Tetrahedron Vol. 34, pp. 3341–3344

0040-4020/78/1115-3341/$05.00/0

STEREOCHEMISTRY AND RELATIVE STABILITY OF THE OXINDOLES DERIVED FROM VENENATINE AND ALSTOVENINE. THE TWO C-3 EPIMERIC 9-METHOXY-D/E-*CIS*-YOHIMBINOID ALKALOIDS OF *ALSTONIA VENENATA* R.Br.†

P. L. MAJUMDER*, S. JOARDAR and T. K. CHANDA
Department of Chemistry, University College of Science, 92, Acharya Prafulla Chandra Road, Calcutta 700009, India

(*Received in UK* 17 *March* 1978; *Accepted for publication* 11 *July* 1978)

Abstract—Contrary to usual observation, both venenatine (**1a**) and alstovenine (**1b**) give initially only a single oxindole derivative (**3**) instead of a pair. This oxindole displays unusual resistance to isomerisation in both acidic and basic media and is unique in its total insensitivity to pyridine. The unprecedented instability of its isomer, formed only in acidic media under very stringent conditions, foiled all attempts at isolating it in the pure state. However, by conformational analysis and from a comparison of the chemical shifts of the aromatic OMe of the pure more stable isomer and of the isomers in mixture, recorded in $CDCl_3$ and CF_3CO_2H, the more stable isomer was assigned the *allo* B (**5b**) and the other *allo* A (**5a**) stereochemistry. The uncommon stereochemistry. basicity relationship has been rationalised.

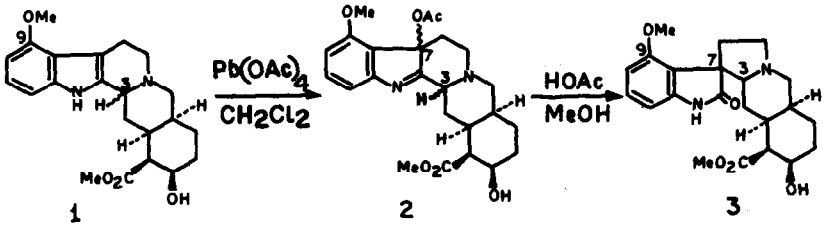
Among the oxindole alkaloids, the 9-oxygenated rhynchophyllinoids display certain peculiarities in their equilibration behaviour[1] which doubtless arise out of some structural and/or stereochemical situation unique in them. In absence of any report of similar studies on oxindoles derived from 9-oxygenated yohimbinoids, the isolation of venenatine (**1a**) and alstovenine (**1b**), the two C-3 epimeric 9-methoxy-D/E-*cis*-yohimbinoid alkaloids of *Alstonia venenata*[2] R.Br., tempted us to undertake the preparation of and delve into the intriguing stereochemical problems associated with and manifest in the behaviour of oxindoles derived from them. In this communication we report an account of this study.

Since **1a** and **1b** belong to the D/E-*cis* yohimbinoid series, the preparation of their oxindole derivatives involved intermediate conversion to the corresponding 7-acetoxyindolenines[3] by the action of $Pb(OAc)_4$ in CH_2Cl_2. The structure and the complete stereochemistry of the isomeric 7-acetoxyindolenines derived from **1a** and **1b**, as expressed by the formulations **2a** and **2b**, respectively, were based on their typical UV, IR, PMR and mass spectral data and a consideration[4] of the stereochemistry of the parent alkaloids.

On reflux in methanol containing a few drops of acetic acid, both **2a** and **2b** yielded the same product (Scheme 1), $C_{22}H_{28}N_2O_5$ (M^+ 400), m.p. 262–63°, which from its typical UV spectrum, showing striking resemblance with those of 9-methoxylated rhynchophyllinoids,[1d] as well as IR, PMR and characteristic mass[5] spectra, was shown to be the corresponding oxindole derivative having the gross structure **3**.

The formation of the same oxindole **3** from either **1a** or **1b** is in conformity with the general observation that in such cases the stereochemistry of the derived oxindole is independent of the C-3H orientation of the starting material.[3] But what appeared to be rather surprising was the isolation of a single oxindole in the foregoing reaction sequence in view of the fact that such procedure had heretofore been reported[3,6] to yield invariably a pair of isomeric oxindoles. Further, each of such oxindoles is known[3,6] to equilibrate to a mixture of the isomeric oxindole pair in either acidic, e.g. aqueous HOAc, or basic, e.g. pyridine, media, although the position of the equilibrium depends much on the structure and stereochemistry of the oxindoles as well as the nature of such media (acidity or basicity, ability to preferentially solvate

†A preliminary account of this work was presented at the Annual Convention of Chemists, 1977, held at Jaipur, India, Abstracts of papers, ORG-11, p. 6.

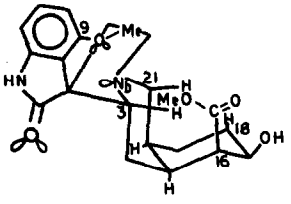


Scheme 1.

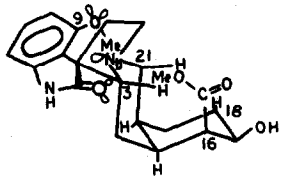
one isomer over the other, etc). It is interesting to note that the oxindole **3** was recovered totally unaffected after submission to conditions (8 hr reflux in pyridine or 10% aqueous HOAc) usually sufficient for the equilibration between similar oxindoles having no 9-oxygen function. Such behaviour of the oxindole **3** is reminiscent to some extent of the comparative difficulty encountered in the equilibration of the 9-oxygenated rhynchophyllinoids.[1] However, a 72 hr reflux in 10% aqueous HOAc or a 48 hr reflux in 30% aqueous HOAc of the oxindole **3** resulted in a mixture comprising **3** and presumably its isomer in about 70:30 proportion. Queerly enough, reflux of **3** in pyridine for even over 72 hr failed to bring about any perceptible equilibration. In this respect the oxindole **3** presents a feature unprecedented even among the structurally similar 9-oxygenated rhynchophyllinoids. But most puzzling was the great problem posed by the attempted separation of the minor component from the acid-equilibrated mixture; attempts at separating even by preparative TLC was frustrated by the ease with which the minor component reverted back to the original oxindole **3** on silica gel surface, thus always resulting in the isolation of a mixture in which the less stable component is only the minor one. Attempted chromatographic resolution over alumina, on the other hand, converted such a mixture completely into **3**. Although the failure to obtain a pure sample of the less stable component, on the one hand, precluded any independent structural study to be made on it, its mode of formation and the very fact that it so readily reverts back to the starting material, on the other hand, clearly established that this new compound is nothing but an oxindole isomer of the latter.

Keeping in mind that the equilibrium constant of any reaction is the ratio of the rate constants of the reaction in the forward and backward directions, the none-too-insignificant equilibrium population of the less stable isomer (~30%) can be reconciled with its remarkably slow rate of formation in aqueous HOAc and equally remarkable fast rate of isomerisation on silica gel surface only on the admission that this does not represent a case of mere acid-catalysis but one of significant interplay of preferential stabilising or destabilising interaction of the catalyst media with one isomer over the other. Thus, it is noted that on a silica gel surface not only does the less stable isomer equilibrate quickly with the more stable one but also the latter, in contrast with the long 48 hr required in 30% aqueous HOAc, attains equilibrium with the former within only about 12 hr, the change being perceptible as early as in the seventh hour.

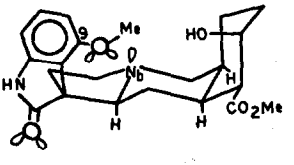
The stereochemistry of the oxindoles derived from venenatine and alstovenine were largely elicited from an examination of their properties in the light of conformational analysis. Of the eight possible stereochemical forms, only four, viz., *epiallo* A (**4a**), *epiallo* B (**4b**), *allo* A (**5a**) and *allo* B (**5b**) need be considered[1d] for these isomeric oxindoles; the flip form corresponding to each of the above four will have practically no contribution to the conformational equilibrium population because of their extreme instability. Construction of Dreiding models shows that in **4b** or **5a** the aromatic OMe is in close proximity with the N_b lone pair of electrons, whereas it is quite far off from the latter in **4a** or **5b**. Thus, if one of the above oxindole isomers does have a stereochemistry represented by **4b** or **5a**, its aromatic OMe protons would be appreciably shielded by the N_b lone pair of electrons and since protonation of the basic nitrogen in **4b** or **5a** would eliminate the shielding effect on the aromatic OMe protons, the isomer having the formulation **4b** or **5a** will have its aromatic OMe signal shifted downfield in its PMR spectrum on changing the solvent from $CDCl_3$ to CF_3CO_2H[1d]. In case of the other isomer possessing the stereochemistry **4a** or **5b**, however, this should result in no appreciable change of the chemical shift of the aromatic OMe function. Although a pure sample of the less stable isomer of **3** was not available for the purpose of such a study, a fruitful comparison of the change in chemical shift positions of the aromatic OMe signals of the two isomers on changing the solvent from $CDCl_3$ to CF_3CO_2H could be made by recording the PMR spectra of the equilibrium mixture in these two solvents. In $CDCl_3$, the PMR spectrum of the equilibrated mixture is virtually superimposable on that of the pure more stable isomer **3**, except for the aromatic OMe region. Thus, while the two three-proton singlets at δ 3.84 (ArO*Me*) and 3.59 (–CO_2*Me*) in the PMR spectrum of **3** in $CDCl_3$ find their equivalents at δ 3.82 and 3.56, respectively, in the PMR spectrum of the mixture in the same solvent, the latter shows, in addition, an upfield singlet at δ 3.51 which may be attributed to the aromatic OMe of the less stable isomer. The approximate ratio of 2:1 of the proton integration of the singlets at δ 3.82 and 3.51 justifies this assignment. Now, the PMR spectrum of



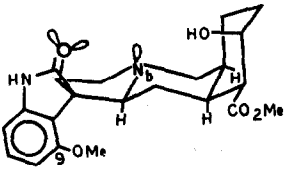
Epiallo A (4a)



Epiallo B (4b)



Allo A (5a)



Allo B (5b)

3 in CF_3CO_2H shows two three-proton singlets at δ 3.98 (ArO*Me*) and 3.76 (–CO_2*Me*) which are also clearly discernible practically at the same positions (δ 3.98 and 3.77, respectively) in the PMR spectrum of the oxindole mixture in CF_3CO_2H. But the latter lacks the singlet at δ 3.51 observed in $CDCl_3$, and, instead, shows an additional downfield singlet at δ 4.10 which from the proton integration ratio is clearly identified as the aromatic OMe signal of the less stable isomer. The carbomethoxy groups of the two isomers in mixture give rise to only one signal in both $CDCl_3$ and CF_3CO_2H, understandably because of identical environment. It follows from the above spectral data that whereas the aromatic OMe signal of the more stable isomer 3 shows only a small shift (0.14 ppm) on changing the solvent from $CDCl_3$ (δ 3.84) to CF_3CO_2H (δ 3.98), the signal assigned to the aromatic OMe of the less stable isomer shows a dramatic downfield shift (0.59 ppm) on changing from $CDCl_3$ (δ 3.51) to CF_3CO_2H (δ 4.10). Thus, of the two oxindole isomers, the less stable one appears to have the aromatic OMe in close proximity with N_b and hence should be represented as either **4b** (*epiallo* B) or **5a** (*allo* A). Consequently, the stereochemistry of the more stable isomer 3 must be assigned as **4a** (*epiallo* A) or **5b** (*allo* B).

Now from the Dreiding models it is clearly seen that in each of the two *epiallo* forms **4a** and **4b**, the axial –CO_2Me group at C-16 experiences severe non-bonded interactions with the axial H-atoms at C-3, C-18 and C-21, as well as with the C-9 OMe group, which are well within the van der Waals distances. Compared to this, the two *allo* forms **5a** and **5b** are totally free from any such non-bonded interaction excepting some interaction of the aromatic OMe with the N_b lone pair of electrons in **5a**. From this consideration, it seems unlikely that the venenatine or alstovenine derived oxindole isomers would exist in the *epiallo* forms either during their formation from the 7-acetoxyindolenines **2a** or **2b**, or in course of their equilibration, when they have the option for assuming a relatively strain-free *allo* configuration. This conclusion is also in accord with the observation that irrespective of the C-3H orientation in the starting material the resultant oxindoles, with the exception of 9-hydroxy-rhynchophyllinoids,[1] invariably have C-3Hα.[3] On the basis of the above arguments, the stereochemistry of the more stable oxindole isomer derived from venenatine/alstovenine is assigned as *allo* B (**5b**) and the less stable isomer as *allo* A (**5a**).

As regards the relative basicity of the two oxindole isomers, the greater sensitivity of the less stable isomer **5a** to basic than to acidic conditions and its lower mobility on silica gel and alumina thin layers, on conventional notion,[6b–d] indicate it to be a stronger base than the more stable isomer **5b**. This is again in contrast with the common observation for similar isomeric oxindole pairs without the 9-OMe function, where the *allo* B isomer by virtue of the greater stability of its conjugate acid due to H-bonding with the lactam CO is the stronger base. Although a comparison of the pK values of the two isomers **5a** and **5b** could not be made in absence of a pure sample of the former, a plausible explanation for the observed departure from the normal behaviour may be as follows. It may be seen that although the electron availability on the lactam oxygen is greater than that on the 9-OMe oxygen, Dreiding models show that the non-bonded orbitals of the latter are much closer to N_b lone pair orbital in **5a** compared to those of the former in **5b**. In fact, since **5b** is totally unaffected by pyridine while **5a** is so remarkably unstable under basic conditions, in the free base form the latter must be experiencing overwhelmingly stronger electronic repulsion between the N_b and OMe oxygen lone pair orbitals than that between the N_b and lactam oxygen lone pair orbitals in the former. This would account for the greater basicity of **5a**, since its conjugate acid would consequently involve a stronger H-bonding than that of the *allo* B form **5b**. Such a possibility was, indeed, visualised by Trager *et al.*,[1d] although no concrete example was then to hand. The fact that under acid conditions the *allo* A form **5a**, though it displays significant improvement in stability, is still the minor component of the equilibrium mixture may then be rationalised as being due to the instability inherent in it because of the crowding of the 9-OMe onto the N_b, which appears to be only partly offset by the greater release of energy, compared to the *allo* B form **5b**, by stronger H-bonding in its conjugate acid.

EXPERIMENTAL

Analytical samples were routinely dried over P_2O_5 *in vacuo* at 80–110° and were tested for purity by TLC and MS. M.ps were determined on a Köfler block and are uncorrected. IR spectra were run in KBr discs or Nujol mulls, as indicated. PMR spectra were recorded in $CDCl_3$ or CF_3CO_2H (as indicated) with TMS as the internal standard.

7-*Acetoxy*-7H-*venenantine* (**2a**). 1.0 g of **1a** was treated with $Pb(OAc)_4$ according to the method described.[3] The product was chromatographed over alumina column using C_6H_6 followed by $CHCl_3$ as eluents. The $CHCl_3$ eluate on evaporation gave a solid which crystallised from $C_6H_6/CHCl_3$ mixture in granules (0.275 g), m.p. 210°; λ_{max}^{EtOH} 230, 268–70 sh. and 302 (log ϵ 3.59, 3.42 and 3.51) nm; ν_{max}^{KBr} 3450 (OH), 1735 (ester $\rangle$C=O) and 1587 ($\rangle$C=N–) cm^{-1}; δ^{CDCl_3} (ppm): 2.03 (3H, s; –OCOC$\underline{H}_3$), 3.77 (3H, s; –$CO_2C\underline{H}_3$), 3.83 (3H, s; ArOC$\underline{H}_3$) and 6.50–7.33 (3H, m; Ar$\underline{H}$); MS: *m/e* (% abundance) *EI*^{20eV} (Intensity × 16 for peaks *m/e* > 390): 225 (23), 251 (14), 323(14), 367 (24), 382 [M–HOAc] (100), 399 (6), 400 (4), 411 (5) and 442 (M^+; 6); *CI* (carrier gas CH_4): 383 [(M + 1)–HOAc] (38), 401 (8), 411 (4) and 443 [M + 1] (100).

7-*Acetoxy*-7H-*alstovenine* (**2b**). 0.2 g of **1b** was treated with $Pb(OAc)_4$ as for **1a**. On similar chromatography of the product, the $CHCl_3$ eluate yielded a solid which crystallised from $C_6H_6/CHCl_3$ mixture in rhombic prisms (0.050 g), m.p. 160°; λ_{max}^{EtOH} 218, 258 and 306–308 inf. (log ϵ 4.22, 3.61 and 3.52) nm; ν_{max}^{KBr} 3445 (OH), 1738 (ester $\rangle$C=O), 1586 ($\rangle$C=N–) cm^{-1}; δ^{CDCl_3} (ppm): 2.06 (3H, s; –OCOC$\underline{H}_3$), 3.78 (3H, s; –$CO_2C\underline{H}_3$), 3.85 (3H, s; ArOC$\underline{H}_3$) and 6.63–7.43 (3H, m; Ar$\underline{H}$); MS: *m/e* (% abundance) *EI*^{30eV} (Intensity × 16 for peaks *m/e* > 410): 225 (12), 251 (7), 323 (7), 367 (12), 382 [M–HOAc] (100), 400 (4), 411 (10) and 442 (M^+; 3); *CI* (carrier gas CH_4): 383 [(M + 1)–HOAc] (72), 401 (17), 411 (29) and 443 [M + 1] (100).

Oxindole 3 *from* **2a**. A soln of 0.250 g of **2a** in 10 ml MeOH, to which 5 drops of glacial HOAc had been added, was refluxed for 2.5 hr. The cooled product was diluted with 20 ml of water and repeatedly extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water, dried and chromatographed over Al_2O_3 column using C_6H_6, $C_6H_6/CHCl_3$ mixtures and $CHCl_3$ as the eluents in order of increasing polarity. The combined early fractions of the $C_6H_6/CHCl_3$ (1:1) eluate after concentration revealed on TLC only a single iodine-staining spot in all the four different systems used (adsorbent: Al_2O_3, developer: $CHCl_3$, R_f 0.8; developer: EtOAc/EtOH = 4:1, R_f 0.65; developer: $CHCl_3$/cyclohexane = 7:3, R_f 0.1; and adsorbent: silica gel G, developer: $CHCl_3/CH_3COCH_3$ = 5:4, R_f 0.35). Removal of the solvent left a granular solid (0.050 g) which crystallised from $C_6H_6/CHCl_3$ mixture in rhombic plates, m.p. 262–63°; λ_{max}^{EtOH} 221, 248 and 290 (log ϵ 4.37, 3.55 and 3.35) nm; ν_{max}^{Nujol} 3600 (OH); 3280 ($\rangle$NH) and

1730 (ester >C=O/lactam >C=O) cm^{-1}; δ^{CDCl_3} (ppm): 1.95 (1H, s, disappears on deuterium exchange; –OH), 3.59 (3H, s; δ –CO_2CH_3), 3.84 (3H, s; $ArOCH_3$), 4.09 (1H, broad signal; –CH–OH), 6.41–7.33 (3H, m; ArH) and 8.25 (1H, br. s, disappears on deuterium exchange; >NH); $\delta^{CF_3CO_2H}$ (ppm): 3.98 (3H, s; $ArOCH_3$) and 3.76 (3H, s; $-CO_2CH_3$); MS: *m/e*(%), 400 (M^+, 77.5), 383 [M–17] (2.90), 370 (2.90), 369 (6.96), 342 (2.90), 341 (4.35), 226 (15.9), 225 (100), 224 (12.3), 210 (3.62), 208 (2.90), 190 (4.35), 189 (3.62), 176 (7.97), 175 (5.07), 174 (5.80), 160 (4.35), 148 (7.25), 146 (7.25), 94 (8.70) and 69 (10.1).

Oxindole **3** *from* **2b**. 0.030 g of **2b** was refluxed for 2.5 hr in 2 ml of MeOH containing 2 drops of glacial HOAc. The resultant soln was worked up as in the case of **2a**. This ultimately gave rhombic plates (0.010 g), m.p. 262–63°, identical in all respects (co–TLC, m.m.p and superimposable IR spectra) with the venenatine-derived oxindole **3**.

Isomerisation of **3**

(A) *Acid-catalysed isomerisation.* (i) The oxindole **3** (0.030 g) was refluxed in 10 ml of 10% aq HOAc for 8 hr. The resultant soln was diluted with 20 ml of water, repeatedly extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water, dried and concentrated. TLC using all the four systems mentioned above, revealed only one iodine-staining spot superimposable on that of the starting material. Evaporation left a residue which crystallised from $C_6H_6/CHCl_3$ mixture in rhombic plates (0.025 g), m.p. 262–63°, identical in all respects with **3**. (ii) The above procedure was repeated in four sets using 48 and 72 hr reflux periods in 10% and 30% aq HOAc. TLC revealed two iodine-staining spots [R_f 0.35 (major) and 0.1 (minor); adsorbent: silica gel G, developer: $CHCl_3/CH_3COCH_3$ = 5:4] having approximate relative intensities of 80:20 in case of 48 hr reflux in 10% aq HOAc and 70:30 in others. Reflux for longer periods did not improve any further the yield of the more polar component indicating that equilibrium had been reached.

(B) *Attempted base-catalysed isomerisation of* **3**. The oxindole **3** (0.010 g) was refluxed in 4 ml pyridine in three successive sets for the periods of 8 hr, 48 hr and 72 hr. In each case pyridine was removed under reduced pressure, the residue diluted with 10 ml of water, extracted with $CHCl_3$, the extract repeatedly washed with water, dried and concentrated to 1 ml. TLC revealed only one iodine staining spot in each of the three sets of experiments. Removal of the solvent left granules, identical in all respects with **3**.

Attempted separation of the oxindole mixture into its components

(A) The oxindole mixture (0.025 g), obtained by acid-catalysed isomerisation, was quickly chromatographed (~6 hr) over alumina resulting in the isolation of only the less polar component (~0.025 g) in the $C_6H_6/CHCl_3$ (1:1) eluate. The more polar component did not migrate even on elution with MeOH.

(B) Another sample (0.025 g) of the oxindole mixture was subjected to preparative TLC using a 0.1 mm thick layer of silica gel G as the adsorbent and two successive runs in $CHCl_3/CH_3COCH_3$ (1:1) as the developer. The horizontal layers corresponding to the upper spot (R_f 0.45) and lower spot (R_f 0.2) were carefully cut out and eluted separately. While the former gave the pure **3** (~0.020 g), the latter gave a residue which showed two iodine staining spots (~80:20) on TLC (adsorbent: silica gel G, developer: $CHCl_3/CH_3COCH_3$ = 5:4) corresponding to those of **5b** and **5a**.

Conversion of the more stable oxindole on silica gel surface. Five silica gel TLC plates of specification as employed for the preparative TLC were taken and at a spot on each of these was delivered a small amount of a very conc soln ($CHCl_3$) of the pure more stable oxindole. The plates were then placed in a vacuum desiccator. The plates were taken out one at a time successively at the intervals of 4 hr, 6 hr, 8 hr, 12 hr and 24 hr and developed in $CHCl_3/CH_3COCH_3$ (5:4) with a comparative spot of the oxindole mixture and stained with I_2. The spot of the less stable isomer was detectable first in the plate developed after 6 hr and the relative intensities of the two spots remained unchanged after the plate developed after 12 hr indicating attainment of equilibrium.

Acknowledgements—We thank Dr. D. N. Roy, University of Toronto, Canada, for PMR spectra and Dr. B. C. Das, Institut de Chimie des Substances Naturelles, Gif-sur-Yvette, France, and Professor K. Nakanishi, Columbia University, New York, for mass spectra.

REFERENCES

[1a] A. H. Beckett, C. M. Lee and A. N. Tackie, *Tetrahedron Letters* 1709 (1963); [b] A. H. Beckett and A. N. Tackie, *Chem. Ind.* 1122 (1963); [c] G. M. Badger, L. M. Jackman, R. Sklar and E. Wenkert, *Proc. Chem. Soc.* 206 (1963); [d] W. F. Trager, C. M. Lee, J. D. Phillipson, R. E. Haddock, D. Dwuma-Badu and A. H. Beckett, *Tetrahedron* **24**, 523 (1968); [e] S. R. Hemingway, P. J. Haughton, J. D. Phillipson and E. J. Shellard, *Phytochemistry* **14**, 557 (1975).

[2a] A. B. Ray and A. Chatterjee, *J. Indian Chem. Soc.* **40**, 1043 (1963); [b] *Ibid.* **41**, 638 (1964); [c] T. R. Govindachari, N. Viswanathan, B. R. Pai and T. S. Savitri, *Tetrahedron Letters* 901 (1964); [d] *Tetrahedron* **21**, 2951 (1965); [e] S. C. Dutta and A. B. Ray, *Indian J. Chem.* **13**, 98 (1975).

[3] N. Finch, C. W. Gemenden, I. H.-C. Hsu and W. I. Taylor, *J. Am. Chem. Soc.* **85**, 1520 (1963).

[4] N. Finch, C. W. Gemenden, I. H.-C. Hsu, A. Kerr, G. A. Sim and W. I. Taylor, *Ibid.* **87**, 2229 (1965).

[5] H. Budzikiewicz, C. Djerassi and D. H. Williams, *Structure Elucidation of Natural Products by Mass Spectrometry*, Vol. I. Alkaloids, Holden-Day, New York (1964).

[6a] J. C. Seaton, M. D. Nair, O. E. Edwards and L. Marion, *Canad. J. Chem.* **38**, 1035 (1960); [b] N. Finch and W. I. Taylor, *J. Am. Chem. Soc.* **84**, 3871 (1962); [c] *Ibid.* **84**, 1318 (1962); [d] J. Shavel and H. Zinnes, *Ibid.* **84**, 1320 (1962).