Tetrahedron. 1967. Vol. 23. pp. 365 to 374. Pergamon Press Ltd. Printed in Northern Ireland

CORYNANTHEIDINE-TYPE ALKALOIDS—I

ESTABLISHMENT OF PHYSICAL CRITERIA FOR THE *NORMAL*, *PSEUDO*, *ALLO* AND *EPIALLO* CONFIGURATIONS BY CONFORMATIONAL ANALYSIS

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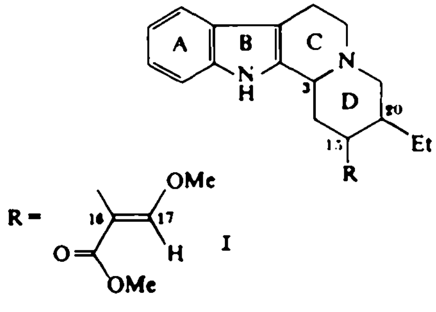
(*Received* 25 *April* 1966; *accepted for publication* 22 *June* 1966)

Abstract—Corynantheidine-type alkaloids have three asymmetric centres (C3, C15, C20); the four possible *configurations* (each an enantiomorphic pair) can each exist in three ring D chair *conformations*. The twelve possible chair conformations are subjected to conformational analysis to try to determine the preferred conformation(s) of each configuration. The analysis demonstrates one preferred conformation for each configuration which allows the assignment of distinguishable physical properties (IR, NMR, ORD, CD) for the eight stereoisomers. Application of these physical criteria allows assignment of absolute configuration to ring substituted or unsubstituted corynantheidine-type alkaloids of unknown configuration.

A compound of corynantheidine-type structure I has three asymmetric centres (C3, C15 and C20); this gives rise to the possibility of four *configurations*, viz. *normal*, *pseudo*, *allo* and *epiallo* (each of which can exist as an enantiomorphic pair). Furthermore, each configuration can exist in three† different ring D chair *conformations* due to inversion of the basic nitrogen atom and chair interconversion of ring D.



I

In this paper, conformational analysis is used to determine the most likely conformation(s) for each configuration. A unique set of physical criteria is deduced for the preferred conformation(s) which should permit configurational assignment to corynantheidine-type compounds of unknown stereochemistry. The physical criteria are compared with the physical data obtained from compounds of known absolute configuration[1] substantiating the conclusions and predictions reached herein; this information is then used to determine the absolute configuration of four *Mitragyna* alkaloids of corynantheidine-type structure.[1]

The conformational analysis is based on the assumption that an estimation of

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* To whom inquires should be directed.

† The conformation with a *trans diaxial* C/D ring junction is not possible.

[1] C. M. Lee, W. F. Trager and A. H. Beckett, *Tetrahedron* **23**, 375 (1967).

the nonbonded interactions in piperidine ring D can be *approximated* by analogy with the nonbonded interactions arising in the correspondingly substituted cyclohexane (c.f. appendix). NMR evidence[1] suggests that the ester and methoxy groups on the C16–C17 double bond are *trans* and UV data[2] shows that the C15 ester–enol ether link (R) in I is planar due to conjugation. It is assumed that the most stable rotational position of R would be the one in which the methoxy groups encounter minimal nonbonded interactions. In all conformations examined, ring C is assumed to be in the half chair conformation by analogy with cyclohexene[3] and only the chair forms of ring D are considered by analogy with cyclohexane.[4] An estimation of the magnitude of the nonbonded interactions of each conformation (ignoring any possible solvation effects) was made with the aid of Dreiding models (see appendix for details).

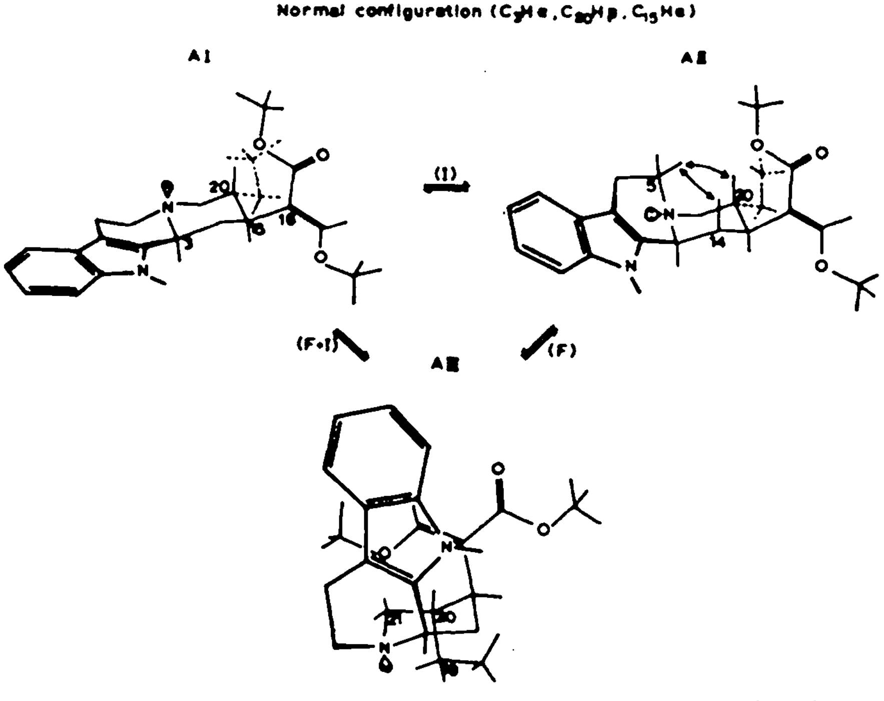

Fig. 1. Conformations of corynantheidine-type alkaloids* (I = nitrogen inversion; F = chair interconversion).

Normal Configuration A (C3 Hα, C15 Hα, C20 Hβ or C3 Hβ, C15 Hβ, C20 Hα) (Fig. 1)

In *conformation* AI the plane of the planar R group lies approximately at right angles to the plane of the piperidine ring thus avoiding interactions with the *equatorial* C20 ethyl group; a fair amount of rotation around the C15–C16 bond seems possible. The preferred rotational conformation of the *equatorial* ethyl group is such that there are no appreciable nonbonded interactions observed in the model.

* Only one enantiomorph (C15Hα) of each pair is illustrated; the same considerations obviously hold for the other enantiomorph (C15Hβ).

[2] M. M. Janot and R. Goutarel, *Bull. Soc. Chim.* (5) **18**, 588 (1951).

[3] C. W. Beckett, N. K. Freeman and K. S. Pitzer, *J. Amer. Chem. Soc.* **70**, 4227 (1948).

[4] E. L. Eliel, *Angew. Chem.* (Int. Ed.) **4**, 761 (1965).

In *conformation* AII, formed by inversion of the basic nitrogen of AI, the groups at C15 and C20 remain in the same relationship as in AI. There are now however, interactions between the C5 β hydrogen and the C14 and C20 *axial* hydrogens equivalent to about 1·7 kcal/mole (see appendix) of destabilization energy compared to AI.

The other chair conformation formed from AII, i.e. *conformation* AIII is much less favourable than AI or AII as the R group is *axial* and interacts with the indole nucleus and the C21 β *axial* hydrogen. Furthermore, the ethyl group, now in the *axial* position, is less stable than in the corresponding *equatorial* position of AI and AII by about 1·8 kcal/mole (see appendix).

Thus a compound possessing the *normal* configuration would be expected to exist mainly in the AI conformation.

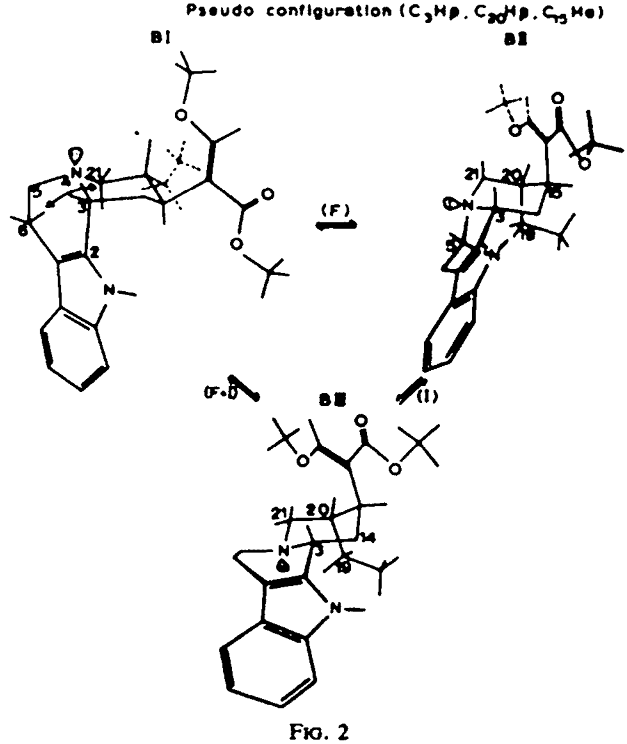

FIG. 2

Pseudo Configuration B (C3 Hβ, C15 Hα, C20 Hβ or C3 Hα, C15 Hβ, C20 Hα) (Fig. 2)

Conformation BI, like AI and AII, has the plane of the *equatorial* R group approximately at right angles to the plane of ring D; the ethyl group is also *equatorial*. A new interaction between the C6 *pseudo axial* α hydrogen and C21 *axial* α hydrogen arises because of the *axial* disposition of the C2–C3 bond. An *estimation* of this interaction is made by assuming that C21, N4, C5 and C6 approximate a butane system. The dihedral angle between N4–C5–C6 and C21 (Ring C half chair) is about 50° leading to an energy value of 1·5–1·8 kcal/mole.[8]

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[8] E. L. Eliel, N. L. Allinger, S. J. Angyal and G. A. Morrison, *Conformational Analysis* p. 9. Interscience, New York (1965).

Interconversion of ring D of BI forms the other chair *conformation* BII and places both the ethyl and R group in *axial* positions but relieves the C6H–C21H interaction seen in BI. The *axial* orientation of the R group in BII leads to nonbonded interactions between the R group and the *axial* C3 and C21 hydrogens; moreover these interactions cannot be relieved by rotation. The *axial* disposition of the ethyl group leads to interactions between the C5 and C19 methylene hydrogens which together with the C19/C14 *axial* H interactions and C5/C14 interactions are assigned a destabilising energy of about 5·5 kcal/mole (cf. appendix). Thus BII is *at least* 3·7 kcal/mole less stable than BI without even considering the destabilization due to the *axial* R group.

Inversion of the nitrogen atom of BII yields *conformation* BIII in which the R and ethyl groups remain *diaxial* as in BII but the C5 interactions of BII are absent. The *axial* ethyl group can be assigned a nonbonded interaction energy of about 1·8 kcal/mole so that BIII is at least 3·7 kcal/mole more stable than BII implying that BI and BIII may be of comparable energy. However, a choice can be made between BI and BIII by consideration of the R group interactions in each conformation. The *equatorial* R group in BI appears to have greater freedom of rotation and less nonbonded interactions than the *axial* R group in BII. Although a quantitative value cannot be assigned to the energy difference between these two R group conformations, the above qualitative considerations suggest that BI will be the preferred conformation present in compounds of the *pseudo* configuration.

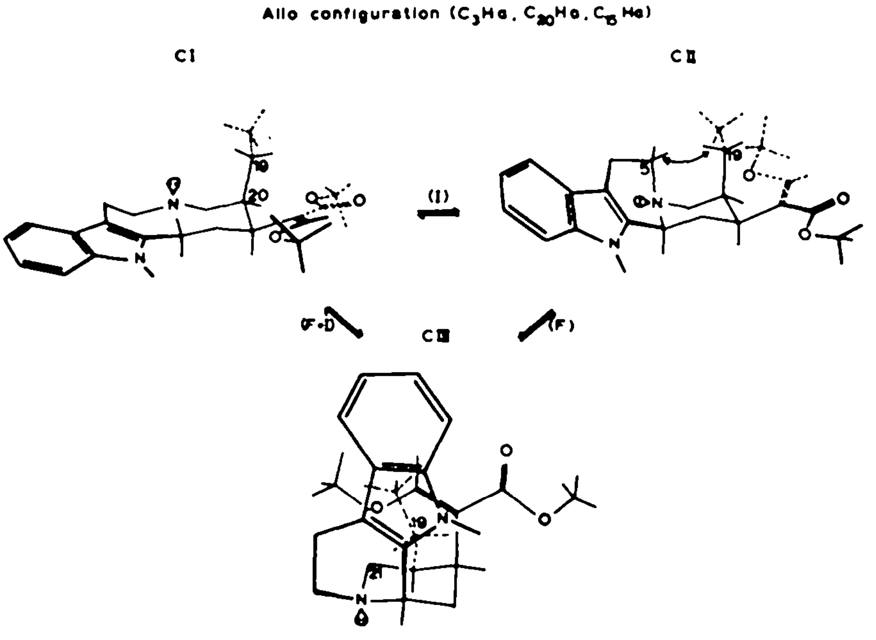

Fig. 3

Allo Configuration C (C3 Hα, C15 Hα, C20 Hα or C3 Hβ, C15 Hβ, C20 Hβ) (Fig. 3)

The bulky *equatorial* R group in *conformation* CI probably lies in the plane of the piperidine ring in order to avoid interactions with the *axial* ethyl group (−ΔG° = 1·8).

Inversion of the nitrogen atom of CI to form *conformation* CII yields new interactions between the hydrogens of C5 and C19 (cf. BII) with a $-\Delta G^\circ$ of about 5·5 kcal/mole. The R and ethyl groups are in the same relative position as in CI and thus CII would be expected to be less stable than CI by about 3·7 kcal/mole.

Interconversion of Ring D of CII to form *conformation* CIII places the ethyl group in the *equatorial* position but the *axial* R group now *unavoidably* interacts with the indole ring, C21 *axial* hydrogens and/or C19 methylene group. This extremely hindered conformation is most unlikely.

Compounds having the *allo* configuration would therefore be expected to exist almost entirely in conformation CI.

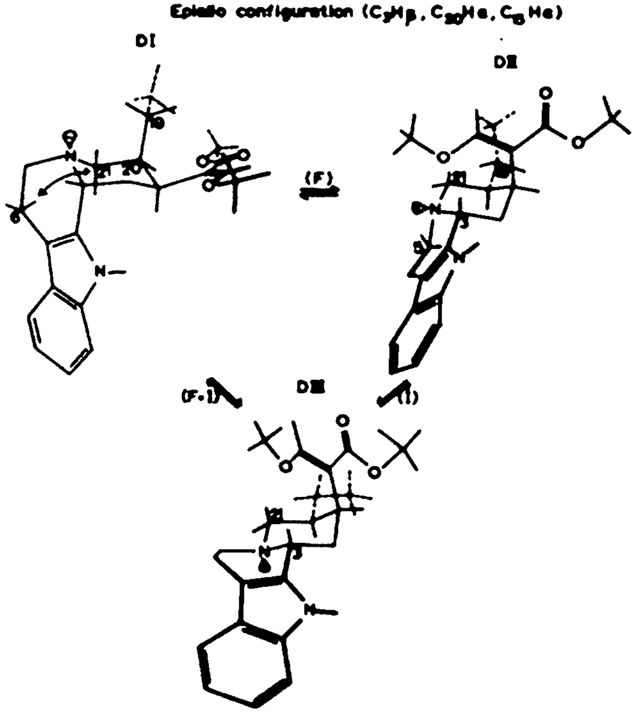

FIG 4.

Epiallo Configuration D (C3 Hβ, C15 Hα, C20 Hα or C3 Hα, C15 Hβ, C20 Hβ) (Fig. 4)

In *conformation* DI, the planar *equatorial* R group lies in the piperidine ring plane to avoid interacting with the *axial* ethyl group ($-\Delta G^\circ = 1·8$). In addition, there is a C6H–C21H interaction as in BI which is assigned a value of 1·5–1·8 kcal/mole.

Interconversion of the D ring of DI to give *conformation* DII relieves the ethyl group and C6–C21H interactions but introduces strong interactions between the *axial* R group and the C3, C21 *axial* hydrogens and/or C19 methylene hydrogens which cannot be relieved by rotation. The C5 methylene hydrogen interactions analogous to those in AII are given a value of 1·7 kcal/mole.

Inversion of the nitrogen atom of DII yields *conformation* DIII which is similar to DII as regards the orientation of the R and ethyl groups. However, the C5 interactions seen in DII are absent in DIII, so conformation DIII is more stable than DII by about 1·7 kcal/mole.

A decision between DI and DIII is not straightforward because in DI the R group is *equatorial* and the ethyl group *axial* whereas in DIII the reverse applies. From models, it would appear that DI is favoured over DIII as no rotational position of the *axial* R group in DIII is free from strong interactions.

Physical criteria for different conformations

The section above suggests that each configuration exists mainly in one preferred conformation (Table 1). The following section will show that a unique set of physical criteria based on IR, NMR, ORD and CD measurements can be deduced for the preferred conformation of each configuration.

TABLE 1. PREFERRED CONFORMATIONS OF CORYNANTHEIDINE-TYPE ALKALOIDS

Configuration	Conformation	C3H	Substituent C15 R Group	C20 Ethyl
Normal	AI	α/ax	β/eq	α/eq
Pseudo	BI	β/eq	β/eq	α/eq
Allo	CI	α/ax	β/eq	β/ax
Epiallo	DI	β/eq	β/eq	β/ax

Infrared correlations

Wenkert and Roychaudhuri (1956)[6] indicated that in compounds of type I the *configuration* of the C3H relative to the nitrogen lone pair can be determined from infrared spectra (solution or disc).[8] Rosen (1961)[9] pointed out that the IR differences seen, reflected changes in the *conformation* at C3 rather than changes in the *configuration* and modified the rule as follows: "All compounds possessing in their stable conformations *axial* hydrogens at C-3 exhibit two or more peaks or distinct shoulders between 2700–2900 cm^{-1} (at least one of which absorbs below 2800 cm^{-1}) on the low wave number side of the major (ca 2900 cm^{-1}) band, whereas those containing *equatorial* hydrogens at C-3 do not." He stressed that secure assignment at C3 by IR requires the existence of the compound in substantially one conformation and that the relationship between conformation and configuration must be known.

Rosen noted his rule was an application of the IR correlation of Bohlmann (1957)[7] which states that a prominent band at 2800–2700 cm^{-1} occurs in the IR spectra of *trans*-fused quinolizidines in which the nitrogen lone pair is *trans* to at least two *axial* hydrogens on adjacent carbons. However, Rosen's modification is too rigid as it implies that bands would be seen for AII, BII, CII and DII (assuming they are the preferred conformations) as they have an *axial* hydrogen at C3. No IR bands would be seen in these conformations, however, as the C3H is *cis* to the nitrogen lone pair so that only *one* adjacent hydrogen is *trans diaxial* to the lone pair. Both II and III

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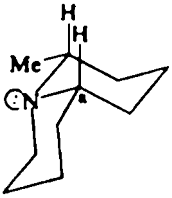
[6] E. Wenkert and D. Roychaudhuri, *J. Amer. Chem. Soc.* **78**, 417 (1956).

[7] F. Bohlmann, *Angew. Chem.* **69**, 641 (1957).

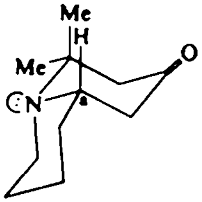
[8] E. Wenkert and D. K. Roychaudhuri, *J. Amer. Chem. Soc.* **80**, 1613 (1958).

[9] W. E. Rosen, *Tetrahedron Letters* 481 (1961).

(in their preferred conformation) have an *axial* hydrogen at a but do *not* show IR *trans* bands.[10,11]



II[10]



III[11]

A more general rule would therefore read: alkaloids of the quinolizidine-type possessing, in their preferred conformation(s), the C3H and at least one more adjacent CH *trans diaxial* to the nitrogen lone pair will exhibit complex IR bands between 2700–2900 cm^{-1}, one or more of which absorb below 2800 cm^{-1}, while those alkaloids possessing, in their preferred conformation(s) the C3H *cis* to the nitrogen lone pair will not.

TABLE 2. PREDICTION OF PHYSICAL CONSEQUENCES OF THE CONFORMATIONS OF CORYNANTHEIDINE-TYPE ALKALOIDS I

Configuration	C3 H *trans* IR bands	C3 H *cis* NMR multiplet below 3·8 δ-bandwidth		C18 NMR triplet resolution	ORD/CD
Normal					
•AI	+	−	—	poor	A
AII	−	+	14 c/s	poor	≠ ≠
AIII	−	+	8 c/s	fair	≠ ≠
Pseudo					
•BI	−	+	8 c/s	poor	B
BII	−	+	14 c/s	poor	≠ ≠
BIII	+	−	−	fair	≠ ≠
Allo					
•CI	+	−	—	fair	A
CII	−	+	14 c/s	poor	≠ ≠
CIII	−	+	8 c/s	poor	≠ ≠
Epiallo					
•DI	−	+	8 c/s	fair	B
DII	−	+	14 c/s	poor	≠ ≠
DIII	+	−	—	poor	≠ ≠

• Preferred Conformation
+ Present
− Not present
A = + or − (B is the opposite sign)
≠ ≠ Not predicted

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[10] T. M. Moynehen, K. Schofield, R. A. Y. Jones and A. R. Katritzky, *J. Chem. Soc.* 2637 (1962).

[11] M. Uskokovic, H. Bruderer, C. von Planta, T. Williams and A. Brossl. *J. Amer. Chem. Soc.* **86**, 3364 (1964).

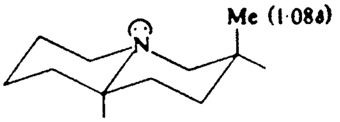
Thus, in compounds of corynantheidine type-I one expects C3H IR bands for the preferred conformation of the *normal* AI and *allo* CI configurations but not for the preferred conformation of the *pseudo* BI and *epiallo* DI configurations (Table 2).

Nuclear magnetic resonance correlations

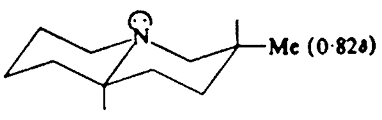
The differences in the IR spectra seen above are related to the orientation of the nitrogen lone pair to the adjacent hydrogen atoms. Differences in orientation are also reflected in the chemical shift of the C3H proton thus permitting an independent determination of the C3H configuration.[12] The criterion used is that the NMR signal of the C3H *cis* to the nitrogen lone pair (whether *axial* or *equatorial*) in quinolizidine type compounds will appear downfield relative to that of the *trans* C3H orientation.[11-13]

Thus, the preferred conformation of the *pseudo* (BI) and *epiallo* (DI) configuration should show a *downfield* (i.e. below 3·8 ppm)[11] one-proton multiplet with a bandwidth of about 8 cps[11,14] since both have the *equatorial* C3H *cis* to the nitrogen lone pair, while in the preferred conformation of the *normal* (AI) and *allo* (CI) configurations, such a one-proton C3H NMR multiplet will not be seen.

A new conformational criterion found in the NMR spectrum arises from the relationship and proximity of the nitrogen lone pair to the methylene protons of the C20 ethyl group. In certain conformations (AIII, BIII, CI, DI) the lone pair is in a *cis* 1,3 *diaxial* relationship to the C20–C19 bond (2·8 Å from the C19 carbon atom) while in the remaining conformations the C20–C19 bond is directed away from the nitrogen lone pair. It might be expected that a chemical shift difference between the C19 methylene hydrogens in the two conformational sets would exist because of their difference in orientation relative to the nitrogen lone pair. Moynehan *et al.*[10] showed that the two possible 3-methyl quinolizidines exist mainly in the *trans* fused ring conformation with the *axial* methyl protons in IV deshielded by 0·26 ppm relative to the *equatorial* methyl protons in V.



IV



V

The C19 methylene protons in AIII, BIII, CI and DI may thus be expected to be *deshielded* by the nitrogen lone pair, other things being equal,* but this effect would not be expected to be seen in the chemical shift of the C19 methylene protons as their signals are overlapped by those of the ring protons. However a difference would be expected in the *degree of resolution* of the triplet signal of the C18 methyl protons as it arises from the spin coupling of the C19 and C18 hydrogens. Anet[15] has pointed out that the triplet signal of the methyl protons of an ethyl group will

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* The shielding effect of the R group double bond on the C19 methylene protons appears to be similar in all conformations.

[12] W. E. Rosen and J. N. Shoolery, *J. Amer. Chem. Soc.* **83**, 4816 (1961).

[13] E. Wenkert, B. Wickberg and C. L. Leicht, *J. Amer. Chem. Soc.* **83**, 5037 (1961).

[14] A. C. Huitric, J. B. Carr, W. F. Trager and B. J. Nist, *Tetrahedron* **19**, 2145 (1963).

[15] F. A. L. Anet, *Canad. J. Chem.* **39**, 2262 (1961).

be well resolved *only* when a significant chemical shift exists between the signals of the methyl and methylene protons; moreover, the methylene protons must be chemically shifted from the other protons to which they are coupled. The C19 methyl signals in I would be expected to appear as a relatively wide and shapeless band if the ratio between the chemical shift difference and J constant ($\Delta\nu/J$) of the methyl and methylene protons in the ethyl group is much less than six. In this case, higher order effects lead to distortion of intensities (*slanting* of methyl bands toward methylene proton signals) *and* extra peaks fill in the usual methyl triplet pattern.[16] When the C20 ethyl group is *cis* 1,3 *diaxial* to the nitrogen lone pair (CI, DI) some increased resolution of the CH_3 is expected due to the deshielding of the C19 methylene protons by the nitrogen lone pair leading to a larger value of $\Delta\nu/J$.

Thus, a better resolved methyl triplet is expected from the preferred conformation of the *allo* CI or *epiallo* DI configuration than from the preferred conformation of the *normal* AI or *pseudo* BI configuration (Table 2) and this is shown experimentally.[1]

Optical rotatory dispersion and circular dichroism considerations

For the purposes of ORD and CD, if one assumes that, in nature, compounds exist in only one enantiomorphic form,[17] at least in the same species, only one natural compound is possible for each configuration. On this assumption, the preferred conformations of the *normal* AI and *allo* CI configurations will have the same absolute geometry around the asymmetric C3 while the absolute geometry of the C3 in the preferred conformation of the *pseudo* BI and *epiallo* DI configurations will be opposite. If the indole portion of the molecule gives rise to an observable optically active transition, it is reasonable to assume that the sign of the Cotton effect will be governed by the geometry of the nearest asymmetric centre viz C3. This being the case, the *normal* AI and *allo* CI compounds should have the same sign (e.g. A) while the *pseudo* BI and *epiallo* DI compounds should have the opposite sign (e.g. B) in the ORD/CD curves; this is also shown experimentally.[1]

Determination of the configuration and conformation of corynantheidine-type alkaloids from physical data

If one has a compound of type I of *known* configuration, the preferred conformation can be readily determined by use of physical measurements as indicated in Table 2. If one assumes that the preferred conformation of each configuration is the one given by this analysis (experimental evidence which validates this premise is given in the following paper[1]), then any corynantheidine-type compound (including indole ring substitution) can be assigned its correct configuration utilizing IR and NMR data (Table 2). Furthermore, use of compounds of known absolute configuration as models for the ORD/CD measurements[1] permits assignment of an *absolute* configuration to the unknown compound.

APPENDIX

Estimation of the nonbonded interactions in conformations of type 1 compounds

Drieding models were constructed for each of the twelve conformations analysed. An *estimation* of the conformational free energy difference between the possible orientations (*axial* or *equatorial*) of

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[16] R. A. Bible Jr, *Interpretation of NMR Spectra* p. 101 ff. Plenum Press, New York (1965).

[17] E. Wenkert and N. V. Bringi, *J. Amer. Chem. Soc.* **81**, 1474 (1959).

piperidine ring D substituents (C- and N-substituted) is made by drawing an analogy to the correspondingly substituted cyclohexane. Allinger, Carpenter and Karkowski[18] showed that the *axial* methyl on nitrogen in N-methylpiperidine has a conformational enthalpy similar to that of the *axial* methyl of methylcyclohexane. Also an *axial* hydrogen on the nitrogen in piperidine is only slightly less favourable than the corresponding *equatorial* hydrogen, indicating that the nitrogen lone pair and hydrogen atom are of comparable size.[18] Chen and Le Fevre[19] have also shown that the principles of conformational analysis as applied to cyclohexane systems can be carried over to six-membered saturated rings contain nitrogen.[19]

Even though the transposition of $-\Delta G^\circ$ values obtained from simple cyclohexane systems to alkaloids is questionable as far as quantitative aspects are concerned, the values are probably not so different as to result in the wrong conformation being chosen. The use of such values allows a semi-quantitative framework to be established in which conformational choices can be made whereas on the basis of strictly qualitative arguments such selections would be far less secure.

Thus the energy difference between an ethyl group in an *axial* verus an *equatorial* position in ring D (AIII, BIII, CI, DI) can be reasonably *approximated* by the $-\Delta G^\circ$ value (1·8 kcal/mole) deduced[4] for ethyl *cyclohexane*. In those cases where the N–C5 bond is in an *axial* orientation, so that the C5 protons interact with the C14 and C20 *axial* hydrogens e.g. in (AII, DII), an estimation of $-\Delta G^\circ$ is obtained from the $-\Delta G^\circ$ value deduced[4] for methyl-cyclohexane (1·7 kcal/mole). Conformations where the N-C5 bond is in a *cis*-1,3-*diaxial* relationship to the C19–20 bond (BII, CII) are assigned a $-\Delta G^\circ$ of about 5·5 kcal/mole in analogy to the $-\Delta G^\circ$ deduced[20] for *cis*-1,3 dimethyl cyclohexane in the *diaxial* conformation.

A preferred conformation for the C15 R group is determined by inspection of models and a *qualitative estimation* is made for the nonbonded interactions of the R groups when no rotational position is free from strong interactions (AIII, CIII). Though no quantitative value could be assigned to these interactions it seemed reasonable from inspection to assume that the sum total of R group interactions in these cases is greater than the sum total of all the above mentioned interactions in the most stable of the remaining conformations of that configuration.

Acknowledgements—C.M.L. was supported by US Public Health Service Fellowship 2-F2-GM-19, 473-03 from the National Institute of General Medical Sciences and W.F.T. by US Public Health Service Fellowship 1-F2-GM-18, 507-01 from the National Institute of General Medical Sciences. We thank R. Brown for the figures which were prepared from photographs of Drieding models.

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[18] N. L. Allinger, J. G. D. Carpenter and F. M. Korkowski, *J. Amer. Chem. Soc.* **87**, 1232 (1965).

[19] C. Y. Chen and R. J. W. Le Fevre, *Tetrahedron Letters* 4057 (1965).

[20] N. L. Allinger and M. A. Miller, *J. Amer. Chem. Soc.* **83**, 2145 (1961).