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SOME APPLICATIONS OF RATES OF METHIODIDE FORMATION TO ALKALOID STRUCTURAL DETERMINATION

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Abstract—The stereochemistry of selagine at C-11 has been determined, and this alkaloid can now be represented by expression IVa.

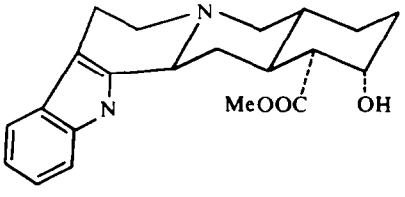
Tetrahydroprotoberberines may exist in any of three different conformations IX, XV, or XVIII, depending upon the substitution pattern at C-1 and C-13. The alkaloids capaurine (XVI) and capaurimine (XVII) exist in conformation XVIII; and no stable B/C *trans* fused analog of these species can exist.

Rates of methiodide formation provide a facile means for differentiating between pavine and isopavine bases, since the latter quaternize at a faster rate.

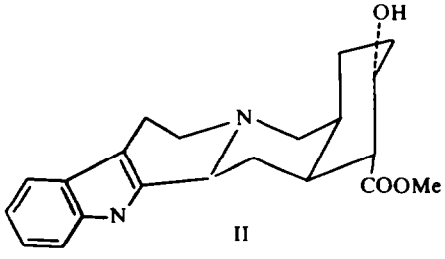
THE utility of rates of methiodide formation in the determination of alkaloid stereochemistry was first demonstrated in 1961 in connection with the heteroyohimbine alkaloids.[1] This physical method has since been useful in the stereochemical assignments for a wide range of other alkaloids including the dihydroheteroyohimbines,[2] the pentacyclic oxindoles,[3] the uleines,[4] and the rhoeadines.[5] Other research groups have also utilized this method in connection with investigations on the structure and stereochemistry of the quinolizidines[6] and some of the Amaryllidaceae bases.[7]

In the present paper three alkaloidal systems will be considered, namely selagine, the tetrahydroprotoberberines, and the pavines–isopavines.

As a preliminary consideration, the following data is relevant. Yohimbine (I) which



I



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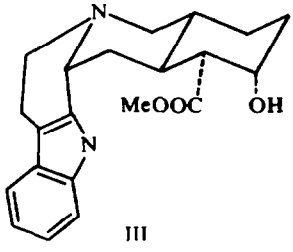
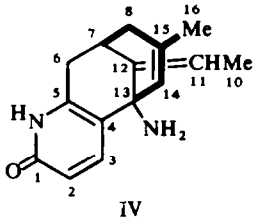


III

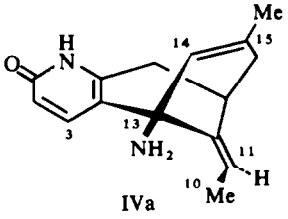
possesses the *normal* configuration shows a moderate pseudo first-order rate of N-methylation of 48×10^{-4}sec^{-1}. α-Yohimbine (II) which is *allo* and possesses a hindered nitrogen, methylates very slowly, the rate value being $1{\cdot}2 \times 10^{-4}$sec^{-1}. Finally, pseudoyohimbine (III) has a very unhindered nitrogen, and the quaternization rate is very fast, namely 7×10^{-2}sec^{-1}.[1a,b,c]

Selagine. The lycopodium alkaloid selagine has been assigned expression IV on the basis of chemical and spectroscopic evidence.[8,9] An unresolved stereochemical point, however, concerned the configuration of the ethylidene side chain, requiring a choice between structures IVa and IVb for the alkaloid. The determination of this feature is of particular importance for any endeavor at total synthesis.

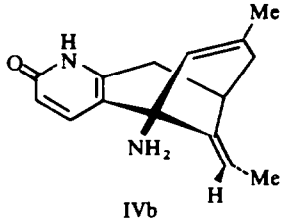
Molecular models indicate that approach to the primary amino function at C-13 in expression IVa would be substantially hindered by the C-11 Me group and the hydrogens at C-14 and C-3. On the other hand, in dihydroselagine (V), a known base derived from selagine by reduction of the C-11(12) double bond, the primary amino function at C-13 is less hindered than in IVa since the C-12 Et group has a chance to rotate. One would expect, therefore, a very slow rate for selagine and a slightly faster rate for dihydroselagine (V), given that rates of N-methylation are usually closely related to steric hindrance about the basic N atom.



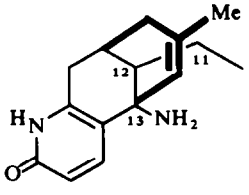
IV



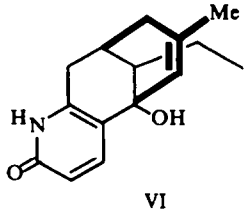
IVa



IVb



V



VI

Conversely, if selagine were to be represented by expression IVb in which the C-13 primary amino function is not substantially hindered, one would expect a somewhat faster rate of N-methylation for selagine than for dihydroselagine (V).

TABLE 1. RATES OF N-METHYLATION FOR SELAGINE SERIES

Base	Rate × $10^4 sec^{-1}$
Selagine (IVa)	5·8
Dihydroselagine (V)	7·4
Dihydroselaginol (VI)	3·5

The experimentally observed pseudo first-order rates of N-methylation are shown in Table 1. The rate for selagine ($5·8 \times 10^{-4} sec^{-1}$) is slow, while that for dihydroselagine is slightly faster. These kinetic data therefore point to expression IVa as being the correct one for selagine.

It will be noticed that dihydroselaginol (VI) has a rate of $3·5 \times 10^{-4} sec^{-1}$, even though it is devoid of the primary amino group at C-13. This value indicates that methylation of the pyridone ring N atom is taking place. The magnitude of pyridone N-methylation should be essentially constant for selagine (IVa) and its derivatives such as V and VI, and the occurrence of such methylation does not alter the stereochemical conclusions. It follows that the true rates of N-methylation at C-13 for selagine and dihydroselagine are even slower than those quoted here.

Molecular models also show that the primary amino group in IVa is so hindered that as a result of treatment with methyl iodide only one or at the most two Me groups can be expected to become attached to the N atom of selagine and its derivatives.

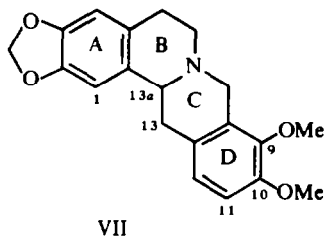
Additional support for the assigment of structure IVa to selagine can be derived from the $CDCl_3$ NMR spectrum of the alkaloid. The C-11 Me group which is in close proximity to the amino group appears as a doublet, at 1·67 δ. On the other hand, the C-15 Me, being relatively distant from the amino function, appears as a singlet upfield at 1·53 δ.

The determination of the configuration about C-11 for selagine (IVa) opens the way for synthetic studies on this compound.

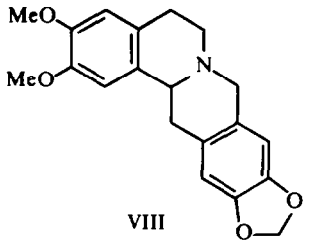
The tetrahydroprotoberberines. Those tetrahydroprotoberberines which are unsubstituted at both C-1 and C-13 exist mainly in the *trans*-quinolizidine conformation IX. The case for the C-13 methylated series is more complex. On the basis of spectral and chemical evidence Jeffs has concluded that when the hydrogens at C-13 and C-13a are *cis* to each other, the tetrahydroprotoberberine molecule will exist in a *trans* B/C fused arrangement. Alternatively, when the two hydrogens in question are *trans*, steric interference between the C-13 methyl and the C-1 hydrogen forces the B/C junction to be *cis*-fused.[10]

As a start, we first measured the rates for the unsubstituted parent compounds VII and VIII.[11] The respective rates were found to be of medium magnitude, namely $35 \times 10^{-4} sec^{-1}$ and $53·6 \times 10^{-4} sec^{-1}$. These values are in good accord with what would be predicted on the basis of conformation IX for these two species, which is somewhat reminiscent of expression I for yohimbine.

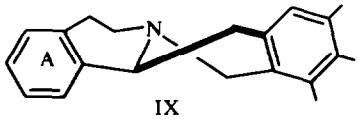
In the case of the β-C-13-Me derivatives X[11] and XI, the rates, $1·1 \times 10^{-4} sec^{-1}$ and $1·3 \times 10^{-4} sec^{-1}$ respectively, were substantially slower than for the parent unsubstituted compounds. This is consistent with a *trans* B/C fusion for X and XI as shown in conformation XII, where approach of the methyl iodide is hindered by the axial C-13 Me.



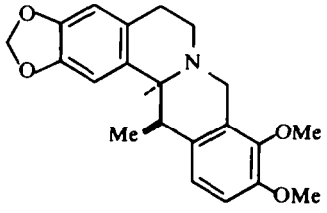
VII



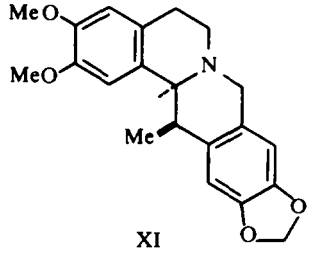
VIII



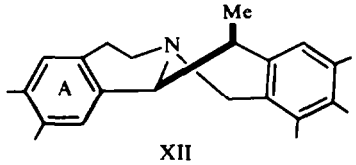
IX



X

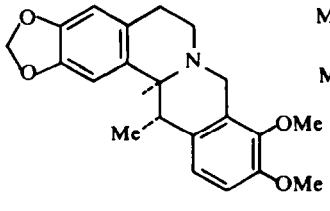


XI

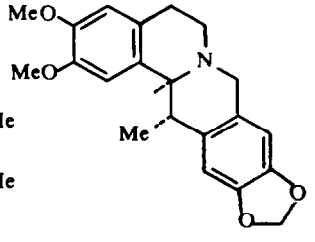


XII

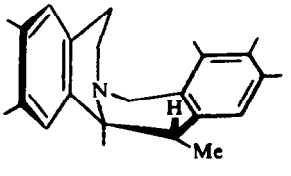
Methylation of the α-Me isomers XIII and XIV, on the other hand, gave very fast rates (Table 2). These reflect the unhindered surroundings of the N atom in the *cis* B/C fused system in conformation XV, and confirm Jeff's conclusions. Conformation XV is reminiscent of expression III for pseudoyohimbine; and in both cases the N atoms are readily available for N-methylation.



XIII



XIV



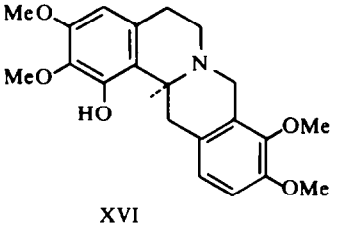
XV

Other characteristics of the *cis*-B/C α isomers (XIII and XIV) are (a) their low mobility on TLC due to the fact that they are relatively strong bases, (b) the absence of Bohlmann bands between 3·3 and 3·4 μ typical of *cis* fused quinolizidine systems, and (c) the appearance of the C-13 Me doublet relatively downfield as compared to the chemical shift for the corresponding Me doublet in the *trans* B/C β series. (Table 2).

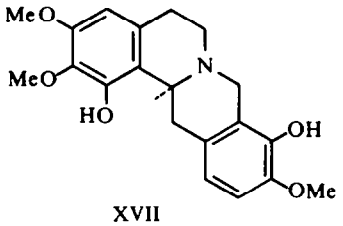
TABLE 2. DATA FOR TETRAHYDROPROTOBERBERINES

Compound	VII	VIII	X	XI	XIII	XIV	XVI	XVII
B/C stereochemistry	*trans*	*trans*	*trans*	*trans*	*cis*	*cis*	*cis* (half chair–half chair)	*cis* (half chair–half chair)
Rate × 10^4 sec^{-1}	35	53·6	1·1	1·3	273	341	78	85
TLC R_f (ether)	0·72	0·75	0·84	0·75	0·57	0·40	—	—
Bohlmann bands	yes	yes	yes	yes	no	no	yes	yes
C-13 Me chem shift	—	—	0·95 δ	0·93 δ	1·43 δ	1·48 δ	—	—

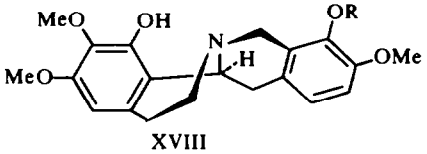
After we had obtained rates for the C-13-methyl tetrahydroprotoberberines, two papers appeared in the literature dealing with the structures and stereochemistry of the interrelated alkaloids capaurine (XVI) and capaurimine (XVII), whose structures had been assigned originally by Manske.[12] In the initial paper, a "synthetic capaurimine" was prepared which was definitely proven to be different from the natural product.[13] But Manske's structural assignments for capaurine (XVI) and capaurimine (XVII) were vindicated in the second paper which described a detailed X-ray analysis of the hydrobromide salt of the former alkaloid.[14]



XVI



XVII



XVIII

The X-ray data showed that capaurine hydrobromide possesses a *cis* B/C system involving half chair to half chair fusion as in XVIII, even though the free base shows the presence of Bohlmann bands in solution.[13] Since the natural isomer is *cis* from the X-ray analysis, it was concluded that "synthetic capaurimine" is *trans* B/C fused, and that "interconversion between *cis* and *trans* conformers does not occur even partially in solution", so that the N atom presumably cannot flip.[14]

We have now found the pseudo first order rates of N-methylation for capaurine (XVI) and capaurimine (XVII) to be 78×10^{-4} sec^{-1} and 85×10^{-4} sec^{-1}, respectively. In agreement with the X-ray results, these fast rates point to the prevalence even in solution of a *cis* B/C juncture with two half chair rings as in expression XVIII. The N atom is now less hindered than in IX or XII, but more hindered than in XV, and the rates reflect this degree of steric hindrance.

Since capaurine (XVI) and capaurimine (XVII) N-methylate about four times slower than species XIII or XIV, it is apparent that two distinct conformations are possible in the *cis* B/C tetrahydroprotoberberine series. The choice as to which actually predominates is dictated by steric factors, specifically the degree of interaction between the C-1 and C-13 substituents.

It has also been reported that "synthetic capaurimine", which is presumably *trans* B/C fused, can be recrystallized from methanol without any change.[13] To verify the claim that species XVI and XVII can each exist in completely stable B/C *cis* and *trans* fused conformations, the isomerization of the naturally occurring *cis*-fused alkaloids to the presumed *trans* B/C fused series was attempted. In our hands, refluxing either natural capaurine (XVI) or capaurimine (XVII) in ethanol for 24 hr afforded no isomerization of any kind that could be detected by careful TLC. Presumably, therefore, the energy of activation for *trans–cis* isomerization would be well over 30 kcal/mole.* A requirement of this magnitude would be most unlikely for what is in essence the inversion of a nitrogen atom. In fact, Stuart–Briegleb models indicate that the C-1 OH group does not even have to squeeze past the C-13 H atoms for isomerization to occur.

It follows that the claim of a completely stable *trans* B/C conformer as distinct from the *cis* species for capaurimine is unfounded, and that the preparation of "synthetic capaurimine" should be reconsidered.[13,14] Natural capaurine (XVI) and capaurimine (XVII) exist in conformation XVIII in the solid state and in solution as indicated by the X-ray and kinetic data respectively.

The pavine–isopavine alkaloids. Pavine (XIX) and isopavine (XX) are representative of two closely related classes of tetracyclic bases which were originally prepared in the laboratory.[16,17] Members of both types were later found in nature.

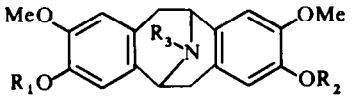
Since no simple non-degradative method was known which would distinguish a pavine from an isopavine molecule, it was decided to study their rates of N-methylation. In the pavine series the N-Me function is bordered by two methine hydrogens, while in the isopavines the N-Me is adjacent to a methine hydrogen and a methylene. It was expected, therefore, that the less hindered isopavines would methylate at a faster rate.

The results of the rate studies are shown in Table 3. The pavine type compounds, XXI–XXIV, all show pseudo first-order rates of N-methylation between 271×10^{-4}sec^{-1} and 273×10^{-4}sec^{-1}; while the lone isopavine alkaloid available to us, amurensine, XXV, N-methylates nearly twice as fast, showing a rate of 508×10^{-4}sec^{-1}. Therefore, methiodide rates present a simple and sensitive method for distinguishing pavine and isopavine alkaloids from each other.

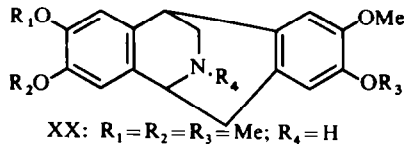
* The calculations are based on the well known relationship $\Delta G = -RT \ln (kh/Kk'T)$.[15] An optimistic 5% reaction was assumed to have taken place, even though there was no indication that even that much reaction had occurred.

TABLE 3. RATES OF N-METHYLATION FOR THE PAVINES–ISOPAVINES

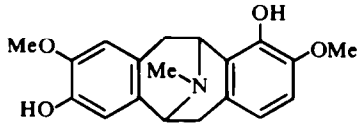
Alkaloid	Rate × 10^4sec^{-1}
Argemonine (XXI)[18]	273
Norargemonine (XXII)[19]	272
Bisnorargemonine (XXIII)[20]	273
Munitagine (XXIV)[21]	271
Amurensine (XXV)[22]	508



XIX: $R_1=R_2=Me$; $R_3=H$
XXI: $R_1=R_2=R_3=Me$
XXII: $R_1=H$; $R_2=R_3=Me$
XXIII: $R_1=R_2=H$; $R_3=Me$



XX: $R_1=R_2=R_3=Me$; $R_4=H$
XXV: R_1, $R_2=CH_2$; $R_3=H$; $R_4=Me$
XXVI: R_1, $R_2=CH_2$; $R_3=R_4=Me$



XXIV

While this work was in progress, a paper appeared dealing with the mass spectra of the isopavine alkaloids, amurensine (XXV) and amurensinine (XXVI).[23] The authors noted that although the mass spectra of the pavine and isopavine-type alkaloids are very similar; it is, nevertheless, possible to distinguish between them on the basis of the presence of a large M^+-43 peak in the spectra of the isopavine compounds, corresponding to the loss of CH_2—N—Me.

EXPERIMENTAL

The rates of methiodide formation were determined on 3 mg of sample in acetonitrile soln at 25°, as described in Ref 1c. The NMR spectra were run at 60 Mc in $CDCl_3$ soln using TMS as an internal standard. The mass spectra were obtained at low resolution on an MS-9 instrument. M.Ps are uncorrected. All TLC was on Merck GF-254.

Synthesis of the tetrahydroprotoberberines XI *and* XIV

Methyl 2-(3,4-*methylenedioxyphenyl*)*propionate*. Alkylation of the methyl ester of homopiperonylic acid was accomplished as follows: 40 g of the ester (0·206 mole) in 50 ml anhyd ether was added dropwise to a suspension of $NaNH_2$ (prepared from 4·95 g (0·215 mole) of Na) in about 500 ml liquid NH_3. After stirring 10 min, MeI, 29·8 g (0·210 mole), in 50 ml anhyd ether was also added dropwise. Stirring was continued for 1 hr, 12·3 g NH_4Cl was added, and the NH_3 evaporated on a steam bath. The yellow residue was taken up in ether and water, the ether was separated, dried over $MgSO_4$, and evaporated to yield a yellow oil. Vacuum distillation provided 34·2 g (80%) of the desired product, b.p. 101°/0·5 mm.

2-(3,4-*Methylenedioxyphenyl*)*propionic acid*. The propionate ester above (31·4 g, 0·16 mole) was refluxed in 200 ml MeOH with 13 g KOH and 25 ml H_2O, for 12 hr. The solvent was evaporated, the residue taken up in H_2O, washed with ether, and then carefully acidified with conc HCl while cooling in an ice-bath. The colorless oil which precipitated was extracted into $CHCl_3$. After drying over $MgSO_4$,

filtration and evaporation of the solvent, a colorless oil was obtained which crystallized on cooling to give white crystals, m.p. 79–80°, reported m.p. 80°,[24] yield 27·25 g (93%).

N-(3,4-*Dimethoxyphenethyl*)-2-(3,4-*methylenedioxyphenyl*)*propionamide*. A mixture of the above acid (27·25 g), $SOCl_2$ (21·40 g), 100 ml anhyd ether, and one drop pyridine were stirred overnight at room temp. The ether and excess $SOCl_2$ were evaporated and the oily acid chloride dissolved in 50 ml anhyd $CHCl_3$. The $CHCl_3$ soln was added dropwise to a stirred mixture of homoveratrylamine (26·20 g), $CHCl_3$ (200 ml), Na_2CO_3 (32 g) and H_2O (150 ml) while cooling in an ice-bath. After stirring an additional 15 min, the $CHCl_3$ layer was separated washed with H_2O, 10% HCl, and H_2O, and dried over $MgSO_4$. Evaporation gave a brown oil which crystallized on trituration with ether to furnish 50 g (99%) cream colored crystals, m.p. 106–107°. Mass spectrum: *m/e* (% base): M^+ 357 (15), 208 (2·5), 192 (1·8), 163 (base), 150 (30), 148 (90). M^+ checks for $C_{20}H_{23}O_5N$. IR ν($CHCl_3$): CONH at 1662 cm^{-1}; NMR: 1·45 δ, C—Me (doublet, $J=7$ Hz); 2·79 δ and 2·81 δ, 6H, 2OMe (2 singlets); 5·76–6·0 δ, 3H, NH and O—CH_2—O (singlet superimposed on broad multiplet); 6·5 to 6·9 δ, 6H, ArH (complex pattern).

1-(α-*Methyl*-3,4-*methylenedioxybenzyl*)-3,4-*dihydro*-6,7-*dimethoxyisoquinoline*. The above amide, 10 g (0·028 mole), $POCl_3$ (20 ml), and dry toluene (60 ml), were refluxed together for 1 hr. The excess reagent and toluene were removed *in vacuo*, and the residue dissolved in a minimun of cold MeOH, then poured into a large excess H_2O. The aqueous soln was washed with ether, basified with NH_4OH, and extracted with $CHCl_3$. Separation of the $CHCl_3$ layer, drying over $MgSO_4$, filtration, and evaporation provided 9·2 g (97%) of a light yellow oil which was not further characterized, but was immediately reduced as described below.

1-(α-*Methyl*-3,4-*methylenedioxybenzyl*)-1,2,3,4-*tetrahydro*-6,7-*dimethoxyisoquinoline*. A mixture consisting of 9·2 g (0·028 mole) of the imine above, 2N H_2SO_4 (60 ml), 4 drops of 10% $CuSO_4$, and 6·5 g powdered Zn, was heated on a steam bath for 5 hr. The now colorless soln was filtered free of excess Zn, chilled, and the hydrosulfate salt extracted into $CHCl_3$. The free base was generated by basification with NH_4OH and after washing with H_2O, the $CHCl_3$ layer was dried over $MgSO_4$. Filtration and evaporation afforded 7·5 g (81%) of the secondary amine mixture of diastereoisomers. NMR spectroscopy indicated this to be approx. a 4:3 ratio of C_{13} isomers. Since the secondary amine free base slowly darkens on standing, it is convenient to store as the monooxalate salt. Mass spectrum: *m/e* (% base): M^+ 341 ± 2(1), 326 ± 2(0·5), 192 (base), 192 (base), 176 (25), 148 (16), 135 (13). M^+ checks for $C_{20}H_{23}O_4N$; NMR: C—Me, 1·15 δ, doublet (J = 7), and 1·35 δ, doublet (J = 7).

13-*Methyltetrahydro-ψ-epiberberine*, 13-α-Me *and* 13-β-Me *mixture* (XIV *and* XI). The benzylisoquinoline above (1·0 g) was dissolved in 6 ml MeOH, and the soln treated with 0·5 g $NaHCO_3$. While warming on the steam bath, 10 ml formalin was gradually added. After a few min, addition of 50 ml H_2O and 20 ml ice precipitated the oily hydroxymethyl adduct. The entire reaction mixture was then transferred to a separatory funnel with the aid of 50 ml $CHCl_3$ to dissolve the oil. The mixture was saturated with NaCl, and after thorough shaking the $CHCl_3$ layer was separated. The organic layer was added to 5 ml of conc HCl, and allowed to stand for 4 hr. Following the addition of 20 ml H_2O, the mixture was basified with NH_4OH. Separation of the $CHCl_3$ layer, drying over K_2CO_3, filtration, and then evaporation of the solvent provided 840 mg of crude light yellow product, consisting primarily of the two diastereoisomeric tetrahydropseudoprotoberberines.

A. (±)-13-β-Me-13a-α-H-*Tetrahydro-ψ-epiberberine* (XI). The light yellow mixture obtained above was warmed with MeOH, then cooled and scratched. The crystals which formed were collected after allowing the mixture to chill at 0° for 1 hr. These crystals consisted of fairly pure higher R_f isomer by TLC, and two recrystallizations from MeOH furnished 550 mg of white, crystalline XI, m.p. 188–189°. Mass spectrum: *m/e* (% base): M^+ 353 (35), 338 (12), 192 (27), 162 (base). M^+ checks for $C_{20}H_{23}O_4N$; NMR: 0·93 δ, 3H, C—Me (doublet, $J=7$ Hz); 3·88 δ, 6H, 2Me (singlets, superimposed); 5·89 δ, 2H, O—CH_2—O (singlet); 6·5 δ to 6·7 δ, 4H, ArH (4 singlets).

B. (±)-13-α-Me-13a-α-H-*Tetrahydro-ψ-epiberberine* (XIV). The mother liquors from the preparation of XI were evaporated to about 3 ml, chilled with dry ice, and scratched. Cream colored crystals appeared, and proved to be the lower R_f isomer, m.p. 132–134°. One recrystallization from MeOH provided 125 mg of colorless crystals, m.p. 134–135°. Mass spectrum: Identical with high R_f isomer except for minor intensity differences; NMR: 1·48 δ, 3H, C—Me (doublet, $J=7$ Hz); 2·82 δ and 3·87 δ, 6H, 2OMe (2 singlets); 5·88 δ, 2H, O—CH_2—O (singlet); 6·5 δ 6·8 δ, 4H, ArH (4 singlets).

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