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A SHORT ROUTE TO THE PHTHALIDEISOQUINOLINES. CONFORMATIONAL ANALYSIS[1]

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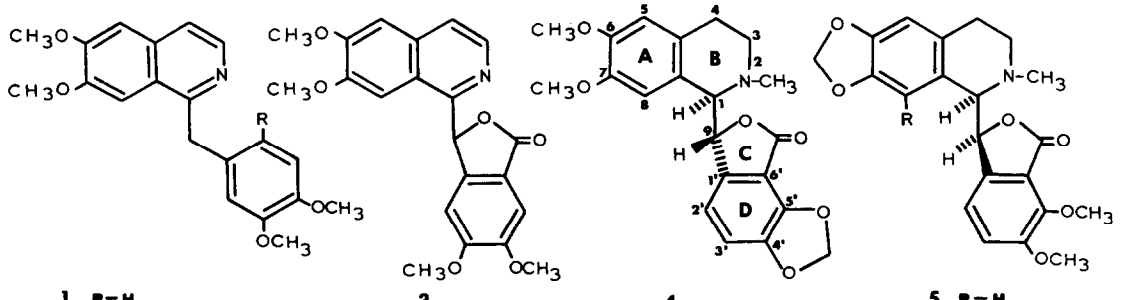
All of the synthetic routes presently available to the phthalideisoquinolines involve the use of the somewhat inaccessible meconine or one of its analogs. Consequently, only a limited number of phthalideisoquinolines have so far been obtained by total synthesis.[2,3]

We wish to describe a short sequence to the 6,7,3',4'-tetramethoxyphthalideisoquinolines starting with the known and readily available 2'-hydroxymethylpapaverine (2) derived in high yield from papaverine (1).[4] CrO_3 in HOAc-H_2SO_4 oxidation of 2 led in 75% yield to the aromatic phthalideisoquinoline 3, $C_{21}H_{19}NO_6$, mp 190-192° (EtOH), $\nu_{max}^{CHCl_3}$ 1760 cm^{-1}, λ_{max}^{EtOH} 233sh, 248, 300 and 335 nm (log ε 3.79, 3.93, 3.10 and 2.84). Catalytic reduction with Adams catalyst in acid solution gave in near quantitative yield a diastereoisomeric mixture of norphthalideisoquinolines 7, $C_{21}H_{23}NO_6$, mp 183-185° (EtOH), λ_{max}^{EtOH} 212, 227, 262, 295 and 310sh nm (log ε 3.88, 3.82, 3.27, 3.19 and 2.98), and 9, mp 205-207° (EtOH), λ_{max}^{EtOH} 215, 228, 263, 295 and 308sh nm (log ε 4.03, 4.08, 3.58, 3.57 and 3.38), which could be separated and its components individually N-methylated (HCOH-$NaBH_4$) to afford phthalideisoquinolines 8, $C_{22}H_{25}NO_6$, mp 157-159° (EtOH), λ_{max}^{EtOH} 218sh, 230, 262, 295 and 307sh nm (log ε 4.20, 4.25, 3.95, 3.89 and 3.73), and 10, mp 115-117° (EtOH), λ_{max}^{EtOH} 230, 262, 296 and 307sh nm (log ε 4.13, 3.97, 3.89 and 3.78), respectively. Alternatively, the mixture of nor bases could be N-methylated and then separated chromatographically into 8 and 10.

The relative stereochemistry and some aspects of the conformation of the phthalideisoquinolines were first considered by Safe and Moir who correctly established adlumine (4) to be threo, and

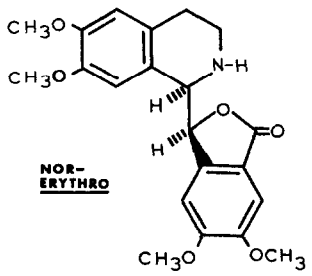


1, R=H
2, R=CH_2OH

3

4

5, R=H
6, R=OCH_3



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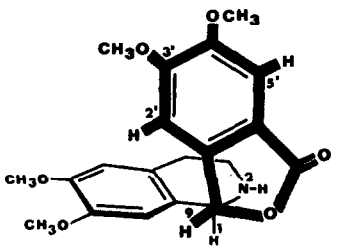

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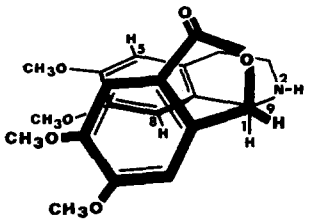

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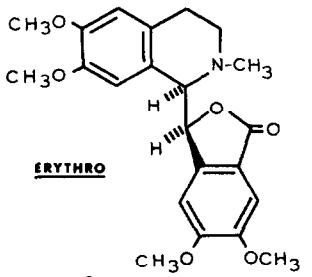

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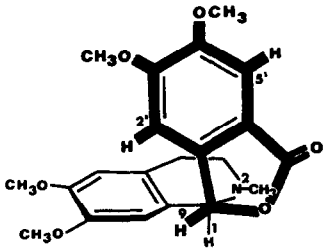

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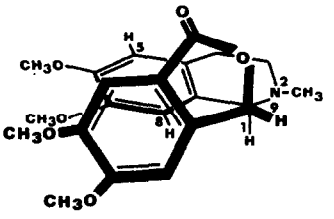

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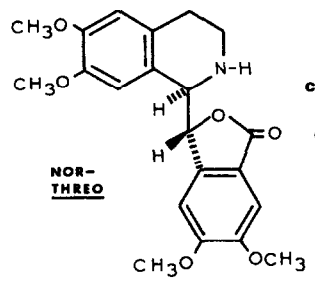

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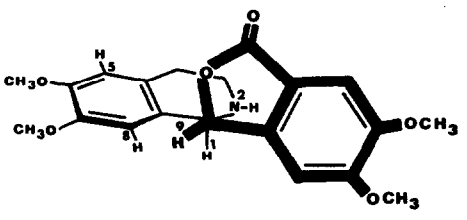

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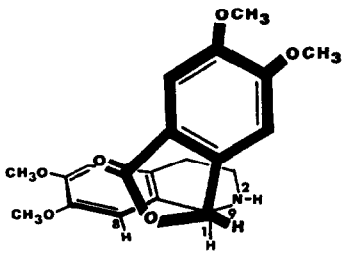

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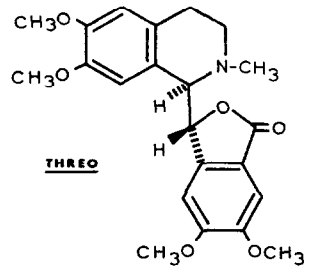

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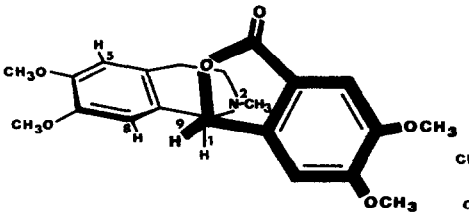

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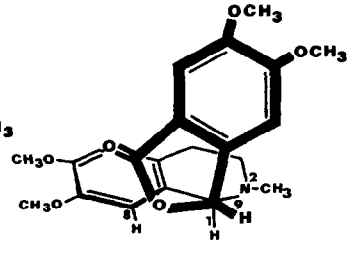

10B

hydrastine (5) and narcotine (6) to be erythro on the basis of nmr data. One of their relevant observations was that the low coupling constant for H-1 and H-9 ($J_{1,9}$ = 3.4-4.3 Hz) implies a dihedral angle of $\approx 50^0$ between these two hydrogens.[5]

The fact that pairs of diastereoisomeric norphthalideisoquinolines and phthalideisoquinolines were now available to us has allowed for a firm establishment of conformations, as well as for explicit assignments of chemical shifts. In each instance, nmr data indicated that the favored conformation was the one with the least steric interaction between rings A and B on the one hand, and C and D on the other. It has been shown that ring C in tetrahydrobenzylisoquinolines lies close to the nitrogen atom if the nitrogen is secondary. After N-methylation, however, ring C is found in the proximity of ring A and away from the relatively bulky N-methyl group.[6] This same steric factor, i.e. N-methylation, has presently been found to prevail in phthalideisoquinolines so that N-methylation forces rings C and D away from the nitrogen and into proximity with ring A.

Of the four aromatic protons present in each of species 7-10, the hydrogen furthest away from the lactone ring and whose chemical shift would be least subject to stereochemical or conformational considerations is H-5, and it can be seen (Table) that the chemical shift for H-5 remains nearly constant around $\delta 6.6$.[7,8] Additionally, the most downfield aromatic signal can be assigned in each case to H-5' which falls within the deshielding zone of the lactone carbonyl. The chemical shift for H-1 is affected by methylation on nitrogen, in both the erythro and threo series, with a resulting upfield shift of ≈ 0.6 ppm (Table).

The signals for H-1 and H-9 may be readily recognized because of their low coupling constant, $J_{1,9}$ = 3.5 Hz (Table), so that the dihedral angle ϕ is near 50^0. In each of the four compounds considered here, there are only two staggered conformations (A and B) which fit this requirement.

Considering the nor-erythro 7 and erythro 8 series first, it can be seen that in erythro 8 the H-8 signal appears upfield at $\delta 6.20$ due to shielding by ring D, so that conformation 8B must prevail. In the nor-erythro base 7, it is the H-2' and 3'-MeO signals, at $\delta 5.84$ and 3.62, respectively, that are upfield, stemming from ring A shielding, so that conformation 7A is predominant.

The chemical shift of H-8 can again be used as the main probe in determining conformation in the nor-threo 9 and threo 10 series. This signal is relatively upfield, at $\delta 6.32$, in the case of threo 10 because of shielding by the lactone carbonyl, thus leading to the assignment of conformation 10B. It is further downfield at $\delta 6.52$ in the nor-threo base 9; no shielding is involved in this instance, and conformation 9A is paramount.

An interesting case is that of the erythro alkaloid narcotine (6) which possesses a methoxyl at C-8, thus forcing the molecule into a 7A type conformation.[5] Substitution at C-8 can also, therefore, play a role in determining the preferred conformation of a phthalideisoquinoline by compensating for substitution on the nitrogen atom.

TABLE: NMR Chemical Shifts of Phthalideisoquinolines (δ, $CDCl_3$)[‡]

Compound	$O-CH_3$	N-H	$N-CH_3$	H-5	H-8	H-1	H-9	H-2'	H-5'
Nor-erythro 7	3.62, 3.87, 3.87, 3.90	2.06	-	6.65	6.76	4.74	5.69	5.84	7.25
Erythro 8	3.75, 3.78, 3.87, 3.92	-	2.60	6.62	6.20	4.08	5.55	6.47	7.25
Nor-threo 9	3.78, 3.82, 3.89, 3.92	1.90	-	6.67	6.52	4.58	5.61	7.01	7.18
Threo 10	3.72, 3.77, 3.82, 3.90	-	2.69	6.65	6.32	4.09	5.62	7.00	7.17

[‡] $J_{1,9}$ = 3.5 Hz. H-5 and H-8 are slightly split ($\leq$1 Hz) by interaction with H-4 and H-1, respectively; H-9 is further split ($\leq$1 Hz) by H-2', and vice versa.

References

1. This research was supported by grant HL-12971 from the National Institutes of Health. Acceptable elemental analyses were obtained for all new compounds.
2. For a review on the phthalideisoquinolines see M. Shamma, The Isoquinoline Alkaloids, Academic Press, New York (1972), p. 359.
3. V. Smula, N.E. Cundasawmy, H.L. Holland and D.B. MacLean, Can. J. Chem., 51, 3287 (1973).
4. P. Mathieu and J. Gardent, C.R. Acad. Sc. Paris, 267 C, 1416 (1968).
5. S. Safe and R.Y. Moir, Can. J. Chem., 42, 160 (1964).
6. D.R. Dalton, M.P. Cava and K.T. Buck, Tetrahedron Lett., 2687 (1965). M. Tomita, T. Shingu, K. Fujitani and H. Furukawa, Chem. Pharm. Bull., 13, 921 (1965).
7. This conclusion requires an exchange in the assignments of the chemical shifts for H-5 and H-8 in the cases of corlumine and bicuculline made in Ref. 5. A similar change is also necessitated for cordrastine I in Ref. 3.
8. The fact that H-5 always appears near δ6.6 allows assignments for the chemical shifts of this proton in bicuculline, cordrastine II, capnoidine and cordrastine I which now become δ6.64, 6.65, 6.64 and 6.66, respectively: S. Teitel, J. O'Brien and A. Brossi, J. Org. Chem., 37, 1879 (1972). Bicuculline and cordrastine II belong to the erythro series and must be represented by a conformation similar to 8B. Capnoidine and cordrastine I are threo bases which exist in conformation 10B. The conformation of the alkaloid adlumine belonging to the threo series is also as in 10B.