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STUDIES IN PROTOBERBERINE ALKALOIDS XVII - NEOOXYBERBERINE ACETONE+

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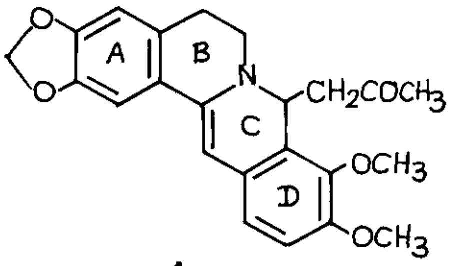
Abstract -- Structure and Stereochemistry of Neooxyberberine acetone, 8,13a-(2'-Oxopropano)-13-hydroxy-2,3-methylenedioxy-9,10-dimethoxydibenzo-(a,g)-quinolizine 4. Chemical, spectroscopic and X-ray crystallographic studies are presented.

+ Dedicated to Professor Dr. Tetsuji Kametani in appreciation of his great contribution to nitrogen heterocyclic chemistry in general, and isoquinoline alkaloids in particular on the occasion of his retirement from the chair of Organic Chemistry in the Pharmaceutical Institute, Tohoku University, Japan in April 1981.

Neooxyberberine acetone obtained in 1911 by Pyman[1] by oxidation of acetoneberberine 1 in acetone solution with aqueous potassium permanganate, has intrigued several research groups[2,3,4]. Among the various structures proposed, 2 of Iwasa and Naruto[4] made in 1966, appeared to be the most acceptable.



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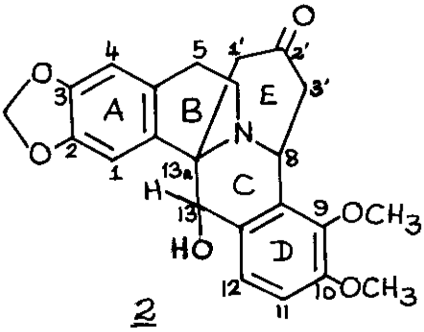

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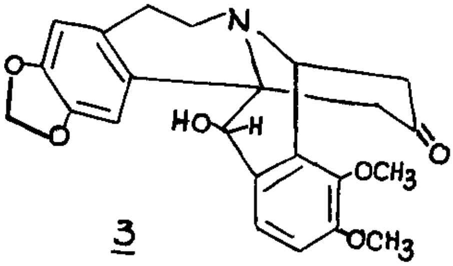
These authors have showed that similar products could be obtained from other acetoneberbines and 13-methylacetoneberberine[5], but left the question of stereochemistry open. Charubala[6] presented evidence in 1969, to show that B and C rings of the protoberberine template in neooxyberberine acetone were cis-fused and that the hydroxyl group at C_{13} and the 2'-oxopropano bridge were probably trans, the molecule being represented by the stereostructure 3.



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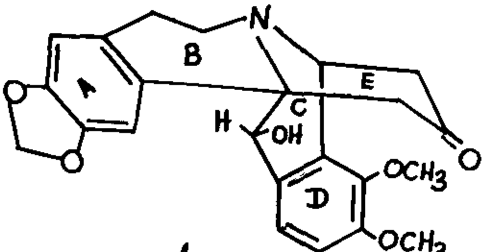
These arguments have been summarised in our review[7] and mainly depended upon, (i) the ^{1}H-NMR spectra of the oxidation product 5 of neooxyberberine acetone 2 and (ii) the results of the sequence of ethyleneketalisation of 2, oxidation of the ketal 11 and sodium borohydride reduction of 12 to a product different from the ketal of 2.

The review[7] noted that the ^{1}H-NMR spectrum of 2 was itself complex and unhelpful for stereochemical speculations, perhaps due to the detachment in solution of the ketone bridge in 2 from C_{13a} and reunion. We subsequently undertook a thorough investigation of the chemistry and UV, IR, Mass and ^{1}H-NMR spectra and also X-ray crystallographic study of neooxyberberine acetone. The results presented below show conclusively that the structure 4 differs from the earlier proposal 3 in having the hydroxyl group and 2'-oxopropano bridge cis to each other.



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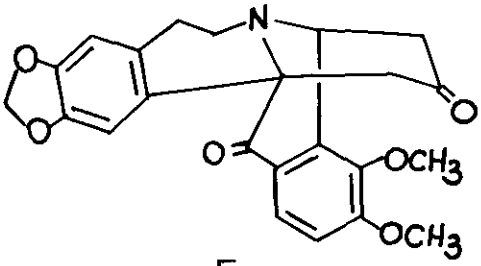
The chemical and spectroscopic studies relate to neooxyberberine acetone 4 and diketone 5 obtained from it by chromic acid oxidation, the O-acetyl derivative[4] of neooxyberberine acetone (6), sodium borohydride reduction product 7 of 4, the ethylene ketal of 4 and its chromic acid oxidation and further reduction products[6] and neooxyberberine 8 obtained by acid treatment of 4[4]. Details of synthesis and UV, IR and mass spectral data are given in the experimental section, while the ^{1}H-NMR data are compiled in Table 1.



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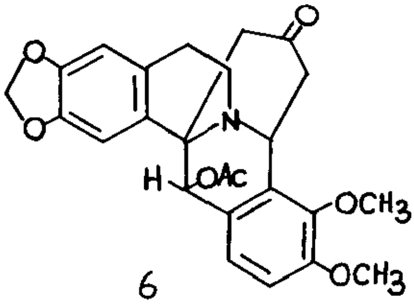

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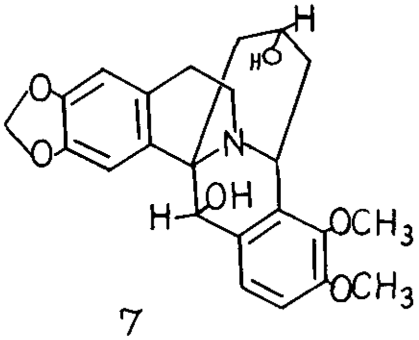

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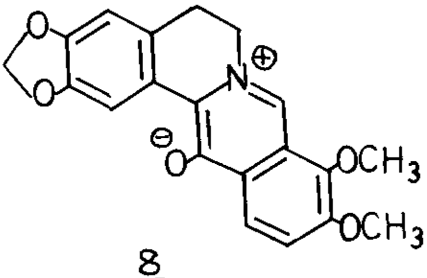

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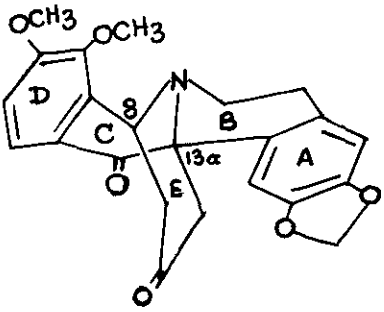
The ^{1}H-NMR spectrum of diketone 5 shows selective and marked deshielding only of the proton at C_{12} (and not of the proton at C_1) which requires that rings B and C must be fused cis to each other, giving a trans-geometry for the fusion of the rings B and E containing the 2'-oxopropano bridge. The same geometry can be extended to neooxyberberine acetone. A trans-fusion of rings B and C in 5a will result in a more pronounced deshielding of proton at C_1 than the one at C_{12}.



5a (trans-fusion of rings B and C)

The stereochemistry of the hydroxyl group at C_{13} was previously derived as shown in 3 from the following arguments^6. The ethyleneketal 9 of neooxyberberine acetone was oxidised by chromic acid to a product presumed to be the diketone 10 which upon further reduction with sodium borohydride gave a product considered to be 11. A hydride ion was supposed to add to the carbonyl group at position 13 from the side opposite to the ketone bridge. A careful study of the proton spectrum of the oxidation product (Table 1 - horizontal entry 8) showed that unlike in 5, one of the two aromatic proton singlets C_1-H or C_4-H was highly deshielded, δ7.67. The deshielding was however, not large enough as envisaged for a B/C trans-fusion[7]. Comparison of the widths at half-height of the two signals at δ7.37 (1 Hz) and δ7.67 (2 Hz) showed the latter to be broader which is thus to be ascribed to C_4-H. Unlike C_1-H, C_4-H has the possibility of small unresolved coupling with benzylic protons at C-5. Additionally, it was noted that all the aromatic protons were deshielded to a greater or smaller degree, and a greater deshielding for the singlet due to the methylenedioxy protons (δ6.22). The multiplet due to the methine proton at C_8 generally seen around δ4.70 had suffered the maximum downfield shift to δ6.55. The high field region showed besides the methoxyl signal, a multiplet at δ3.78 due to the ethyleneketal protons. The rest was complex and unanalyzable, but seemed to indicate the disappearance of some protons. However, recently the mass spectrum of the compound under controlled conditions showed the presence of a peak at m/e 479, in addition to the ion at m/e 451 expected for 10. This along with UV, IR and ^{1}H-NMR data are best reconciled by reformulating the structure of ketoketal as 12 which was further supported by analytical data. The sodium borohydride reduction product previously formulated as 11 needs also structural revision. The product was homogeneous on tlc and showed molecular ion at m/e 483, corresponding to a molecular formula $C_{25}H_{25}NO_9$. The ^{1}H-NMR spectrum showed a multiplet at δ6.30 due to the proton at C_8, requiring the presence of a lactam carbonyl group at C_6 which was further confirmed by an IR band at 1640 cm^{-1}. However, the multiplicity of signals in the aromatic region and the presence of four singlets due to the protons at C_5 and C_{13} in the spectrum of the D_2O treated sample at δ4.84, 4.90, 4.93 and 5.01, all together integrating for 2 protons, indicate that the product has the gross structure 13, but it perhaps is a mixture of two epimers or diastereoisomers (at centres C_5 and C_{13}).

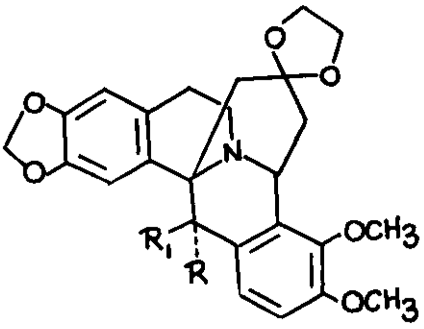
Table 1. ^{1}H-NMR Spectral Data of Neooxyberberine acetone derivatives

COMPOUND	δ values for Protons in ppm										
	C_1-H	C_4-H	C_{12}-H	C_{11}-H	OCH_2O	C_{13}-H	C_8-H	OCH_3 (C_9)	OCH_3 (C_{10})	OH (C_{13})	Others
4^+	7.23	6.58	7.17 (d) (J=8.8 Hz)	6.83 (d) (J=8.8 Hz)	5.92	4.81 (d) (J=9 Hz)	4.67 (m)	3.84	3.84	2.17 (d) (J=9 Hz)	...
$4b^+$	6.97	6.46	6.90 (d) (J=8.5 Hz)	6.71 (d) (J=8.5 Hz)	5.92	5.03	4.67 (m)	3.90	3.90	1.63(bs)	...
5^+	6.99	6.56	7.78 (d) (J=8.5 Hz)	6.92 (d) (J=8.5 Hz)	5.93	..	4.84 (m)	3.93	3.93	..	...
6	6.78	6.60	6.85 (d) (J=8.2 Hz)	6.92 (d) (J=8.2 Hz)	5.92	6.22	4.67 (m)	3.92	3.83	..	2.23 (O-CO-CH_3)
7	7.20	6.55	7.03 (d) (J=8.2 Hz)	6.82 (d) (J=8.2 Hz)	5.92	4.67	4.67	3.78	3.78	..	4.03 (m)
8	7.90	6.97	8.33 (d)	8.00 (d)	6.10	..	9.28	4.30	4.19	..	4.87 (m)++ N-CH_2
11	7.20	6.53	7.20 (d) (J=8.0 Hz)	6.83 (d) (J=8.0 Hz)	5.90	4.85 (d) (J= 12 Hz)	4.38 (m)	3.90	3.87	3.37 (d) (J=12 Hz)	3.83(m) O-CH_2CH_2O
12	7.37	7.67	7.60 (d) (J=8.0 Hz)	7.10 (d) (J=8.0 Hz)	6.22	..	6.55 (m)	3.92	3.92	..	3.78(m) OCH_2-CH_2O

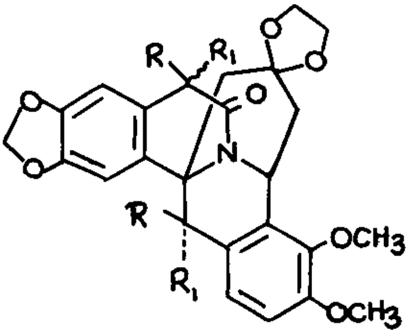
\+ Spectra of 4, 4b and 5 are at 90 MHz. All the others at 60 MHz.

++ Ar-CH_2 is seen as multiplet at δ 3.25.

Solvents: 4, 4b, 5, 6 and 11 in $CDCl_3$
7 and 12 in DMSO-d_6
8 in CF_3COOH.

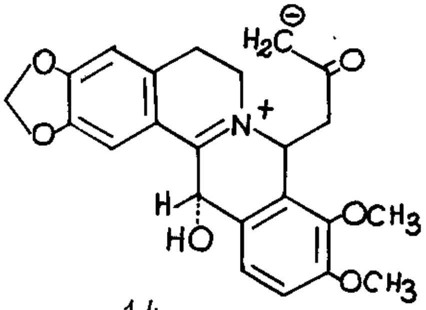


9 $R=OH$; $R_1=H$
10 $R, R_1 = O$
11 $R=H$; $R_1=OH$



12 $R, R_1 = O$
13 $R=H$; $R_1=OH$

Largely prompted by these results we reevaluated the ^{1}H-NMR spectrum of neooxyberberine acetone. We had noted earlier[7] that the spectrum in CDCl$_3$ showed more than one species to be present, while the spectra of the acetate 6, diketone 5, diol 7 and ketal 11 were straight forward. This led us to speculate that neooxyberberine acetone might exist in solution as an equilibrium mixture of diastereoisomers formed through the intermediacy of the immonium compound 14. This would arise by detachment of the 2'-oxopropano bridge from C$_{13a}$, epimerisation of centres C$_{13}$ and/or C$_8$ and reattachment of the three carbon bridge. While the role of ketone was obvious, the substituent at C$_{13}$ has no role to play in this phenomenon. Further, the UV spectrum of neooxyberberine acetone 4 in alcohol, λ_{max} 285, 234, 208 nm (log ε, 3.97, 4.18, 4.25) was very similar to that of diol 7 or ketal 11 with no evidence for the presence of species 14, which would be expected to absorb at longer wavelengths[8]. Also, sodium borohydride reduction of neooxyberberine acetone gave only one product viz., the diol 7 and none corresponding to ring opening and reduction[8]. A better explanation for the observed complexity in the NMR spectrum seemed to be that the hemiketal 4b is formed partially in solution.



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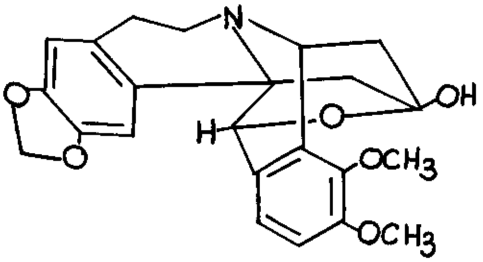
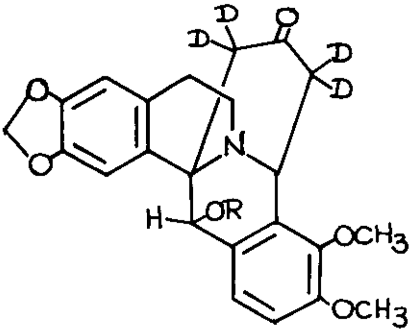


4b

In ^{1}H-NMR spectrum of 4 at 60 MHz, most signals are broadened and ill-understood. But the 90 MHz spectrum in $CDCl_3$ (Table 1) of 4 shows that it exists as a mixture of 4 and 4b in the ratio of approximately 7:3. A full assignment of all the signals except the high field methylene resonances has been made. The most pertinent observation is a singlet integrating for about 0.3 proton at δ5.03 due to the proton at C_{13} in 4b. The signals due to the protons at C_1 and C_{12} in 4 are deshielded by about 0.25 ppm compared to their position in 4b, while the protons at C_4 and C_{11} are negligibly affected. Models of 4 and 4b show that the free hydroxyl group at C_{13} in 4 can exert a deshielding influence on C_1- and C_{12}-H, while the formation of the cyclic hemiketal 4b pulls the oxygen atom farther away. On the other hand, the proton at C_{13} in 4b would be expected to resonate at lower field (δ5.03) compared to its position (δ4.81) in 4 due to an additional oxygen atom at β-position. The methylenedioxy protons in 4 and 4b being farther away from the site of charge, were not differentiated except in certain combination of solvents or at 360 MHz. But the methoxyl ones are separated slightly, the spectrum of 4 in DMSO-d_6 likewise has signals for both 4 and 4b in about the same ratio as in $CDCl_3$. The tetradeutero derivative 15 showed at 360 MHz the same two species distinctly. Especially interesting was to note that the signals that are due to the protons at C_8 had become singlets at δ4.67 and δ4.74.



15 R=H

16 R=D

The ^{13}C-NMR spectrum of neooxyberberine acetone in a mixture of $CDCl_3$ and DMSO-d_6 at 22.63 MHz also showed duplicate sets of signals for many carbon atoms. Two were recognisable for the methylenedioxy carbon at 100.6 and at 100.8 ppm.

The new interpretation of the ^{1}H-NMR spectrum in terms of ketoalcohol-hemiketal equilibrium demands that the hydroxyl group and 2'-oxopropano bridge in 4 should be cis to each other as depicted in the stereostructure and in accordance with the X-ray studies. The ketal of 4 is thus represented by 11. Models show that the hydroxyl groups in 4 and 11 are more enveloped by other atoms than in epimeric structure 3 and 9 respectively. Accordingly, in 4 and 11 the proton and the hydroxylic proton at C_{13} are seen to couple each other, the coupling being washed out with D_2O. Such coupling has been noted for similar molecules[5] but not commented upon.

A rather puzzling observation is that Dreiding model of 4 indicates that C_{13} hydroxylic hydrogen and carbonyl oxygen can come as close as 2.8Å, but in the solid state X-ray does indicate a weak-intermolecular O-H...O bonding. A plausible explanation is that the hydroxyl bond is turned away from the carbonyl group to avoid interaction with equatorial hydrogen α to >C=O. Such an interaction is avoided in the hemiketal 4b by distortion of the appropriate rings and bonds. Evidently, dissolution of crystals of 4 in $CDCl_3$ breaks the O-H...O bond and allows an equilibrium to be set up between 4 and 4b.

Hemiketal of the type 4b with an extra methyl group at C_{13} have been obtained earlier by other workers[5] as by-products of oxidation of acetone adducts by deliberate base-catalysed isomerisation of 4. It is not inconceivable that neooxyberberine acetone 4 may be admixed with hemiketal 4b. However, we found our sample to be sharp melting and homogeneous on tlc: [silica gel:-chloroform containing 2 or 5 methanol, chloroform-ethyl acetate (1:1)]. On this basis and on the basis of X-ray studies which indicated only one species to be present in the solid state, we are convinced that the NMR spectrum of 4 is best explained by postulating an equilibrium of 4 with 4b set up in solution.

Mass spectral fragmentation of 4

The mass spectral fragmentation of 4 also deserves special comment. Besides the molecular ion peak M^+ at m/e 409 (58%), peaks are seen at m/e 394 (6%, M-CH_3), 392 (8%, M-OH), 381 (13%, M-CO), the last two being supported by metastable peaks at m/e 324 and 354 respectively. The prominent peaks at m/e 378 (55%), 350 (100%), 216 (65%) and 189 (100%) require explanation and interpretation. The fragment at m/e 350 could arise from 4 by the loss of acetone molecule (58 u) first to form neooxyberberine 8, with subsequent loss of a hydrogen atom. This was ruled out, since there is no M-1 peak in the mass spectrum of 8 itself. Detailed studies described below, using high resolution mass spectrometry and tetra- and penta-deutero derivatives of 4 helped to rationalise the fragmentation pattern (Fig. 1).

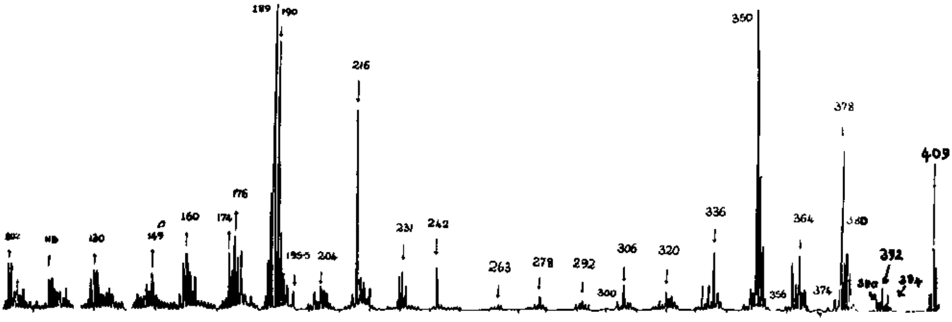


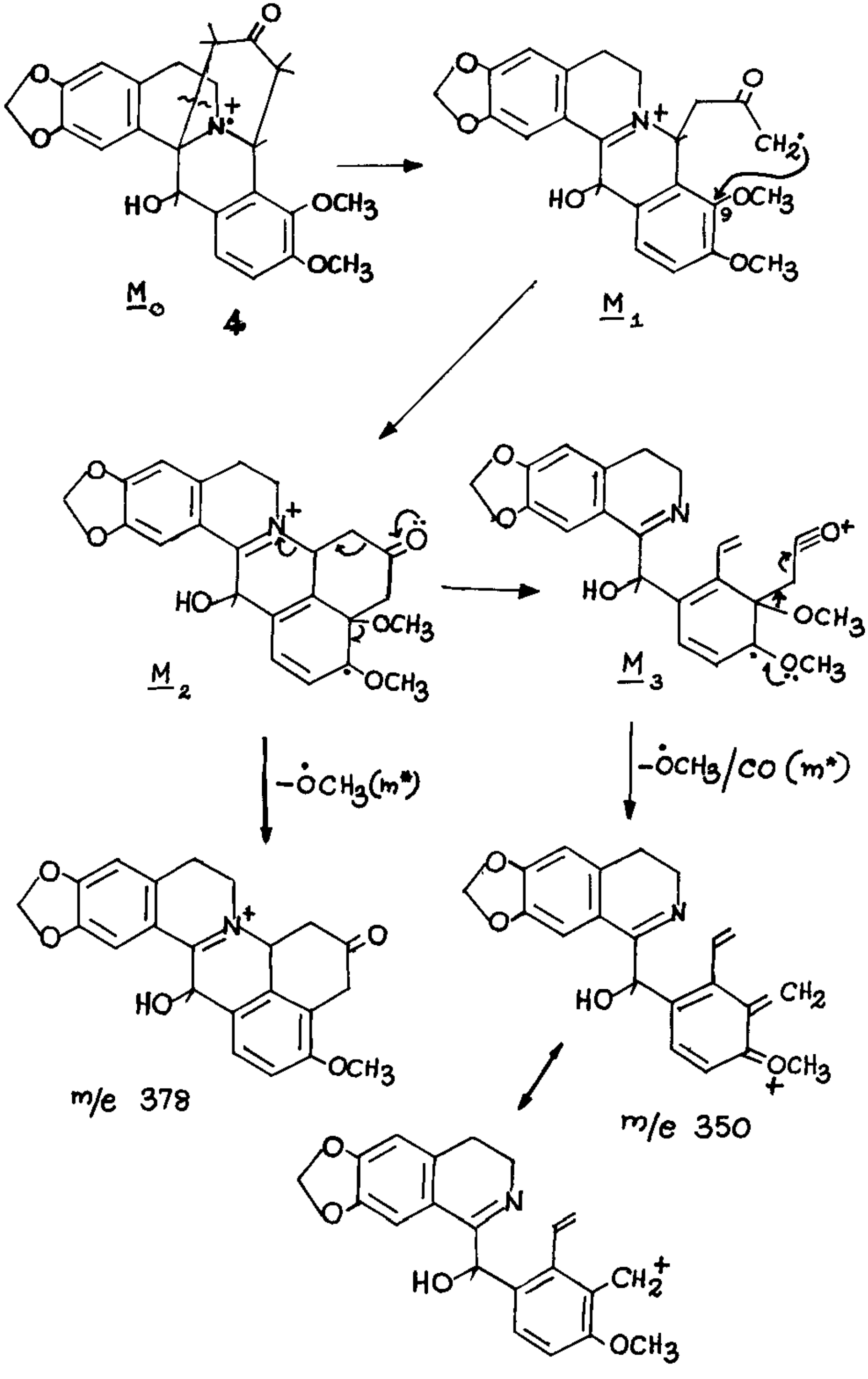
Figure 1. Mass spectrum of 4

Besides a pronounced molecular ion M^+ (m/e 409, $C_{23}H_{23}NO_6$ determined through accurate mass measurement at high resolution), the electron impact (EI) mass spectrum of 4 exhibits two major fragment ions in the upper mass range, m/e 378 and m/e 350. They have $C_{22}H_{20}NO_5$ and $C_{21}H_{20}NO_4$ compositions respectively, i.e., they correspond to losses of CH_3O and $C_2H_3O_2$ from M^+. In two deuterated analogues studied 15 (α,α'-labelled with respect to carbonyl function by direct D_2O/K_2CO_3 exchange) and 16 (15 incubated in CH_3OD leading to additional H/D exchange of the 13-OH function), the label is completely retained in these fragments (mass shifts to 354/382 and 355/383 by 4 and 5 u respectively). This suggests the ejection of a methoxyl (rather than hydroxymethyl) radical for m/e 378, and of a $COOCH_3$ radical for m/e 350. In view of the structures of 4, it is obvious that neither of these losses can result from simple bond breaking processes.

For loss of a methoxyl radical from aromatic positions, i.e., from sites unfavourable under normal circumstances, there is however, ample precedence within the tetrahydroprotoberberine alkaloids as far as regiospecific ejection from the 9-position is concerned[9]. The enhanced loss of OCH_3 from that position has in fact been used in structure elucidation as a probe into the 9,10,11-substitution pattern of unknown of this class in atleast one case[10]. As rationalised in Scheme 1, specific loss of OCH_3 from C_9 is thought to be a consequence of facile α-cleavage with respect to nitrogen ($\underline{M}_0 \longrightarrow \underline{M}_1$), followed by radical type substitution at the ejection site (recyclisation to $\underline{M}_2$) triggering the loss of the former substituent in the course of rearomatisation.

As for the signal at m/e 378 for the loss of methoxyl, a metastable transition signal ($m^* = 299.5$) is also observed for the loss of 59 u at m/e 350. Together with the elemental composition of the latter (second most abundant ion) this indicates a loss of $COOCH_3$ as one intact unit, which is however, nowhere present in the structure. Yet, it has to be kept in mind that a two-step ejection of $CH_3O^\bullet/CO$ in a mechanistically coupled fashion (e.g., in a slower rate determining first step, generating an intermediate, apt to decompose much more rapidly than without this preceding event) would with conventional means, be indistinguishable from an actual

SCHEME 1

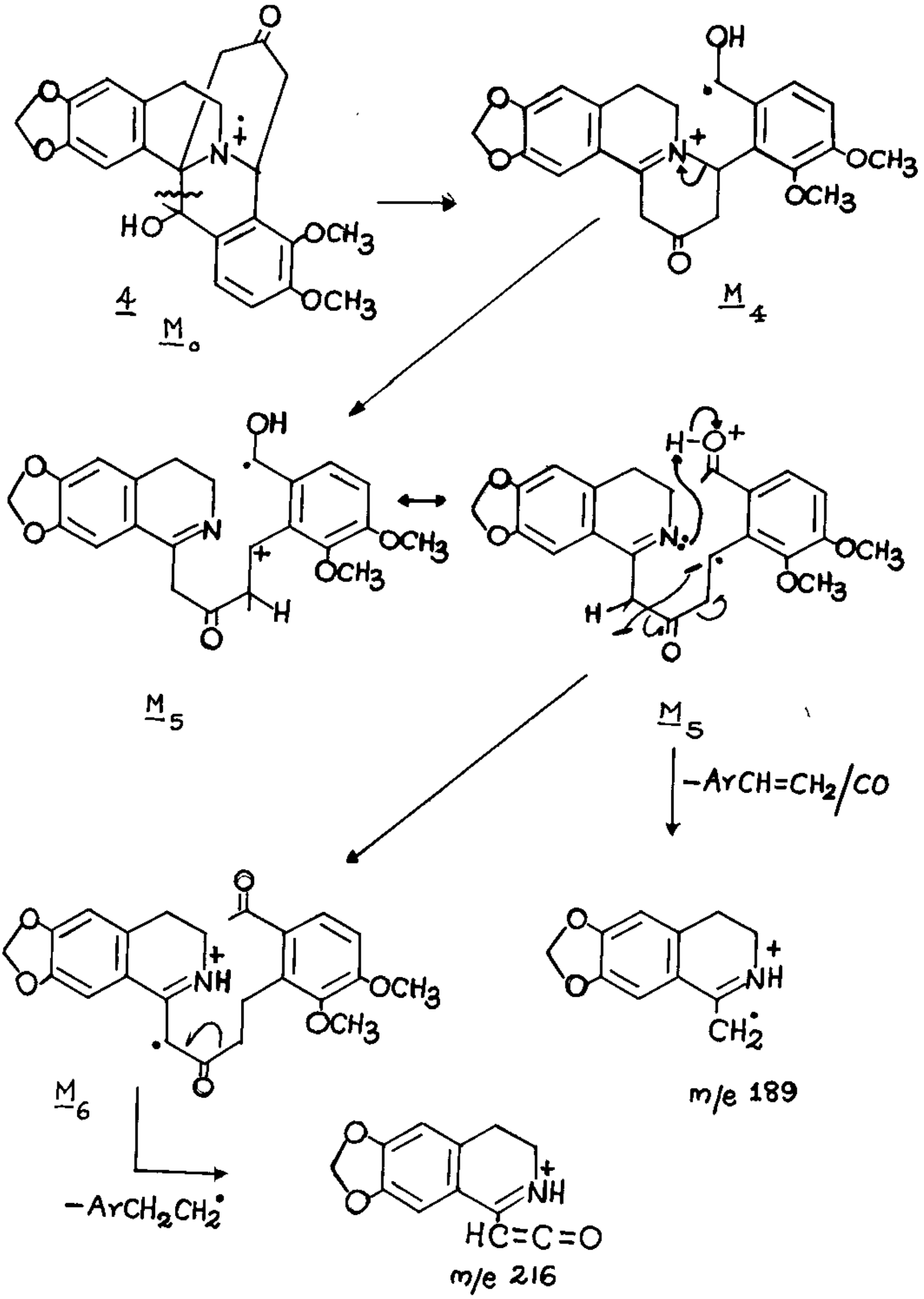


one step $^{\bullet}COOCH_3$ loss when viewed through the 'metastable time windows' of the mass spectrometer. Such 'apparent' one step ejections of structurally independent, distant moieties have been occasionally noted before[11]; a situation allowing for such coupled two step loss can indeed be visualised for 4, once the customary C/N heterolysis of the immonium ion M_2 triggers concommittant (or consecutive) further heterolyses within the new cycloketone system in a Grob-fragmentation like manner, to yield M_3. As an ideal intermediate of a two-step loss of separate OCH_3/CO entities (yet, admittedly, also for methoxyl migration to form a new $COOCH_3$ function to be lost in one piece), M_3 could rearomatize in a rate-determining initial methoxyl loss, thus opening a fast route to heterolytic loss of CO by dissociating into a benzylic rather than plain aliphatic carbenium ion with considerable extension of conjugation. In view of the high abundance of the m/e 350 ions, this coupled two-step decomposition appears to offer the more plausible mechanistic rationale than the loss of a $COOCH_3$ moiety just formed through methoxyl migration as an additional prerequisite.

The low mass region of the spectrum of 4 is likewise characterised by two fragment ions of major abundance, m/e 189 (base peak) and m/e 216. Accurate mass determination yields $C_{11}H_{11}NO_2$ and $C_{12}H_{10}NO_3$ compositions respectively. In 15, the major portion of ion current of the former is shifted to m/e 191, the remainder split between 190 and 192. Grossly, this reveals the incorporation of one of the α-carbons flanking the carbonyl group, though with reciprocal H-transfer between especially activated sites. Similarly, this is true for m/e 216 which is shifted in an approximate 1:1 ratio to 217 and 218. The spectrum of 16 shows that the hydroxyl H is also largely incorporated in these ions (shifts by 1 u in addition to those observed in 15). The elemental compositions and the retention of the N atom in these two fragments clearly indicate that the A/B ring moieties are involved. Pathways of their most likely formation are given in Scheme 2.

In this scheme, fragmentation is initiated by a mode of α-cleavage alternative to the one operative in scheme 1, effecting benzylic C/C cleavage. This is the preferential mode of nitrogen-triggered initial bond rupture

SCHEME 2



4
M₀
HO
OCH3
OCH3
M₄
OH
M₅
M₅
-ArCH=CH₂/CO
M₆
-ArCH₂CH₂•
NH
HC=C=O
m/e 216
m/e 189
CH₂•

highly characteristic of the regular (bicyclic with respect to B/C ring fusion) tetrahydroprotoberberines[12]. In the special case of the tricyclic derivative **4**, a still bicyclic $\underline{M}_4$ should readily undergo the usual C/N heterolysis to the open-chain species $\underline{M}_5$, in which the various $\underline{H}$ transfers evident in incomplete shifts, can take place between the sites indicated. Final C/C bond ruptures to these fragments reflect, nonetheless, the ease with which the alicyclic interface of **4** is ruptured inspite of its more intricate tricyclic framework which constitutes enhanced crosslinkage of the two aromatic portions of the molecule.

Crystal data[++]

Neooxyberberine acetone **4**

$C_{23}H_{23}NO_6$, Mol. wt. = 409.4, monoclinic (unique axis b)

Space group $P2_1/a$, a = 13.337 (3), b = 7.673 (2),

c = 18.494 (5) Å, β = 92.90 (3)°, V = 1890 Å,

D_m = 1.44 gcm^{-3}, DC = 1.439 gcm^{-3}, Z = 4, F (0,0,0) = 864.

Approximate dimensions of the crystal used in data collection were 0.2 x 0.2 x 0.3 mm.

Linear absorption coefficient $\mu = 8.75\ cm^{-1}$ (CuK_α)

The data were collected on a four circle CAD-4 diffractometer in the $\omega/2\Theta$- scan mode with CuK_α radiation ($\bar{\lambda} = 1.542$ Å). The stability and orientation of the crystal during data collection was monitored by frequently remeasuring a number of check reflexions. Corrections were made for Lorentz and polarisation factors but not for absorption. A total of 3200 reflexions were collected, of which 2497 were significant [$I > 3\sigma(I)$].

Structure solution and refinement

The structure was solved using the MULTAN programme[13]. All thirty non-hydrogen atoms could be identified in the E-map based on the set of signs

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[++] The X-ray crystallographic results were presented at the X National Conference on Crystallography, 21-23 February 1979 held at Banaras Hindu University, Varanasi, India.

with the highest figure of merit. The positional and isotropic thermal parameters were refined block-diagonally using the programme written by Shiono[14] and modified by B.S. Reddy. Hydrogen atom were then located at stereochemically reasonable positions from a difference map. Further refinement of positional and anisotropic thermal parameters of C,N and O atoms and of positional and isotropic thermal parameters of the hydrogen atoms led to a final R = 0.050 (significant reflexions only) scattering factors for non-hydrogen atoms were taken from ref.15 and for hydrogen atoms from ref.16. The quantity minimised was $\sum\omega(/F_o/-k/F_c/)^2$ with $\omega= 1/\alpha+ b/F_o/ + C/F_o/^2$ where, a = 2.061, b = -0.208 and C = 0.018. Final positional and thermal parameters for non-hydrogen atoms are listed in Table 2 and 2A, those for hydrogen atoms are listed in Table 3. A table of observed and calculated structure factor can be obtained from the author (K.V) on request.

Crystal packing

The crystal packing is shown in Fig. 2. The molecules are packed so as to form O-H...O intermolecular hydrogen bond O(17)...O(18) = 2.877 (4) Å, ∠O-H...O = 166.4° and ∠H-O...O = 9.5°. The envelope head carbon atom C (15) which is flanked on either side by oxygen atoms O(14) and O(16) makes short intermolecular contact with the oxygen from O(16), [C(15)...O(16) = 2.896 (5) Å]. However, this cannot be considered as C-H...O type hydrogen bond [C...O = 2.896 (5)Å, ∠C-H...O = 95.1° and ∠H-C...O = 64.5°], but a weak interaction.

Discussion

In the quinolizidine ring system, the B/C ring junction is cis-fused and both the component rings are in the half-chair conformation. The torsion angles within the rings B and C are shown in Fig. 3. The -OH group at C(13) is in the same direction as that of 2'-oxopropano bridge, a conclusion which is different from the expectations of the spectroscopic studies[7]. The five membered ring takes up an envelope conformation (C_s symmetry). The deviation of the atom C(15) from the plane through the remaining four atoms of the five membered ring is 0.105 Å. The aromatic rings A and D are planar within the experimental errors.

Table 2. Final positional (fractional) parameters (x 10^4) for non-hydrogen atoms

E.S.D's are given in parentheses

ATOM	X	Y	Z
C(1)	-183(3)	5998(5)	8701(2)
C(2)	-886(3)	5680(6)	9192(2)
C(3)	-1037(3)	4032(6)	9464(2)
C(4)	-487(3)	2648(6)	9253(2)
C(4a)	238(3)	2920(5)	8746(2)
C(5)	878(3)	1405(5)	8533(3)
C(6)	1419(3)	1748(6)	7852(3)
N(7)	1892(3)	3465(4)	7911(2)
C(8)	2667(3)	3735(5)	7394(2)
C(8a)	2251(3)	4181(5)	6633(2)
C(9)	2863(3)	4010(5)	6050(2)
C(10)	2503(3)	4452(6)	5349(2)
C(11)	1541(4)	5124(6)	5249(3)
C(12)	946(3)	5331(6)	5828(3)
C(12a)	1281(3)	4854(6)	6526(2)
C(13)	594(3)	5024(5)	7140(2)
C(13a)	1160(3)	4905(5)	7897(2)
C(13b)	398(3)	4586(5)	8470(2)
O(14)	-1518(3)	6851(4)	9503(2)
C(15)	-2138(3)	5840(6)	9950(3)
O(16)	-1768(3)	4087(4)	9959(2)
O(17)	3020(2)	8235(4)	7527(2)
O(18)	43(2)	6613(4)	7058(2)
O(19)	3799(2)	3276(4)	6185(2)
C(20)	4647(4)	4230(8)	5955(3)
O(21)	3141(3)	4187(5)	4805(2)
C(22)	2719(5)	4222(7)	4079(3)
C(1')	1741(3)	6615(6)	8071(2)
C(2')	2732(3)	6820(6)	7731(2)
C(3')	3349(3)	5211(6)	7678(2)

Table 2A. Anisotropic temperature factors (x 10^4) for non-hydrogen atoms
E.S.D's are given in parentheses
Temperature factor is of the form

$$T = \exp-(h^2\beta_{11} + k^2\beta_{22} + \ell^2\beta_{33} + 2hk\beta_{12} + 2h\ell\beta_{13} + 2k\ell\beta_{23})$$

ATOM	β11	β22	β33	β12	β13	β23
C(1)	38(2)	83(7)	22(1)	3(3)	3(1)	6(2)
C(2)	32(2)	100(7)	22(1)	4(3)	2(1)	1(3)
C(3)	37(3)	115(8)	19(1)	-8(4)	6(1)	0(3)
C(4)	44(3)	88(7)	24(1)	-8(4)	5(2)	4(3)
C(4a)	34(2)	86(7)	19(1)	-3(3)	0(1)	1(2)
C(5)	40(3)	71(7)	28(2)	3(3)	4(2)	5(3)
C(6)	43(3)	90(7)	25(1)	5(4)	3(2)	0(3)
N(7)	33(2)	79(6)	21(1)	10(3)	3(1)	6(2)
C(8)	32(2)	92(7)	19(1)	16(3)	3(1)	3(2)
C(8a)	35(2)	75(7)	19(1)	0(3)	0(1)	-2(2)
C(9)	38(2)	82(7)	20(1)	4(3)	2(1)	-3(2)
C(10)	49(3)	108(8)	18(1)	-3(4)	3(2)	-7(3)
C(11)	49(3)	147(9)	19(1)	-3(4)	-5(2)	1(3)
C(12)	39(3)	131(8)	22(1)	-1(4)	-5(2)	7(3)
C(12a)	35(2)	94(7)	19(1)	-5(3)	-3(1)	-1(2)
C(13)	28(2)	94(7)	22(1)	1(3)	-1(1)	7(3)
C(13a)	30(2)	82(7)	20(1)	3(3)	1(1)	6(2)
C(13b)	30(2)	82(7)	19(1)	4(3)	0(1)	1(2)
O (14)	52(2)	115(6)	33(1)	18(3)	18(1)	3(2)
C(15)	39(3)	123(8)	25(2)	-1(4)	9(2)	-10(3)
O(16)	59(2)	130(6)	33(1)	-1(3)	23(1)	5(2)
O(17)	40(2)	128(6)	31(1)	-14(3)	5(1)	5(2)
O(18)	41(2)	150(6)	29(1)	33(3)	5(1)	20(2)
O(19)	42(2)	143(6)	24(1)	16(3)	7(1)	6(2)
C(20)	42(3)	254(13)	32(2)	-1 (5)	7(2)	19(4)
C(21)	65(2)	193(7)	17(1)	11(3)	5(1)	-8(2)
C(22)	87(4)	181(11)	17(1)	24(6)	2(2)	-2(3)
C(1')	34(2)	93(7)	24(1)	-1(3)	3(1)	-2(3)
C(2')	31(2)	112(8)	17(1)	-11(3)	-2(1)	-2(2)
C(3')	27(2)	147(9)	19(1)	3(4)	0(1)	4(3)

Table 3. Fractional Coordinates (x 10^3) for hydrogen atoms with their isotropic temperature factors. E.S.D's are given in parantheses. The temperature factor is of the form: $T = \exp^{-}(B\sin^2\theta/\lambda^2)$

BONDED TO		X	Y	Z	B(Å^2)
H(1)	C(1)	-11(4)	721(6)	851(3)	2.7(1.0)
H(2)	C(4)	-58(4)	151(6)	945(3)	2.7(1.0)
H(3)	C(5)	139(4)	114(6)	895(3)	2.8(1.0)
H(4)	C(5)	48(4)	33(7)	846(3)	3.1(1.0)
H(5)	C(6)	197(4)	92(7)	781(3)	3.7(1.2)
H(6)	C(6)	95(4)	164(7)	741(3)	2.9(1.0)
H(7)	C(8)	303(3)	267(6)	737(2)	2.0(.9)
H(8)	C(11)	129(4)	554(7)	477(3)	3.8(1.2)
H(9)	C(12)	28(4)	584(6)	574(3)	2.7(1.0)
H(10)	C(13)	11(3)	408(5)	713(2)	1.0(.7)
H(11)	C(15)	-285(4)	583(7)	973(3)	3.3(1.1)
H(12)	C(15)	-215(4)	630(8)	1046(3)	4.1(1.2)
H(13)	O(18)	-56(5)	649(9)	723(3)	4.9(1.4)
H(14)	C(20)	462(7)	541(13)	609(5)	10.1(2.6)
H(15)	C(20)	528(6)	369(11)	614(4)	8.2(2.1)
H(16)	C(20)	467(6)	424(11)	547(5)	8.5(2.3)
H(17)	C(22)	245(5)	542(9)	394(4)	5.3(1.5)
H(18)	C(22)	330(5)	383(9)	377(3)	5.2(1.5)
H(19)	C(22)	207(6)	339(10)	403(4)	7.2(1.8)
H(20)	C(1')	192(4)	667(8)	862(3)	4.1(1.2)
H(21)	C(1')	129(4)	764(6)	793(3)	2.9(1.0)
H(22)	C(3')	361(4)	487(6)	816(3)	2.7(1.0)
H(23)	C(3')	391(3)	537(6)	740(3)	2.5(.9)

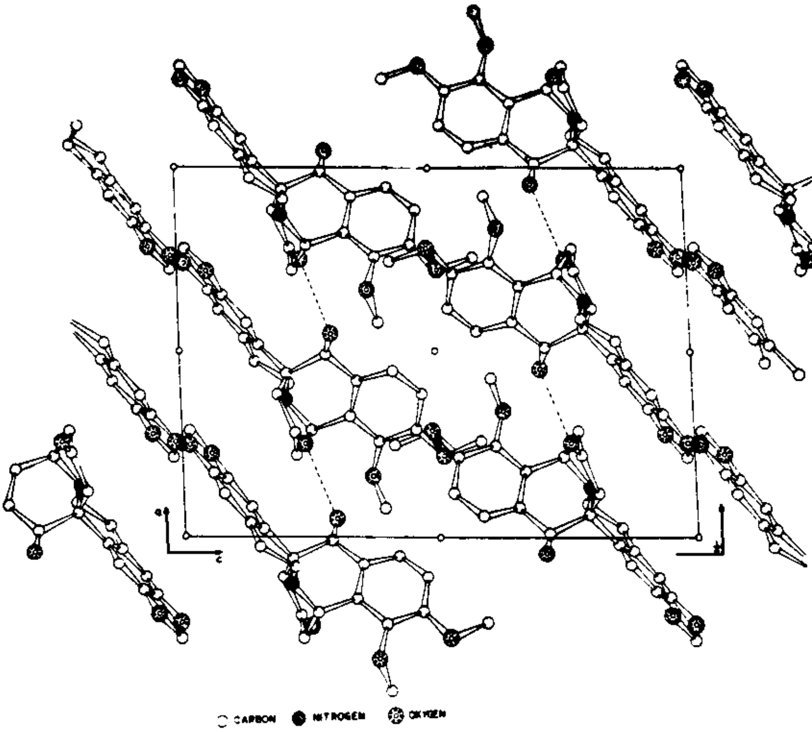

Figure 2. Packing of the molecules as viewed down the b-axis.

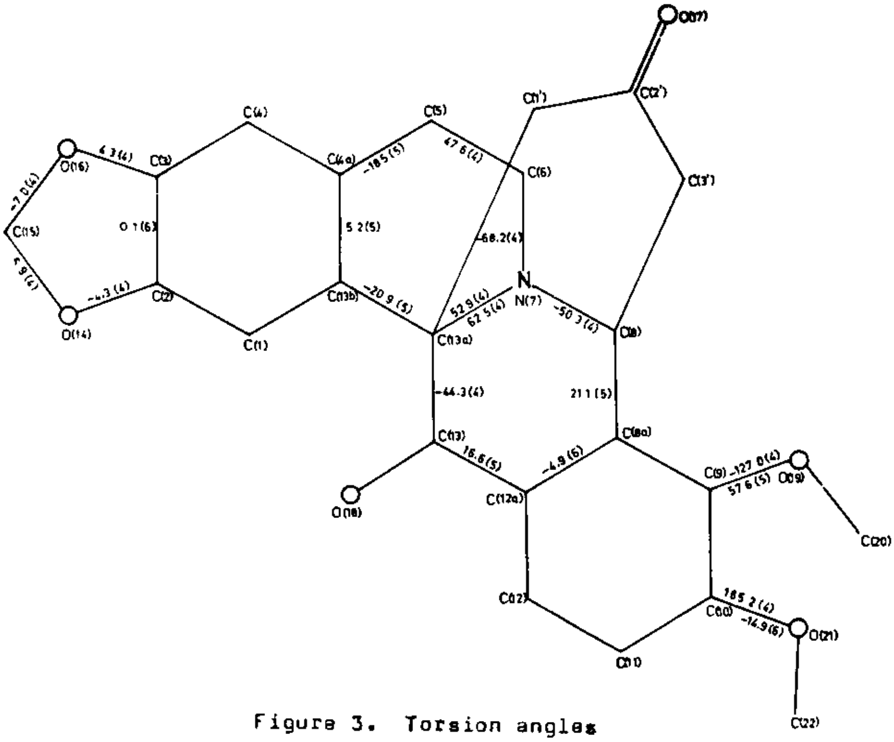

Figure 3. Torsion angles

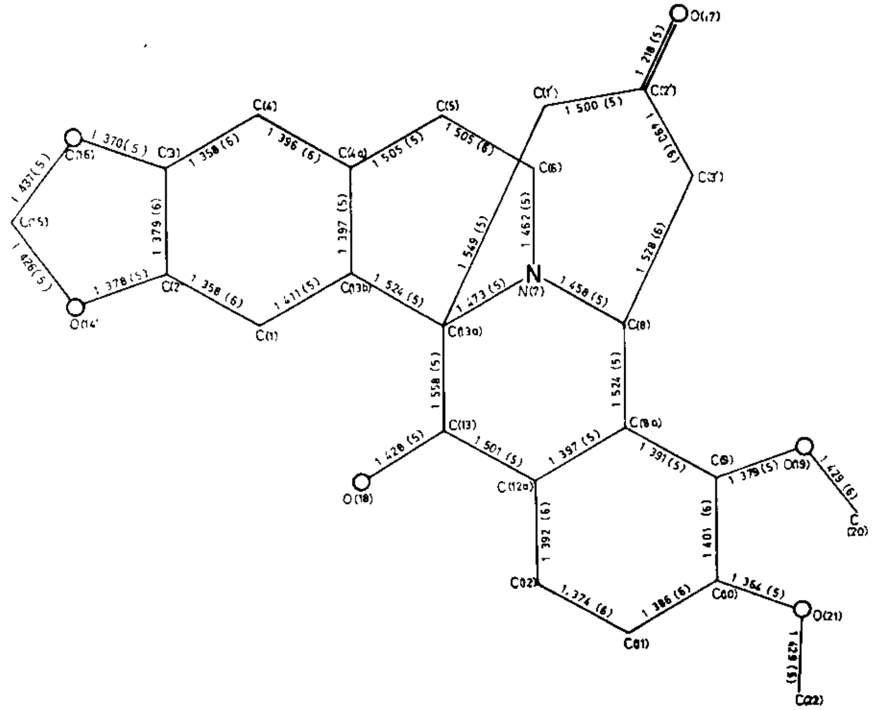

Figure 4. Bond lengths involving non-hydrogen atoms

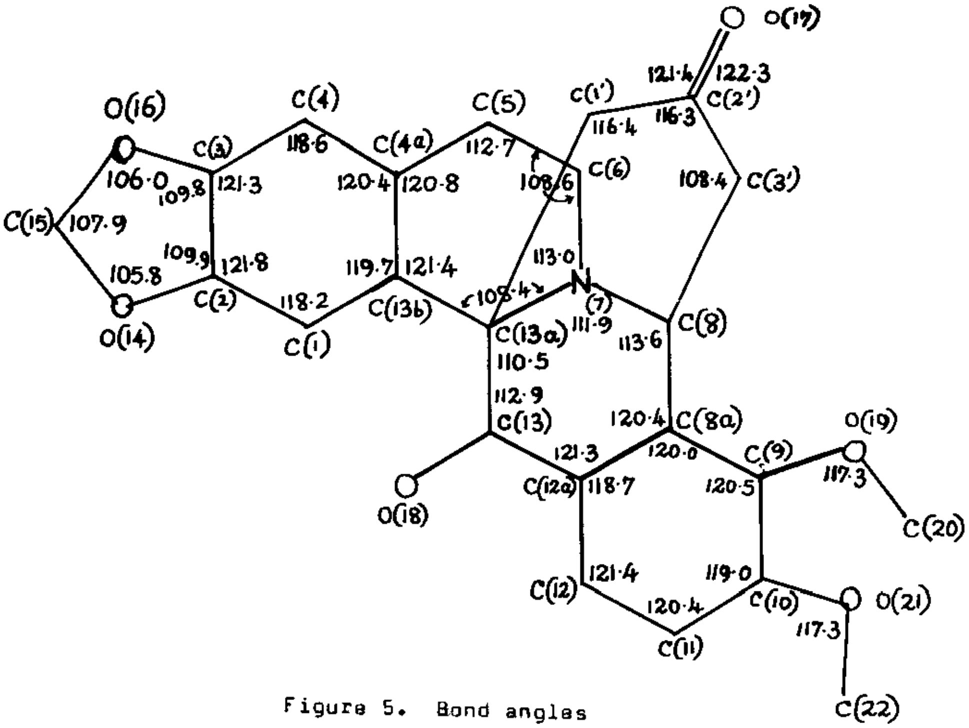

Figure 5. Bond angles

Table 4. Bond angles (°) involving the non-hydrogen atoms. The e.s.d's are given in parantheses.

C(2)-C(1)-C(13b)	118.2(4)	C(10)-C(11)-C(12)	120.4(4)
C(1)-C(2)-C(3)	121.8(4)	C(11)-C(12)-C(12a)	121.4(4)
C(1)-C(2)-O(14)	128.3(4)	C(12)-C(12a)-C(8a)	118.7(4)
O(14)-C(2)-C(3)	109.9(4)	C(12)-C(12a)-C(13)	119.9(4)
C(2)-C(3)-C(4)	121.3(4)	C(8a)-C(12a)-C(13)	121.3(4)
C(2)-C(3)-O(16)	109.8(4)	C(12a)-C(13)-C(13a)	112.9(3)
O(16)-C(3)-C(4)	128.9(4)	C(12a)-C(13)-O(18)	108.9(3)
C(3)-C(4)-C(4a)	118.6(4)	C(13a)-C(13)-O(18)	111.6(3)
C(4)-C(4a)-C(13b)	120.4(4)	C(13)-C(13a)-N(7)	110.5(3)
C(4)-C(4a)-C(5)	118.8(4)	C(13)-C(13a)-C(13b)	108.9(3)
C(5)-C(4a)-C(13b)	120.8(4)	C(13)-C(13a)-C(1')	110.5(3)
C(4a)-C(5)-C(6)	112.7(4)	C(13b)-C(13a)-N(7)	109.4(3)
C(5)-C(6)-N(7)	108.6(4)	C(13b)-C(13a)-C(1')	109.7(3)
C(16)-N(7)-C(8)	113.4(3)	N(7)-C(13a)-C(1')	107.9(3)
C(6)-N(7)-C(13a)	113.0(3)	C(13a)-C(13b)-C(4a)	121.4(4)
C(13a)-N(7)-C(8)	111.9(3)	C(13a)-C(13b)-C(1)	118.9(4)
N(7)-C(8)-C(8a)	113.6(3)	C(1)-C(13b)-C(4a)	119.7(4)
N(7)-C(8)-C(3')	108.0(3)	C(2)-O(14)-C(15)	105.8(3)
C(8a)-C(8)-C(3')	109.5(3)	O(14)-C(15)-O(16)	108.0(4)
C(8)-C(8a)-C(9)	119.6(4)	C(15)-O(16)-C(3)	106.1(3)
C(12a)-C(8a)-C(9)	120.0(4)	C)(9)-O(19)-C(20)	117.3(4)
C(12a)-C(8a)-C(8)	120.4(4)	C(10)-O(21)-C(22)	117.3(4)
C(8a)-C(9)-C(10)	120.5(4)	C(13a)-C(1')-C(2')	116.4(3)
C(8a)-C(9)-O(19)	117.3(4)	C(1')-C(2')-C(3')	116.3(4)
C(10)-C(9)-O(19)	122.0(4)	C(1')-C(2')-O(17)	121.4(4)
C(9)-C(10)-C(11)	119.0(4)	C(3')-C(2')-O(17)	122.3(4)
C(9)-C(10)-O(21)	116.6(4)	C(2')-C(3')-C(8)	108.4(3)
C(11)-C(10)-O(21)	124.4(4)		

Bond lengths involving non-hydrogen atoms are shown in Fig. 4 and bond angles in Fig. 5 and Table 4. It is noteworthy that the bond lengths C(9) - O(19) (1.379(5)Å) and C(10) - O(21) (1.364(5)Å) are significantly different. This is consistent with the observed differences in the torsion angles about these bonds[17]: C(10) - C(9) - O(19) - C(20) = 57.6(5)° and C(11) — C(10) — O(21)— C(22) = 14.9(6)°.

Experimental

Melting points are uncorrected. UV spectra are run on DK2A spectrophotometer. 95% ethanol solutions were used. IR spectra are run on Perkin-Elmer Infracord. Mass spectra are from a Varian MatCH7 mass spectrometer.

Pyridine-Chromium trioxide oxidation of neooxyberberine acetone

To pyridine (20 ml), cooled in ice-bath at 0° was added slowly chromium trioxide (2 g) so that the temperature did not exceed 25°. Neooxyberberine acetone[1] (1 g) in Pyridine (10 ml) was then added gradually to the pyridine-chromium trioxide complex, maintaining the temperature below 15°. The mixture was stirred for 7 h at 15° and left overnight at room temperature. The mixture was centrifuged and the residue was repeatedly extracted with ethyl acetate. The combined ethyl acetate extracts were concentrated in vacuo to yield a gum 5 (0.8 g) which was chromatographed on silica gel using chloroform as eluant. The combined eluates were concentrated and crystallised from chloroform-methanol, (250 mg), m.p. 228-230°. λ_{max} 234, 290 nm (log ε, 4.4, 4.2); γ^{KBr}_{max} 1680, 1710 cm^{-1}.

$C_{23}H_{21}NO_6$ Calc. C,67.80; H,5.20; N,3.44
Found C,67.77; H,5.34; N,3.78%

Ethyleneketal of 8,13a (2'-oxopropano)-13-hydroxy-9,10-dimethoxy-2,3-methylenedioxy dibenzo-(a,g)-quinolizine (11)

A mixture of neooxyberberine acetone (2 g), methylene chloride (250 ml), diethylene glycol (10 ml) and borontrifluoride etherate (2 ml) was stirred at room temperature for 72 h. It was then poured into an ice-cold saturated solution of sodium bicarbonate. The methylene chloride layer was separated, washed, dried (Na_2SO_4) and evaporated to leave a gum (2 g) which on chromatography on silica gel using benzene-methylene chloride as eluant yielded the ketal 11, crystallised from benzene-hexane, (1.2 g), m.p. 200°. λ_{max} 208, 234, 285 nm (log ε, 4.25, 4.18, 3.97); MS: m/e, 453 (M^+), 438, 436, 422, 408 and 394.

$C_{25}H_{27}NO_7$ Calc. C, 66.21; H, 6.00
Found C, 66.29; H, 6.35%

Pyridine-chromium trioxide oxidation of the ethyleneketal 11

To pyridine (20 ml) cooled in ice-bath at 0° was added slowly chromium trioxide (2 g), so that the temperature did not exceed 25°. The above ketal 11 (1 g) in pyridine (10 ml) was then added gradually to the pyridine-chromium-trioxide complex, maintaining the temperature below 15°. The mixture was stirred for 7 h. at 15° and left overnight at room temperature. The mixture was centrifuged and the residue was repeatedly extracted with ethyl acetate. The combined ethylacetate extracts were concentrated *in vacuo* to yield a gum (0.9 g) which was chromatographed over silica gel using chloroform as eluant. The combined eluates were crystallised from chloroform-hexane to yield a white solid 12, (240 mg), m.p. 297-298° (d). λ_{max} 235, 292-293 nm (log ε, 4.29, 4.48); γ_{max}^{KBr} 1660 cm^{-1}; MS: m/e 479 (M^+), 465, 451, 423, 422, 420, 406, 392, 364 and 336.

$C_{25}H_{21}O_9$ Calc. C, 62.63; H, 4.42; N, 2.92
Found C, 62.39; H, 4.80; N, 2.63%

Sodium borohydride reduction of ketone 12

A solution of the above ketone 12 (100 mg) in tetrahydrofuran (20 ml) and methanol (20 ml) was treated with sodium borohydride (250 mg). After 1 h. at room temperature, the solution was diluted with water and extracted with methylene chloride. The methylene chloride layer after washing, drying (Na_2SO_4) and evaporation yielded a solid 13, (40 mg) which was crystallised from methanol-ether, m.p. 230°. λ_{max} 234, 284 nm (log ε, 4.2, 3.77); γ_{max}^{KBr} 1640 cm^{-1}; MS: m/e 481 (M^+), 466, 465, 448, 432, 405, 274 and 263.

$C_{25}H_{25}O_9N$ Calc. C, 62.10; H, 5.21
Found C, 62.72; H, 5.90%

Deuterated neooxyberberine acetone 15 by exchange reaction

Neooxyberberine acetone (100 mg), dioxane (10 ml), deuterium oxide (8 ml), sodium carbonate (125 mg) were heated on a water bath for 12 h. The solvents were removed *in vacuo* and the resulting mixture was extracted in methylene chloride. The methylene chloride layer was washed with water, dried ($MgSO_4$) and evaporated to yield 15, (75 mg) which was crystallised from methylene chloride-methanol, m.p. 214°. MS: m/e 413 (M^+), 382, 354.

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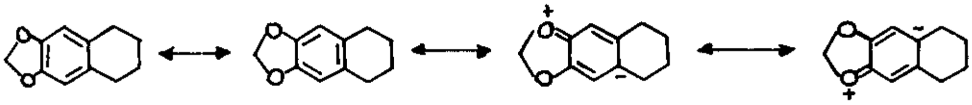
17. It is worth noting that the bond lengths of C(3) - C(4) and C(1) - C(2) are significantly shorter than the others in ring A indicating that among the various valence bond structures that are possible, the following ones are more important:



Another significant observation is that angle C(13a) - C(1') - C(2') (116.4(3)^{o}) is much larger than angle C(8)-C(3')-C(2') (108.4(3)^{o}) which would be expected to be equal. The widening of the angle at C(1') probably relieves the intramolecular short contact between O(18) and C(1').

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