The Determination, by ^1H Nuclear Magnetic Resonance Studies, of Some Stereochemical Features in the Alkaloids Isocorymine, Erinine, Erinicine, and Eripine

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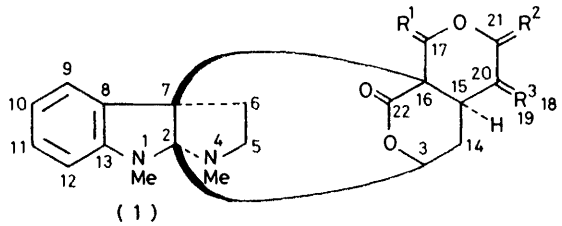
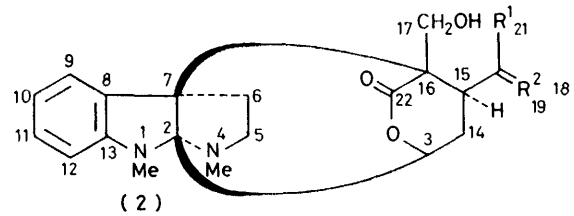
The structure of isocorymine (1a) has been confirmed and the relative stereochemistry at C-3 and C-16 for (1a), erinine (1b), erinicine (1c), and eripine (2a), at C-17 in (1a), and at C-19 in (1c), and the geometry of the 18,19-double bond in (1a), (1b), and (2a) elucidated by a combination of ^1H–^1H spin–spin coupling and nuclear Overhauser enhancement data measured at 300 MHz.

FOUR alkaloids from *Hunteria umbellata* (K. Schum) Hall F., isocorymine,[1] erinine,[2] erinicine,[2] and eripine,[3] have been assigned related structures (1a—c) and (2a) respectively, placing them in that sub-group [4] of indole alkaloids which are derived from tryptamine and an unrearranged secologanin unit but lacking the usual 21,N-4-bond and having additionally a 7,16-bond.†



(1)

a; R^1 = H,OH, R^2 = H_2, R^3 = CHMe
b; R^1 = H_2, R^2 = O, R^3 = CHMe
c; R^1 = H_2, R^2 = O, R^3 = H,Et



(2)

a; R^1 = CO_2Me, R^2 = CHMe
b; R^1 = CH_2OH, R^2 = H,Et
c; R^1 = Me, R^2 = H,Et

Alkaloids (1b and c) and (2a) were chemically interrelated in that (2a) was lactonised [3] by heating to give (1b) [together with the 18,19-double bond isomer of (1b); the same mixture of double bond isomers was obtained by similarly heating either erinine or its double bond isomer], and (1b) was cleanly, catalytically reduced [2] to give (1c).

The absolute configurations at C-2 and -7 in erinine and erinicine (and by correlation therefore in eripine) were established [2] by o.r.d. comparisons. The β linking of C-16 to C-7 is the irrevocable consequence of the ubiquitous α-H configuration at C-15 found in all indole alkaloids. An assumption of this absolute configuration at C-15 for isocorymine too would therefore imply analogous C-2 and -7 stereochemistry.

Several points of stereochemical uncertainty remained to be established for these bases. Firstly the geometry of the 19,20-double bond in isocorymine (1a) and erinine (1b) [and thus in eripine (2a)] was not elucidated; the *E*-configuration would be expected by comparison with nearly all established instances [6] in other indole alkaloids which possess unsaturation at the 19,20-position.

Secondly, the stereochemistry of the fusion of the eserine unit to the lactone ring, *i.e.* the stereochemistry of C-3 and -16 relative to C-15 was not considered [1] for isocorymine and only tentatively assigned [2] for erinine (and by implication for erinicine and eripine) by noting the similarity in the i.r. spectra of an erinine degradation product (2b) and that of a compound (2c) derived from the alkaloid echitamine, the stereochemistry of which had been established [7] by *X*-ray crystallography. The stereochemical question-mark concerning C-16, and implicitly C-3, has acquired more significance in the wake of the more recent isolation [8] of members of this sub-group of indole alkaloids, of both possible C-16 epimeric types. Thus, *a priori*, considering the hexacyclic bases (1a—c), they could have stereochemical structures represented by either (3) or (4), whilst in each case retaining the same configuration at C-15, shown in these diagrams on the assumption of the ubiquitous H-15 α-configuration.

Finally, neither the configuration at C-17, the hemiacetal carbon, in isocorymine (1a), nor the stereochemistry of reduction of erinine, *i.e.* the configuration at C-20 in erinicine, had been elucidated.

Reported here is a detailed re-examination of the n.m.r. spectra of isocorymine, erinine, and erinicine which now allows us to answer each of the questions above and to arrive at clear representations of the molecular geometry of these alkaloids in solution, in detail which it would be impossible to derive otherwise without resort to *X*-ray crystallographic examination of their structures in the solid state. The structures have been determined by a combination of ^1H–^1H spin–spin coupling and nuclear Overhauser enhancement (nOe)

† Numbering is the standard system for indole alkaloids.[5]

data, the former giving information on dihedral angles between C–H bonds and the latter information on the spatial proximity of proton pairs. The nOes were determined in their transient form following selective inversion of a single resonance (or group of overlapping resonances). Further details and original references to transient nOes are given in a recent study [9] of the conformation of the alkaloid apparicine by this method.

EXPERIMENTAL

Spectra were recorded on a Varian Associates SC-300 pulsed Fourier transform spectrometer operating at 300 MHz. Selective inversion of single resonances was achieved by pulsing the homonuclear decoupler; π-pulse widths of *ca.* 20 ms were employed. The transient nOes were evaluated by comparing the peak heights of spectra recorded at thermal equilibrium with those recorded during the relaxation of the inverted peak. To ensure an accurate representation of the peak profile, free induction decays were accumulated into 32 K data points and weighted with an exponential function of time constant −1 s to reduce noise.

2% (w/v) Solutions in [$^2H_6$]acetone were used. The samples were degassed and sealed *in vacuo*. The temperature of measurement was 23 ± 1 °C.

RESULTS

The ^1H spectra of isocorymine, erinine, and erinicine were investigated in detail at 300 MHz. All three compounds gave generally well resolved spectra. Those of isocorymine and erinine were essentially first order, but that of erinicine was considerably more complicated in the aliphatic region (δ 1.2—2.25) because of the larger number of aliphatic protons resulting from hydrogenation of the 19,20-double bond. In isocorymine, H-15 and one of the protons on C-14 were strongly coupled, giving essentially the AB part of an ABX spectrum with small additional splittings due to weak coupling to protons at C-3, -18, -19, and -21.

The major part of the assignments of peaks to protons on particular carbon atoms was accomplished by spin–spin decoupling starting from obvious assignments such as the 18-methyl group at highest field. The ambiguities remaining at this stage were the assignment of specific protons within the geminal pairs on C-5, -6, -14, and -21 in isocorymine, C-5, -6, -14, and -17 on erinine, and C-5, -6, -14, -17, and -19 in erinicine, together with the distinction in the aromatic region of H-9 and -12 (both giving doublets) and H-10 and -11 (both giving triplets). Some of these uncertainties were resolved by nOe experiments. Interpretation of the nOe data is inextricably linked also to the conformational analysis of the molecules, so the two topics are discussed for each compound individually below. First, however, several general points need mentioning. Transient nOes are characterised by two parameters, the maximum fractional enhancement, η^*, and the time of maximum enhancement, t^*. For a given interaction both parameters of course depend on the degree of inversion of the selectively perturbed nucleus, η^* more so than t^*. In the following discussion, the values of η^* and t^* quoted in particular experiments are for a degree of inversion of the perturbed nucleus of *ca.* 75%. In discussing the structural implications of nOe data, it is necessary to establish that relaxation is controlled by intramolecular dipole–dipole interactions. That this condition held is demonstrated by the selected spin-lattice relaxation time measurements (T_1) for isocorymine given in Table 1. (Table 1 anticipates the peak assignments discussed below.) The T_1 values cover a wide range, from 6.2 for H-10 to 1.2 s for H-14. Thus intermolecular interactions (which would be the same for all protons) play a minor role. All protons in methylene groups have short

TABLE 1

Selected spin–lattice relaxation times (T_1) for isocorymine in degassed [$^2H_6$]acetone at 23 °C. Errors are ±5%.

Proton [a]	T_1/s	Proton [a]	T_1/s
3	3.16	12	5.73
5a	1.32	14a	1.15
5b	1.25	14b	1.17
6a	1.26	15	1.57
6b		17	4.66
9	2.70	21a	1.55
10	6.21	21b	1.39
11	6.09		

[a] Protons are referred to by the number of the carbon atom to which they are bound, except for *N*-methyl and hydroxy-groups.

T_1 values in the range 1.2—1.5 s, since the geminal interaction at *ca.* 180 pm is by far the largest relaxation mechanism. The minor differences between methylene proton T_1 values arise from differences in vicinal and longer range interactions. The aromatic protons generally have longer T_1 values because the principal interaction is between *ortho*-protons separated by *ca.* 248 pm. (The exceptional case of H-9 is discussed below.) Now T_1 depends on the sixth power of internuclear distances, hence, assuming that the relaxation of H-10 is dominated by *ortho*-interactions with H-9 and -11 and that T_1 of an isolated methylene group is 1.8 s, one would anticipate a T_1 of $1.8/2 \times (248/180)^6 = 6.2$ s for H-10; agreement with the observed value is excellent.

In some instances, support for the interpretation of the nOe data was obtained from chemical shift and coupling constant data. Dreiding molecular models were used as a guide to internuclear distances and dihedral angles in the various configurational options open to the molecules.

TABLE 2

^1H Chemical shifts and coupling constants for isocorymine in [$^2H_6$]acetone at 23 °C

Proton [a]	δ	J/Hz
1–CH_3	3.15	
3	5.22	2.5 (14a), 2.5 (14b)
4–CH_3	2.61	
5a	2.86	8.5 (5b), 1.5, 8.5 (6a + 6b)
5b	2.38	8.5 (5a), 5, 11 (6a + 6b)
6a	2.23	1.5, 8.5, 5, 11 (5a + 5b)
6b	±0.04	
9	7.20	7.5 (10), 1 (11), 0.5 (12)
10	6.79	7.5 (9), 7.5 (11), 1 (12)
11	7.30	1 (9), 7.5 (10), 7.5 (12)
12	6.53	0.5 (9), 1 (10), 7.5 (11)
14a	2.51	2.5 (3), 12.5 (14b), 10.5 (15)
14b	2.02	2.5 (3), 12.5 (14a), 6.5 (15)
15	2.58	10.5 (14a), 6.5 (14b), 0.8 (18), 1 (21a)
17	5.18	12 (17–OH)
17–OH	5.09	12 (17)
18	1.57	0.8 (15), 7 (19), 0.8 (21a), 0.8 (21b)
19	5.46	1 (15), 7 (18), 1 (21a), 1 (21b)
21a	4.40	1 (15), 0.8 (18), 1 (19), 13 (21b)
21b	3.91	0.8 (18), 1 (19), 13 (21a)

[a] See footnote to Table 1.

The chemical shift and coupling constant assignments resulting from the following discussions are given in Tables 2—4.

TABLE 3

^{1}H Chemical shifts and coupling constants for erinine in [$^2H_6$]acetone at 23 °C

Proton [a]	δ	J/Hz
1–CH_3	3.17	
3	5.27	2.2 (14a), 3.2 (14b)
4–CH_3	2.63	
5a	2.94	10.5 (5b), 1.5, 6.5 (6a + 6b)
5b	2.47	10.5 (5a), 5.5, 9 (6a + 6b)
6a	2.09	1.5, 5.5, 6.5, 9 (5a + 5b)
6b	±0.04	
9	7.22	7.5 (10), 1 (11), 0.5 (12)
10	6.78	7.5 (9), 7.5 (11) 1 (12)
11	7.31	1 (9), 7.5 (10), 7.5 (12)
12	6.56	0.5 (9), 1 (10), 7.5 (11)
14a	2.57	2.2 (3), 14 (14b), 10.5 (15)
14b	1.92	3.2 (3), 14 (14a), 7.3 (15)
15	2.90	10.5 (14a), 7.3 (14b), 2.3 (18), 3 (19)
17a	4.93	11.5 (17b)
17b	4.56	11.5 (17a)
18	1.79	2.3 (15), 7.5 (19)
19	7.05	3 (15), 7.5 (18)

[a] See footnote to Table 1.

TABLE 4

^{1}H Chemical shifts and coupling constants for erinicine in [$^2H_6$]acetone at 23 °C

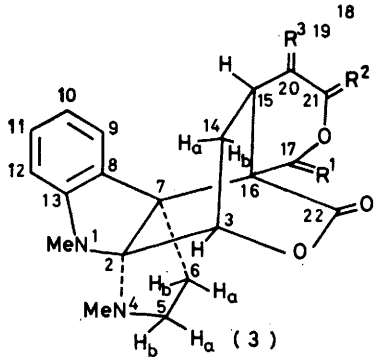
Proton [a]	δ	J/Hz
1–CH_3	3.12	
3	5.32	1.5, 4 (14a + 14b)
4–CH_3	2.63	
5a	2.93	9 (5b), 1, 6.5 (6a + 6b)
5b	2.45	9 (5a), 5, 11 (6a + 6b)
6a	2.09	1, 5, 6.5, 11 (5a + 5b)
6b	2.01	
9	7.34	7.5 (10), 1 (11), 0.5 (12)
10	6.78	7.5 (9), 7.5 (11), 1 (12)
11	7.29	1 (9), 7.5 (10), 7.5 (12)
12	6.53	0.5 (9), 1 (10), 7.5 (11)
14a	2.09	1.5 (3)
14b	1.87	4 (3)
15	1.98	
17a	5.05	12.3 (17b)
17b	4.84	12.3 (17a)
18	0.85	7.4 (19a, 19b)
19a	1.87	7.4 (18), 14 (19b), 4 (20)
19b	1.62	7.4 (18), 14 (19a), 6 (20)
20	2.19	12 (15), 4, 6 (19a + 19b)

[a] See footnote to Table 1.

(I) *Isocorymine.*—(i) *Assignment of the aromatic and* N-*methyl signals.* A strong enhancement of the lower field aromatic doublet (δ 7.20, η* *ca.* 0.1, *t** *ca.* 2 s) was observed following inversion of H-17. A weaker enhancement of the same doublet (η* *ca.* 0.04, *t** *ca.* 3 s) was observed on inversion of the overlapping resonances of H-6a and -6b. Therefore H-9 was assigned to that aromatic doublet, and H-12 to the doublet at δ 6.53 by elimination. A simple decoupling experiment then led to the assignment of H-10 to the triplet at δ 6.79 and H-11 to the triplet at δ 7.30. The 1-CH_3 signal was assigned to the peak at δ 3.21 since inversion of that peak led to an enhancement of the H-12 signal (η* *ca.* 0.07, *t** *ca.* 3.5 s).

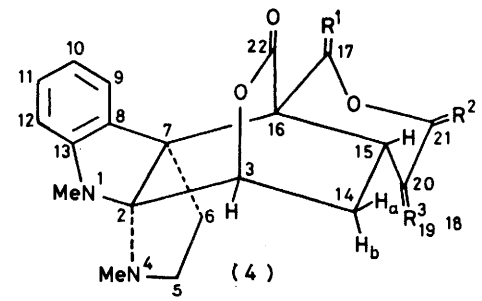
(ii) *Assignment of* H-14a *and* -14b *and the configurations at* C-3 *and* -16. The significant item of experimental nOe data leading to these assignments is the enhancement of the lower field 14-H resonance (η* *ca.* 0.03, *t** *ca.* 2 s) observed on inverting the 1-CH_3 peak. The two possible pairs of configurations at C-3 and -16 are shown in (3a) and (4a). A choice between these structures can be made by the following semi-quantitative argument.

In the Dreiding model of (3a), assuming coplanarity of the N-1–CH_3 bond and the dihydroindole benzene ring, H-14a lies in the range 220—320 pm from a 1-CH_3 proton depending on the angular position of the methyl group. In contrast with the alternative configuration, (4a), the minimum



(3)

a; R^1 = H, OH, R^2 = H_2, R^3 = CHMe
b; R^1 = H_2, R^2 = O, R^3 = CHMe
c; R^1 = H_2, R^2 = O, R^3 = H, Et



(4)

a; R^1 = H, OH, R^2 = H_2, R^3 = CHMe
b; R^1 = H_2, R^2 = O, R^3 = CHMe
c; R^1 = H_2, R^2 = O, R^3 = H, Et

distance between H-14 and a 1-CH_3 proton is 420 pm. Now it can be shown that in an AMX spin system, the steady-state nOe of the M proton on continuous saturation of the A proton is, to a good approximation, equal to $\frac{1}{2}[r_{AM}^{-6}/(r_{AM}^{-6} + r_{MX}^{-6})]$ when intramolecular dipole–dipole interactions are dominant.[10] The M-X internuclear distance, r_{MX}, is *ca.* 180 pm if M and X are geminal, *e.g.* H-14a and -14b, and the steady-state nOes then expected for r_{AM} values of 200, 250, and 300 pm are 0.174, 0.061, and 0.022, respectively. However, the observed value of the transient nOe for H-14 on inversion of the 1–CH_3 peak differs from these steady-state values for three reasons. First, the transient nOe is less than the corresponding steady-state nOe since saturation is not maintained. Secondly, the methyl group contains three protons and therefore larger nOes will be obtained than if only one proton is perturbed. Thirdly, the methyl group will experience some degree of internal rotation, giving shorter correlation times for interactions in-

volving methyl protons than for proton pairs rigidly attached to the molecular framework, and hence lower nOes. It is likely that the first and third effects will be compensated by the second, so that the observed values of η^* for H-14 on inversion of 1-CH_3 should depend on the interproton distance to a comparable extent to that calculated for the AMX system above. The observed value of η^* for this experiment is therefore consistent only with the formulation (3a) with H-14a assigned to the lower field 14-H resonance and H-14b to the upper.

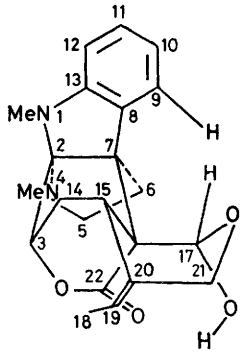
Two other features of the nOe data support this structure. First a small enhancement of H-9 (η^* *ca.* 0.03, t^* *ca.* 2 s) was observed on inverting the partially overlapping 4-CH_3, H-15, and low field H-14 resonances. This enhancement must arise from the H-9–H-15 interaction since the distance between these protons is the shortest of the three choices in any reasonable conformation of either (3a) (*ca.* 500, 320, and 530 pm, respectively) or (4a) (*ca.* 570, 520, and 570 pm, respectively). However, the magnitude of the enhancement is consistent only with the H-9–H-15 separation of *ca.* 320 pm occurring in (3a), and not with the separation of 520 pm in (4a). Secondly, no transient enhancements of the peaks for the C-21 protons were observed on inversion of the signal corresponding to the C-6 protons. In (4a), the 6- and 21-methylene groups are close together, the shortest H-6–H-21 distance being 220 pm. An interaction as close as this would give a measurable enhancement of *ca.* 0.08. In (3a) on the other hand, the shortest H-6–H-21 distance is 440 pm and no enhancement would be expected.

(iii) *Configuration of* C-17. As mentioned above in connection with the aromatic proton assignment, a large transient nOe is observed for H-9 on inversion of H-17, showing that they are near neighbours. The close approach of these two protons is also indicated by spin–lattice relaxation times (Table 1). The T_1 value for H-10 is more than twice that of H-9, though on the basis of the number of *ortho*-neighbours alone, the ratio should be reversed. The H-9–H-17 interaction is therefore twice as effective as an *ortho*-interaction. Assuming an *ortho*-proton distance of 248 pm, the H-9–H-17 distance is then approximately 248 × $(\frac{1}{2})^{1/6}$ or 220 pm. A distance as short as this is obtainable only for the configuration of C-17 shown in (3a) and (5), the conformation of the six-membered hemiacetal ring being more easily seen in the representation (5), which shows (3a) from an alternative viewpoint.

This assignment is further supported by the 17-OH chemical shift and the H-17, OH coupling constant. The 17-OH chemical shift lies towards the low field limit of the range for aliphatic hydroxy groups and is insensitive to temperature, indicating a fair degree of intramolecular hydrogen bonding. The H-17, OH coupling constant is 12 Hz, indicating a *trans*-relationship. Both these features are accommodated in (3a) [(5)], the hydrogen bond being formed with the 22-carbonyl oxygen. A model indicates that the distance between the carbonyl oxygen and the hydroxy-proton is *ca.* 200 pm.

(iv) *Configuration of the* 19,20-*double bond.* On inversion of the 18-methyl resonance, transient enhancements were observed for H-14a and -15. Only with the *E*-configuration for the 19,20-double bond does the methyl group approach H-14a and -15 sufficiently closely to produce these effects.

(II) *Erinine and Erinicine.*—The assignment of the aromatic proton signals, the configurations at C-3 and -16 and the assignment of signals for H-14a and -14b in erinine followed an identical course to that for isocorymine. It was also concluded that the analogous structure (3b) represents this alkaloid. The spectrum of erinicine was not so clearly resolved as those of (3a and b) and nOe experiments proved impractical. However the conversion [2] or erinine into erinicine and the structure, (3b), now derived



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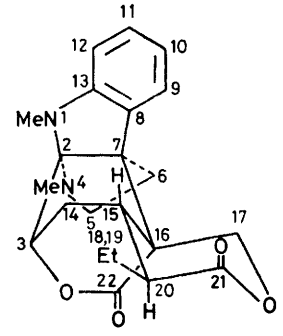

(6)

for the former allows (3c) to be written for erinicine, with the configuration at C-20 remaining to be settled. Although a number of coupling constants remained undertermined, fortunately it was possible to obtain the coupling constant between H-15 and -20. The value of 12 Hz obtained (Table 3) shows that these two protons are *trans* to one another, thus fixing the configuration of C-20; the alternatively viewed representation (6) illustrates this stereochemistry.

Each of the four alkaloids considered here is shown, then, to have the same *R* configuration at C-16, the configuration which is most generally found in alkaloids of this skeletal type,[4] also confirming the tentative assignment made for erinine earlier.[2] There are so far only two exceptions, lonicerine [8b] and rhazinaline [11] having the *S*-configuration at C-16.

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REFERENCES

[1] C. W. L. Bevan, M. B. Patel, A. H. Rees, and A. G. Loudon, *Tetrahedron*, 1967, **23**, 3809.
[2] B. W. Bycroft, M. Hesse, and H. Schmid, *Helv. Chim. Acta*, 1965, **48**, 1598.
[3] Y. Morita, M. Hesse, and H. Schmid, *Helv. Chim. Acta*, 1968, **51**, 1438.

[4] J. A. Joule, 'The Monoterpenoid Indole Alkaloids: Chemistry and Pharmacology,' ed. J. E. Saxton, Humana Press, Clifton, ch. 4, in the press.
[5] J. Le Men and W. I. Taylor, *Experientia*, 1965, **21**, 508.
[6] For exceptions see S. Sakai, *Heterocycles*, 1976, **4**, 131.
[7] J. A. Hamilton, T. A. Hamor, J. M. Robertson, and G. A. Sim, *Proc. Chem. Soc.*, 1961, 63.
[8] For an example see the pair (*a*) aspidodasycarpine, J. A. Joule, M. Ohashi, B. Gilbert, and C. Djerassi, *Tetrahedron*, 1965, **21**, 1717; (*b*) lonicerine, J. Naranjo, M. Hesse, and H. Schmid, *Helv. Chim. Acta*, 1970, **53**, 749.
[9] F. Heatley, L. Akhter, and R. T. Brown, *J. Chem. Soc., Perkin Trans. 2*, 1980, 919.
[10] J. H. Noggle and R. E. Shirmer, 'The Nuclear Overhauser Effect,' Academic Press, New York, 1971.
[11] A. Chatterjee, A. Banerji, L. Majumder, and R. Majumder, *Bull. Chem. Soc. Jpn.*, 1976, **49**, 2000.