Tetrahedron Letters No.31, pp. 2687-2690, 1965. Pergamon Press Ltd.
Printed in Great Britain.

HINDERED ROTATION IN 1-BENZYL-1,2,3,4-TETRAHYDRO-6,7-DIMETHOXYISOQUINOLINES

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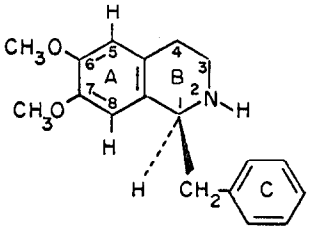
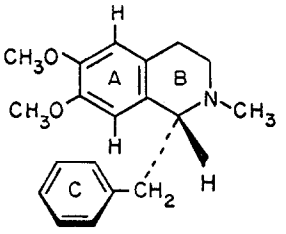
(Received 3 June 1965)

We wish to report some unusual observations in the NMR spectra[1] of some 1-benzyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinolines. We have found some remarkable anomalies resulting from a difference in the size of the substituent on the nitrogen atom. In the parent compound, 1-benzyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (I)[2], the molecule may be assumed to exist, preferentially, in the conformation in which ring C lies close to the nitrogen atom and away from ring A. In accord with this assumption, the two aromatic protons of ring A appear as a broad singlet at 6.61 δ whereas the two methoxyl groups appear at the almost equivalent positions of 3.84 δ and 3.78 δ. The spectrum of the corresponding N-methyl derivative (II),[3] on the other hand, clearly indicates that the N-methyl exerts a sufficiently important steric repulsion to force ring C into a preferred conformation underneath ring A. This effect is clearly seen in the NMR spectrum of II in which the proton at C-5 appears at the normal value of 6.57 δ while that at C-8 is shifted upfield (integration shows 1.0 proton) as a result of shielding by ring C to 5.99 δ. Similarly, the 6-methoxyl group of II appears in the normal position of 3.82 δ whereas the 7-methoxyl group is shifted upfield (integration shows 3.0 protons) to 3.52 δ as a result of shielding by ring C.

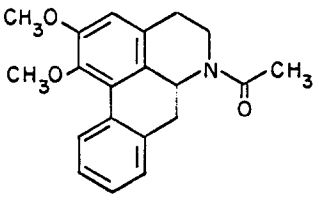
The NMR spectrum of the corresponding N-acetyl derivative (III)[4] clearly shows the presence of two relatively stable rotational isomers in approximately equal quantities at room temperature. In one of these isomers (isomer IIIa, acetyl methyl up) the acetyl methyl affords no repulsion to ring C which, as in the unsubstituted compound (I), appears in the preferred conformation under the nitrogen atom. In this conformation, the protons at position 5 and 8 appear at the relatively normal values of



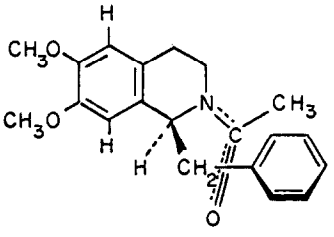
I



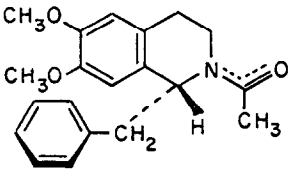
II



IV



III a



III b

6.63 δ and 6.59 δ, respectively, while the methoxyls at 6 and 7 appear at 3.85 δ and 3.78 δ, respectively. As anticipated, however, the methyl of the N-acetyl group experiences considerable shielding by ring C, appearing at the unusually high field position of 1.60 δ. In the opposite rotational isomer (isomer IIIb, acetyl methyl down) the acetyl methyl exerts a steric repulsion upon ring C at least as great as that observed in the N-methyl derivative (II). Consequently, the hydrogens at C-5 and C-8 are shifted upfield to 6.48 δ and 6.11 δ, respectively,[5] while the methoxyls at C-6 and C-7 appear at 3.82 δ and 3.58 δ and the acetyl methyl appears at the relatively normal position of 2.11 δ.[6]

TABLE I[1]

Chemical Shifts of Substituents
in 1-Benzyl-1,2,3,4-Tetrahydro-6,7-Dimethoxyisoquinolines

Compound	O-Methyl Position		Aromatic Hydrogen Position		Substituent on Nitrogen
	6	7	5	8	
I	3.84	3.78	6.61	6.61	1.94 (hydrogen)
II	3.82	3.52	6.57	5.99	2.53 (methyl)
IIIa	3.85	3.78	6.63	6.59	1.60 (acetyl)
IIIb	3.82	3.55	6.48	6.11	2.11 (acetyl)
IV[6]	3.92	3.71	6.75	---	2.20 (acetyl)

As expected, the complex spectrum of the N-acetyl compound (III) is simplified upon heating and, at 120°, the rotational barrier for the N-acetyl group is overcome. The acetyl methyl now appears as a broad singlet at 1.96 δ, the four equal methoxyl peaks collapse to two equal peaks at 3.68 δ and 3.84 δ and the aromatic protons at C-5 and C-8 appear as two equal peaks at 6.38 δ and 6.65 δ.

In view of the importance of NMR data in the determination of alkaloid structures[6,7] the results outlined above show that conformational effects may cause serious unexpected complications in the interpretation of the NMR spectra of simple benzylisoquinoline alkaloids and their derivatives.

Further details of the spectra of the above mentioned and other closely related compounds, as well as a discussion of the quantitative aspects of the phenomena involved will be presented in the full paper.

Acknowledgment. This investigation was supported by a Public Health Service Fellowship (7-F2-GM-14,470-01A1) from the National Institute of General Medical Sciences (D.R.D.) and a grant (NB 04529) from the National Institute of Neurological Diseases and Blindness.

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(1) Spectra were determined on a Varian Associates A-60 recording spectrometer at 60 Mc. in deuteriochloroform. Chemical shifts are reported in ppm from TMS = 0.

(2) J. W. Huffman and E. G. Miller, J. Org. Chem., 25, 90 (1960).

(3) J. Knabe and J. Kubitz, Arch. Pharm., 296, 532 (1963)

(4) Prepared by acetylation of I with acetyl chloride. M.p. 110-111° (corr.) (from methanol or benzene-cyclohexane). A satisfactory analysis was obtained.

(5) Careful examination of models reveals that ring C may be held even more closely to ring A in this isomer than in the corresponding N-methyl compound. Consequently, the C-7 methoxyl (the chemical shift of which results from time averaging) should spend less of its time in the vicinity of ring C, thus pushing the C-6 methoxyl upward into the vicinity of the hydrogen on C-5. This explanation accounts for both the slightly decreased C-8 proton shielding and the slightly increased C-5 proton shielding relative to those observed in the N-methyl analog

(6) W. H. Baarschers, R. R. Arndt, K. Pachler, J. A. Weisbach and B. Douglas, J. Chem. Soc., 4778 (1964).

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