for dregamine methine (20) because it is possible to transform this compound simply to a product (22) of known stereochemistry. This was achieved by $LiAlH_4$ reduction of (20) to the expected mixture of epimeric diols which was heated under reflux with dilute hydrochloric acid in methanol. The clean product from this sequence had physical properties which showed it to be dihydrotaberpsychine methine (22).[26] Similar conditions have been employed to form taberpsychine from vobasine diol.[27] It is noteworthy that the suggested stereochemistry of hydrogenation of taberpsychine is verified by this correlation with dregamine.

The possibility that the hydroxymethylene group underwent epimerization prior to ether formation in the conversion (20) → (22) has been excluded by a second correlation of dregamine methine (20) with taberpsychine (23). Hydrogenation of dihydrotaberpsychine methine (22) gave crystalline tetrahydrotaberpsychine (24) which was then treated with equimolar quantities of $LiAlH_4$ and $AlCl_3$ in tetrahydrofuran solution to hydrogenolyse the ether linkage. The product from this sequence (25) was shown to be the same as that obtained from dregamine methine by $LiAlH_4$ reduction followed by catalytic hydrogenation. This correlation clearly establishes the β-configuration for the methoxycarbonyl group in dregamine methine.

The mechanism of the facile migration of the double bond in the isomethines to give the methines remains both an interesting and unexplained phenomenon. A sigmatropic migration involving a thermal uncatalysed [1,3] hydrogen shift is considered highly improbable. This would require a symmetry-allowed antarafacial [1,3] shift, considered difficult, if not impossible, due to the distortion of the carbon framework of the π-system this requires.[28] An examination of a model of (21) clearly demonstrates this difficulty. On the other hand, a suprafacial transfer of hydrogen is symmetry forbidden[28] and yet this would be necessary to obtain the observed stereochemistry of the methines from most C-ring conformations (including the most probable conformation with the 3-carbonyl group coplanar with the indole nucleus). For these reasons a one-step concerted mechanism for the isomerization must be rejected in favour of a step-wise process.

Experimental

Base Treatment of Dregamine (2)

Dregamine (300 mg) was added to a solution prepared from sodium (300 mg) in methanol (15 ml) and the mixture heated under reflux for 5 h. After removal of the methanol by evaporation under reduced pressure, the residue was partitioned between ether and water. The ether was removed leaving an oil (250 mg). Crystallization directly from ethyl acetate afforded impure dregamine (2) (80 mg), m.p. 115–130°. On standing in ether, the mother liquors deposited prisms of *epidregamine* (6), m.p. 213–215°, $[\alpha]_D$ −181° (*c*, 1·2) (Found: C, 67·6; H, 7·4; N, 7·7. $C_{21}H_{26}N_2O_3,H_2O$ requires C, 67·7; H, 7·6; N, 7·5%). λ_{max} 239, 325 nm ($\log\varepsilon$ 4·24, 4·30); ν_{max} 1740 cm^{-1} (methyl ester); n.m.r. (δ): 3·58 (3H, s, CO_2CH_3) and 2·54 (3H, s, NCH_3); m.s.: *m/e* 354 (M^+, 16%), 322 (16), 182 (100), 152 (20), 122 (22).

[26] Burnell, R. H., and Medina, J. D., *Can. J. Chem.*, 1971, **49**, 307.
[27] Dugan, J. J., Hesse, M., Renner, U., and Schmid, H., *Helv. Chim. Acta*, 1969, **52**, 701.
[28] Woodward, R. B., and Hoffmann, R., 'The Conservation of Orbital Symmetry' Ch. 7 (Academic Press: New York 1970).

Base Treatment of Tabernaemontanine (3)

Tabernaemontanine (300 mg) was treated with sodium methoxide as described above for dregamine. The ether soluble material was further extracted with 5% citric acid solution. The solvent was removed from the neutral fraction to give a white semi-solid material (129 mg). The acid solution was basified with NH_3 solution and recovered with ether to give an oil (160 mg).

Preparative t.l.c. of a portion of the neutral fraction (50 mg) separated two components. The less polar fraction (21 mg) crystallized from ethyl acetate to give thick needles of *lactam A* (7), m.p. 259–262°, $[\alpha]_D$ −388° (*c*, 1·3) (Found: C, 74·2; H, 6·8; N, 8·5. $C_{20}H_{22}N_2O_2$ requires C, 74·5; H, 6·9; N, 8·7%). λ_{max} 232, 252, 323 nm (logε 4·11, 4·17, 3·99); ν_{max} 1658 (lactam) and 1640 cm^{-1} (2-acylindole); n.m.r. (δ): 6·52 (1H, d of d, *J* 11, 8·5 Hz, vinyl proton) and 2·92 (3H, s, NCH_3); m.s.: *m/e* 322 (M^+, 100%), 294 (31), 280 (21), 265 (20), 251 (28), 222 (16), 208 (13), 194 (13), 183 (18), 182 (17), 181 (15), 180 (34), 168 (12), 167 (21), 154 (31).

The more polar material (14 mg) crystallized from ethyl acetate–light petroleum as fine needles of *lactam B* (8), m.p. 249–251°, $[\alpha]_D$ +332° (*c*, 1·0) (Found: C, 74·4; H, 6·7; N, 8·3. $C_{20}H_{22}N_2O_2$ requires C, 74·5; H, 6·9; N, 8·7%). λ_{max} 232, 254, 323 nm (logε 4·08, 4·16, 4·00); ν_{max} 1640–1650 cm^{-1} (lactam and 2-acylindole); n.m.r. (δ): 6·10 (1H, d of d, *J* 11, 8 Hz, vinyl proton) and 3·02 (3H, s, NCH_3); m.s.: *m/e* 322 (M^+, 100%), 294 (10), 279 (10), 265 (11), 251 (10), 194 (11), 185 (50), 183 (32), 180 (34), 167 (22), 154 (32), 138 (28).

Crystallization of the basic fraction from ethyl acetate yielded impure tabernaemontanine (3), m.p. 211–213°. Purification of the mother liquors (70 mg) by preparative t.l.c. yielded a fraction (30 mg) which crystallized from ether–light petroleum as prisms of epitabernaemontanine (6), m.p. 183–185° (lit.[3] 189–191°); n.m.r. (δ): 3·56 (3H, s, CO_2CH_3) and 2·55 (3H, s, NCH_3); m.s.: *m/e* 354 (M^+, 11%), 322 (10), 182 (100).

Hydrogenation of Vobasine (1) over Platinum

Crude vobasine (3 g) in ethanol (100 ml) containing a suspension of Adams catalyst (200 mg) was hydrogenated at room temperature and pressure for 4 h.[3] The catalyst was removed by filtration, washed with chloroform and the combined filtrates removed to give a residue (3 g). This material was oxidized with CrO_3–pyridine reagent to give a dark residue (2·5 g) which was filtered through a short column of alumina with benzene to remove the more polar material, leaving an oil (1·9 g). This oil was applied to the countercurrent distribution apparatus (pH 5·2) which was programmed as described for the initial separation of the crude alkaloids (see Part I[2]).

Lower-phase fractions 140–200 (900 mg) could be crystallized directly from ethyl acetate to give solvated prisms of dregamine (2), m.p. and m.m.p. 122–127°, then 138–142°.[2]

Hydrogenation of Epivobasine (4)

Vobasine (1) (500 mg) was epimerized as described by Renner *et al.*[3] to give an oil (434 mg). Chromatography on alumina (15 g) and elution with benzene–light petroleum (7 : 3) afforded oily epivobasine (4) (340 mg); n.m.r. (δ): 3·52 (3H, s, CO_2CH_3) and 2·50 (3H, s, NCH_3); m.s.: *m/e* 352 (M^+, 20%) and 180 (100).

Part of this oil (50 mg) in ethanol (5 ml) containing a suspension of Adams catalyst (8 mg) was hydrogenated at room temperature and pressure overnight. Filtration of the catalyst and removal of the solvent left a residue (30 mg) showing one main spot on t.l.c. Purification by preparative t.l.c. gave a band (7 mg) which crystallized from ether–light petroleum as prisms of epitabernaemontanine (5), m.p. 180–183°.

Rates of N-*Methylation*

The kinetics of the methiodide formation were measured by following the conductivity of the reaction mixture as a measure of the amount of salt formed. The apparatus was assembled as described in the literature.[12]

A solution of the alkaloid (15 mg) in acetonitrile (50 ml) was introduced into the cell which was maintained at 25±0·05° by suspending in a constant-temperature bath. Methyl iodide (5 ml) was added and resistance readings were taken at appropriate intervals over the first 30 minutes of reaction time. Infinity readings were normally taken overnight except in the case of the slow rates.

Vobasine Methine (10)

Vobasine methiodide (70 mg), prepared as described,[3] in aqueous solution was treated with concentrated ammonia. The resulting precipitate was extracted into ether which was evaporated under minimum heat conditions to give an oily residue (50 mg). This was shown to be a single compound by n.m.r. and t.l.c. techniques. N.m.r. (δ): 5·60 (1H, q, J 7 Hz, vinyl proton); 3·59 (3H, s, CO_2CH_3); 2·17 (6H, s, $N(CH_3)_2$) and 1·87 (3H, d, J 7 Hz, vinyl methyl).

Part of this material (25 mg) was heated at reflux in benzene (3 ml) for 1 h. Removal of the solvent left a semicrystalline fraction (23 mg) which crystallized from ether–light petroleum as long needles of vobasine methine (10), m.p. 144–145°, $[\alpha]_D$ −103° (*c*, 0·9) (lit.[3] m.p. 145–146°, $[\alpha]_D$ −103·7°); λ_{max} 228, 253 and 323 nm ($\log\varepsilon$ 3·96, 4·10, 3·88); n.m.r. (δ): 6·27 (1H, d of d, J 11, 8 Hz, B proton of ABX system); 5·59 (1H, q, J 7 Hz, vinyl); 3·59 (3H, s, CO_2CH_3); 2·04 (6H, s, $N(CH_3)_2$) and 1·73 (3H, d, J 7 Hz, vinylic methyl); m.s.: *m/e* 366 (M^+, 60%), 321 (12), 58 (100).

Hofmann on Epivobasine (4)

Epivobasine (80 mg) was subjected to the Hofmann reaction with NH_4OH as described[3] and worked up by ether extraction to give an oil (40 mg). N.m.r. and t.l.c. comparison showed this oil to be identical to the initial product formed from the Hofmann degradation of vobasine (see above). Attempts to crystallize the isomethine from ether–light petroleum resulted only in the separation of an oily precipitate. This precipitate was shown to contain about 25% of the methine (n.m.r. spectrum).

The material was heated in benzene for 1 h, then filtered through a short plug of alumina before removal of the solvent. The eluate (33 mg) crystallized from ether–light petroleum as needles of vobasine methine (10), m.p. and mixture m.p. 142–144°.

Mild Hofmann Degradation of Dregamine (2)

Dregamine methiodide was prepared as described[3] using chloroform as the solvent in preference to ethyl acetate.

This material (200 mg) was subjected to the Hofmann conditions described above to afford an oil (150 mg); n.m.r. (δ): 3·64 (3H, s, CO_2CH_3), 2·19 (6H, s, $N(CH_3)_2$).

Crystallization from ether–light petroleum gave prisms of m.p. 130–133° shown by n.m.r. and t.l.c. techniques to be a mixture of the methine and isomethine.

The above oil was heated in benzene as has been described. The product was sublimed at 130° and 2×10^{-3} mm to give dregamine methine (20) as a glass of m.p. 60–70°, $[\alpha]_D$ −24° (*c*, 1·0) (lit.[3] $[\alpha]_D$ −24·1°) (Found: C, 71·8, H, 8·0; N, 7·7. Calc. for $C_{22}H_{28}N_2O_3$: C, 71·7; H, 7·7; N, 7·6%). λ_{max} 230, 254, 327 nm ($\log\varepsilon$ 4·29, 4·41, 4·10); ν_{max} 1730 cm^{-1} (methyl ester); n.m.r. (δ): 6·27 (1H, d of d, J 11, 8 Hz, B proton of ABX system); 3·66 (3H, s, CO_2CH_3) and 2·08 (6H, s, $N(CH_3)_2$); m.s.: *m/e* 368 (M^+, 50%), 180 (13), 154 (18) and 58 (100).

Hofmann on Epidregamine (6)

Epidregamine (45 mg) in ether (2 ml) was treated with excess methyl iodide overnight at room temperature. The white crystals of epidregamine methiodide were subjected to the Hofmann conditions above to give an oil (20 mg). T.l.c. and n.m.r. techniques showed this to be dregamine isomethine (21).

$LiAlH_4$ Reduction of Dregamine Methine (20)

Dregamine methine (200 mg) was reduced with $LiAlH_4$ in tetrahydrofuran solution in an exactly analogous procedure to that described for vobasine (1).[3] Removal of the solvent left a froth (150 mg) which was shown by t.l.c. techniques to be an inseparable mixture of epimers.

Acid Treatment of the Diol Mixture

The mixture (100 mg) from $LiAlH_4$ reduction of dregamine methine was dissolved in a solution of methanol (8 ml) and 2% HCl (2 ml) and heated on a steam bath for 90 min. Half of the methanol was removed by distillation under reduced pressure and the residue was diluted with water, basified with ammonia and extracted with ether. The ether layer was removed to leave an oily residue

(70 mg). This was filtered through a short plug of alumina with benzene and the eluted material (60 mg) crystallized from ether–light petroleum as prisms of dihydrotaberpsychine methine (22), m.p. 154–155° (lit.[26] 153–155° from acetone), $[\alpha]_D$ +442° (*c*, 1·0); λ_{max} 231, 272, 285, 295 nm (log ε 4·35, 3·81, 3·78, 3·64sh); n.m.r. and m.s. identical to the reported spectra.[26]

Hydrogenation of Dihydrotaberpsychine Methine (22)

The methine (160 mg) in ethanol (20 ml) with Adams catalyst (40 mg) was hydrogenated at room temperature and pressure for 6 h. Removal of the catalyst by filtration and evaporation of the solvent left a semicrystalline residue (150 mg). This residue was purified by preparative t.l.c. to give a crystalline material (100 mg). Crystallization from benzene–light petroleum afforded prisms of tetrahydrotaberpsychine methine (24), m.p. 193–195° (lit.[26] 184–186° from acetone), $[\alpha]_D$ −127° (*c*, 1·2); λ_{max} 227, 279, 286, 294 nm (log ε 4·42, 3·79sh, 3·82, 3·77); n.m.r. and m.s. as published.[26]

Hydrogenolysis of Tetrahydrotaberpsychine Methine (24)

The methine (60 mg) in dry tetrahydrofuran (4 ml) was added dropwise to a stirred suspension of $LiAlH_4$ (100 mg) and $AlCl_3$ (325 mg) in dry tetrahydrofuran (5 ml) under nitrogen. Stirring was continued at room temperature for 90 min. Excess saturated Rochelle salt solution was carefully added to decompose the aluminium complexes after which the mixture was basified with ammonia. The aqueous layer was thoroughly extracted with methylene chloride which was evaporated leaving an oily residue (48 mg). This material failed to crystallize even after extensive purification. N.m.r. (δ): 2·20 (6H, s, $N(CH_3)_2$); m.s.: *m/e* 328 (M^+, 100%), 283 (16), 281 (11), 270 (34), 168 (36), 167 (23), 156 (54), 144 (67), 143 (86), 130 (62), 58 (>100%).

Hydrogenation of the Dregamine Methine Diol Mixture

The mixture (100 mg) in ethanol (10 ml) containing Adams catalyst (25 mg) was hydrogenated for 5 h at room temperature and pressure. Workup as before gave an oil (100 mg). Purification by preparative t.l.c. (chloroform–methanol 99 : 1) gave a fraction (40 mg) which failed to crystallize or sublime. This substance was shown to be identical to the above hydrogenolysed material by n.m.r. and t.l.c. techniques.

Base Isomerization of Lactam A (7)

Lactam A (19 mg) was added to a solution prepared from sodium (40 mg) in methanol (4 ml) and the mixture refluxed for 2·5 h. Recovery of the organic material as before gave a semicrystalline residue (19 mg). Purification by preparative t.l.c. gave two bands. The upper fraction (9 mg) crystallized from ethyl acetate to give needles of lactam A (7), m.p. and m.m.p. 259–262°. The more polar band (8 mg) crystallized from ethyl acetate–light petroleum as needles of lactam B (8), m.p. and m.m.p. 249–251°.

Reduction of the Lactam Mixture

(i) *$LiAlH_4$ in dioxan.*—The neutral mixture (54 mg) in dioxan (4 ml) was added dropwise to a stirred suspension of $LiAlH_4$ (90 mg) in dry dioxan (10 ml). Stirring was continued while the suspension was heated at reflux for 18 h. The excess $LiAlH_4$ was decomposed with saturated Na_2SO_4 solution and the precipitate filtered under vacuum and washed with warm tetrahydrofuran. The combined filtrates were concentrated under reduced pressure, then partitioned between ether and dilute citric acid solution. Recovery of the acid layer gave a yellow oil (36 mg) which was separated into two fractions by preparative t.l.c. The upper band (4 mg) crystallized from benzene–light petroleum as plates of the oxygen free *compound A* (13), m.p. 221–225° (dec., phase change to needles from 205°), $[\alpha]_D$ +521° (*c*, 0·8) (Found: C, 81·7; H, 8·9; N, 9·3. $C_{20}H_{26}N_2$ requires C, 81·6; H, 8·9; N, 9·5%). λ_{max} 232, 265–278, 290 nm (log ε 4·11, 3·90, 3·76sh). N.m.r. (δ): 6·76 (1H, d, *J* 11 Hz, A proton of ABX system); 5·98 (1H, d of d, *J* 11, 8·5 Hz, B proton of ABX) and 2·29 (3H, s, NCH_3); m.s.: *m/e* 294 (M^+, 100%), 279 (19), 265 (18), 194 (19), 182 (26), 180 (32), 168 (35), 167 (51), 150 (31), 149 (69), 137 (56), 136 (63).

The more polar band (8 mg) crystallized from benzene–light petroleum to give prisms of the oxygen free *compound B* (14), m.p. 235–238° (phase change from 200°), $[\alpha]_D$ −448° (*c*, 0·9); λ_{max} 233, 263–278, 289 nm (log ε 4·07, 3·95, 3·85sh); n.m.r. (δ): 6·75 (1H, d, *J* 11 Hz, A proton of ABX

system), 5·27 (1H, d of d, *J* 11, 8 Hz, B proton of ABX) and 2·26 (3H, s, NCH_3); m.s.: M^+ at 294·2089 (calc. for $C_{20}H_{26}N_2$: 294·2096); low resolution *m/e* 294 (100%), 279 (18), 265 (17), 194 (17), 182 (25), 180 (35), 168 (43), 167 (57), 150 (30), 149 (27), 138 (38), 137 (73), 136 (70).

(ii) *With $LiAlH_4/AlCl_3$*.—The mixture (100 mg) in tetrahydrofuran (8 ml) was added dropwise to a stirred suspension of $LiAlH_4$ (400 mg) and $AlCl_3$ (1300 mg) in tetrahydrofuran (20 ml) under nitrogen. Stirring was continued for a further 2 h. Excess saturated Rochelle salt solution was then slowly added followed by basification with ammonia. The mixture was thoroughly extracted with methylene chloride which was removed to give a froth (82 mg). Separation by preparative t.l.c. (chloroform–methanol 49 : 1) isolated a fraction (15 mg) which crystallized from benzene–light petroleum as plates of (13), m.p. and mixed m.p. 221–225° (dec.). The more polar materials (60 mg) obtained from the remainder of the plate proved to be a complex mixture of alcohols which were recombined for oxidation.

CrO_3-Pryidine Oxidation of Polar Products of Reaction (ii) Above

The mixture (60 mg) was oxidized with CrO_3–pyridine reagent to give a semi-solid residue (40 mg). Preparative t.l.c. separated this material into two fractions. The upper band (13 mg) crystallized from ether–light petroleum to yield prisms of *ketone A* (11), m.p. 186–188° (phase change to needles from 170°), $[\alpha]_D$ +227° (*c*, 1·0); λ_{max} 232, 253, 330 nm ($\log\varepsilon$ 4·32, 4·36, 4·03); n.m.r. (δ): 6·61 (1H, d of d, *J* 11, 8 Hz, B proton of ABX system) and 2·25 (3H, s, NCH_3); m.s.: M^+ at 308·1881 (calc. for $C_{20}H_{24}N_2O$: 308·1889); low resolution *m/e* 308 (100%), 180 (54), 168 (64), 167 (74), and 154 (58).

The lower fraction (25 mg) crystallized from benzene–light petroleum to give prisms of *ketone B* (12), m.p. 263–265° (dec.), $[\alpha]_D$ −273° (*c*, 1·0) (Found: C, 77·5; H, 7·9, N, 9·2. $C_{20}H_{24}N_2O$ requires C, 77·9; H, 7·8; N, 9·1%); λ_{max} 231, 252, 325 nm ($\log\varepsilon$ 4·21, 4·29, 3·96); n.m.r. (δ): 6·01 (1H, d of d, *J* 11, 8 Hz, B proton of ABX system), 2·27 (3H, s, NCH_3); m.s.: *m/e* 308 (M^+, 100%), 180 (36), 168 (64), 167 (66), 154 (36).

Lactam A (7) (38 mg) was reduced as above and subsequently oxidized to yield only ketone B (12) (25 mg). This crystallized from benzene–light petroleum as prisms, m.p. 260–263° (dec.).

Classical Hofmann Degradation of Ketone B (12)

Ketone B (30 mg) in chloroform (1 ml) was treated with excess methyl iodide. The solution was left to stand overnight and the precipitate collected. This was dissolved in distilled water and passed slowly through an OH^- form ion exchange resin as has been described for ervatamine methiodide.[29] Removal of the solvent under reduced pressure left a gummy residue (20 mg) which was pyrolysed at 0·01 mm and 180°. The residue was shaken between ether and water and the ether layer evaporated to give an oil (12 mg). After purification by preparative t.l.c., the fraction (10 mg) crystallized from ether–light petroleum to yield long needles of *N_a-methyl ketone B* (15), m.p. 160–162°, $[\alpha]_D$ −289° (*c*, 1·0) (Found: C, 78·4; H, 8·2; N, 8·4. $C_{21}H_{26}N_2O$ requires C, 78·2; H, 8·1; N, 8·7%). λ_{max} 233, 254, 321 nm ($\log\varepsilon$ 4·27, 4·39, 4·08); n.m.r. (δ): 5·88 (1H, d of d, *J* 11, 8 Hz, B proton of ABX system), 4·01 (3H, s, N_a-methyl) and 2·24 (3H, s, NCH_3); m.s.: *m/e* 322 (M^+, 100%), 294 (25), 226 (18), 194 (30), 182 (32), 181 (26), 180 (22), 168 (28), 167 (40).

Tabernaemontanine Methine (16)

Tabernaemontanine (3) (90 mg) in chloroform (2 ml) was treated with excess methyl iodide to give white crystals (100 mg). These were dissolved in water (10 ml) and treated with ammonia as described for vobasine (1). Ether workup left a semicrystalline residue (60 mg) shown by n.m.r. techniques to be a 2 : 1 mixture of methine and isomethine. Heating this mixture in benzene for 1 h gave an oil (59 mg), which could only be obtained in the semicrystalline state by slow evaporation of an ether–light petroleum solution to give *tabernaemontanine methine* (16), m.p. 60–70°; n.m.r. (δ): 6·36 (1H, d of d, *J* 11, 8 Hz, B proton of ABX system), 3·68 (3H, s, CO_2CH_3) and 2·21 (6H, s, $N(CH_3)_2$).

[29] Knox, J. R., and Slobbe, J., *Aust. J. Chem.*, 1975, **28**, 1825.

The Methine Alcohol (17)

Tabernaemontanine methine (80 mg) was reduced with $LiAlH_4$ in ether (as for dregamine methine) to give a froth (53 mg). This material was oxidized with CrO_3–pyridine reagent giving a yellow oil (40 mg). Purification by preparative t.l.c. gave a fraction (32 mg) which by slow ether evaporation afforded the solid *methine alcohol* (17), m.p. 65–80°; n.m.r. (δ): 6·37 (1H, broadened d of d, J 11, 8 Hz, B proton of ABX system) and 2·23 (6H, s, $N(CH_3)_2$); m.s.: M^+ at 340·2147 (calc. for $C_{21}H_{28}N_2O_2$: 340·2151); low resolution m/e 340 (11%), 58 (100).

Tosylation of the Methine Alcohol (17)

Tosyl chloride (100 mg) was added to a solution of the alcohol (30 mg) in dry pyridine (1 ml) and the resulting mixture left to stand at room temperature for 15 h after which it was heated on a steam bath for a further hour. The solvent was removed under vacuum and the residue eluted through a column of basic alumina (10 g, activity III) with chloroform–methanol (9 : 1) to give an oil (18) (25 mg) which was not further purified.

$LiAlH_4$ Reduction of Cyclic Tosylate (18)

The above tosylate (17 mg) was suspended in tetrahydrofuran (5 ml), $LiAlH_4$ (20 mg) was added, and the mixture heated at reflux overnight. The aluminium complexes were decomposed with saturated ether solution, the precipitate was filtered, washed with ether and the solvent evaporated from the combined filtrates to give a residue (7 mg). This material was oxidized with CrO_3–pyridine reagent to yield a semicrystalline material (2·5 mg). After purification by preparative t.l.c., the residue was crystallized from benzene–light petroleum to yield long needles of ketone B (12), m.p. and m.m.p. 258–260° (dec.).

Classical Hofmann Degradation of the Cyclic Tosylate (18)

The tosylate (18) (100 mg) in distilled water was passed slowly through a column of ion exchange resin (OH^- form). Removal of the solvent left a residue (36 mg). The material was pyrolysed at 180° and 10^{-2} mm and the residue partitioned between ether and water. The ether layer was evaporated leaving a semicrystalline residue (28 mg). Preparative t.l.c. separated this material into two bands.

The less polar fraction (20 mg) crystallized from ether–light petroleum as needles of N_a-methyl ketone B (15), m.p. and m.m.p. 160–162°. The more polar fraction (3 mg) crystallized from benzene–light petroleum as long needles of ketone B (12), m.p. and m.m.p. 261–264° (dec.).

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