isolated olefins was also confirmed by infrared analysis (Nujol mull) and mixture melting points.

Deuterium Exchange Studies. Standard Solutions. A standard solution of N-deuteriopiperidine and piperidinium chloride-N,N-d_2 in stock DMF was prepared in the same manner as were the solutions of the protium species. Thus 3.4457 g (0.03999 mole) of the deuterated amine and 1.1236 g (0.0010 mole) of the deuterated amine salt were weighed into a 100-ml volumetric flask which was then filled to the mark with stock DMF. The resulting solution was 0.3999 *N* in N-deuteriopiperidine and 0.0100 *N* in the deuterated amine salt.

Reactant Isolation from Half-Life Reactions. In a typical run, 163.4 mg of *trans*-I tosylate and 129 mg of piperidinium chloride-N,N-d_2 were dissolved in 10.0 ml of stock DMF and equilibrated in the constant temperature bath at 30.00 ± 0.02°. A 10.0-ml aliquot of the standard solution of the deuterated base, which had also been equilibrated at 30.00°, was added to the sulfonate solution. This gave a reaction mixture which was initially 0.02 *M* in tosylate, 0.20 *M* in N-deuteriopiperidine, and 0.06 *M* in the deuterated amine salt. After proceeding for a calculated half-life, the reaction mixture was quenched by pouring it into a mixture of 150 g of ice and 10 ml of concentrated hydrochloric acid, and the resulting mixture was stored in the refrigerator overnight. The solid which had precipitated from this mixture was filtered, washed thoroughly with water, and dried in a vacuum desiccator. Preparative thin layer chromatography of the crude mixture using the procedure described at the beginning of the Experimental Section afforded, after recrystallization from benzene–petroleum ether (30–60°), 38 mg of recovered *trans*-I tosylate, mp 111–112°, for excess deuterium analysis.[45]

Other runs were made using a similar procedure.

Acknowledgment. The authors gratefully acknowledge financial assistance from the Research Corporation during the early stages of this work. A portion of this work was also supported by a grant from the Petroleum Research Fund administered by the American Chemical Society, to whom the authors are also grateful.

Hindered Rotation in 1-Benzyl-1,2,3,4-tetrahydro-6-7-dimethoxyisoquinolines[1]

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Contribution from the Evans Chemical Laboratory, The Ohio State University, Columbus, Ohio 43210. *Received July 14, 1966*

Abstract: The conformation of several of the title compounds have been inferred from nmr data. It is shown that certain 1,2,3,4-tetrahydro-2-acetylisoquinolines substituted in the 1 position with benzyl exist as equilibrium mixtures of two conformers in nearly equal amounts. With increasing temperature the resonances for the two conformers average to a single spectrum. In the case of 1-benzyl-1,2,3,4-tetrahydro-1-acetyl-6,7-dimethoxyisoquinoline, rates of exchange due to conformer interconversion as obtained from the aromatic and acetyl line shapes are the same and both yield an activation energy of 7.8 kcal.

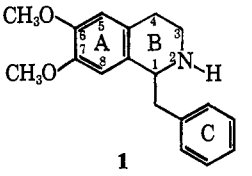
Recent empirical nmr correlations[2] of the structures of benzyl and bisbenzylisoquinoline alkaloids have, while permitting some extension to those of unknown structure, ignored possible anomalies which might arise in these structures because of steric inhibition of free rotation.[3]

In conjuction with the examination of nmr spectra of some new members of these families we felt it would be of value to examine simple cases where steric effects might be more readily observed.

Since all benzylisoquinoline alkaloids (dimerization of which produces the bisbenzylisoquinoline analogs) are substituted with oxygen-bearing moieties in the 6 and 7 positions, the parent compound chosen for this investigation was 1-benzyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline, **1**.[4]

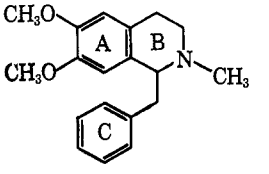
Results and Discussion

Examination of the nmr spectrum of **1**, Figure 1a, indicates that ring C exists, preferentially, in that conformation which permits minimum steric interaction with ring A. Thus the aromatic hydrogens of ring A appear as a broad singlet at τ 3.39 ± 0.02 whereas the two methoxyl groups are found at the almost equivalent positions of τ 6.16 and 6.22. The spectrum of the



1

corresponding N-methyl derivative, 1-benzyl-2-methyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (**2**,[5] (Figure 1b), however, shows that the 2-methyl group exerts a steric repulsion on ring C which is sufficient to force ring C close to ring A. Thus while the hydrogen at C_5 appears in the normal position of τ 3.43, that at C_8 is shifted upfield as a result of shielding by ring C to τ 4.01. The methoxyl group at C_7 is similarly affected,



2

(1) A preliminary communication of part of this work has appeared: D. R. Dalton, M. P. Cava, and K. T. Buck, *Tetrahedron Letters*, 2687 (1965).

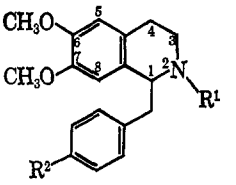
(2) I. R. C. Bick, J. Harley-Mason, N. Sheppard, and M. J. Vernengo, *J. Chem. Soc.*, 1897 (1961).

(3) D. H. R. Barton, private communication.

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

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

Table I. Chemical Shifts, τ Scale, $CDCl_3$, 34°



R^1	R^2	1-H	5-H	8-H	6-OCH_3	7-OCH_3	R^1
H	H	5.83	3.39	3.39	6.16	6.22	8.06
CH_3	H	6.32	3.43	4.01	6.18	6.48	7.47
CH_3	OH	6.22	3.44	4.06	6.20	6.54	7.68
H	$OCH_2C_6H_5$	5.92	3.42	3.40	6.22	6.29	8.31
CH_3CH_2	H	6.15	3.46	4.07	6.18	6.50	7.70[a]

[a] Methylene.

appearing at τ 6.48. That this correlation does in fact hold true is indicated in Table I. Thus the shift for H_5 varys only slightly, τ 3.43 ± 0.04, as does that for the 6-methoxy group, τ 6.19 ± 0.04. When R′ = H the 7-methoxy has an average shift of 6.26 ± 0.04 while that for H_8 is τ 3.39 ± 0.02. However, when R′ is larger than H the 7-methoxy shift assumes the

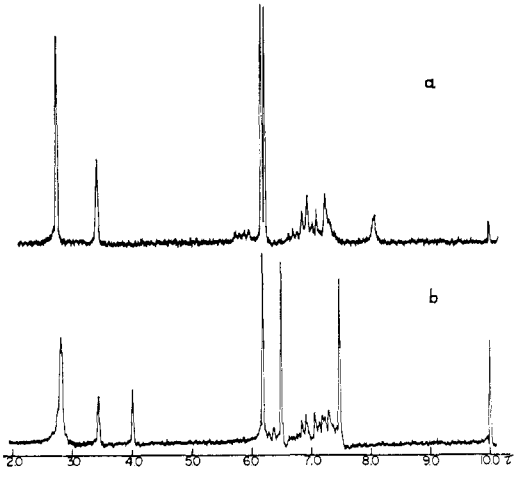
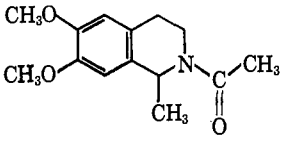


Figure 1. Nmr spectra, 60 MHz; a, compound **1**; b, compound **2**; both 5% in $CDCl_3$, 35°.

value τ 6.51 ± 0.03 while the value for H_8 is now τ 4.05 ± 0.04. Furthermore, when ring C is replaced by a methyl group as in 1-methyl-2-acetyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (**3**), the shift of H_8 is τ 3.33.



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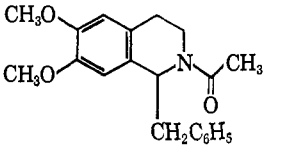
Johnson and Bovey have calculated the magnetic field contours around a benzene ring freely tumbling in a magnetic field.[6] Inspection of their tables[7] reveals that in the latter conformation, the coordinates of H_8 are approximately 1.4–3.0 A on the hexagonal and 1.8–2.1 A on the radial axes, respectively, of ring C. Thus the orientation of ring C with respect to ring A in these compounds may be easily inferred from the nmr shifts of substituents on ring A.

The conformational assignments made above are now applied to the case of 1-benzyl-2-acetyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (**4**). The nmr



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spectrum obtained at 0°, Figure 2, consists of two sets of peaks of equal amplitude for H_1, H_2, H_8, methoxy$_7$, methoxy$_6$, and the acetyl methyl. In the case of **3**

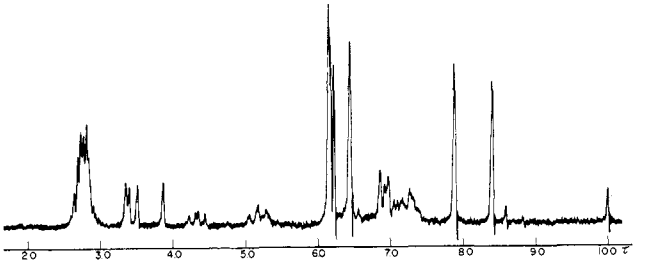
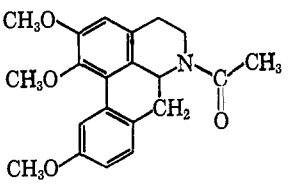


Figure 2. Nmr spectra for compounds **4a** and **4b**, 5% in $CDCl_3$, 35°.

there are two absorptions of nearly equal amplitude for H_1, C–CH_3 and acetyl (Table II). By analogy to the results in Table I, the low-field absorptions in Table II are assigned to species **a** in which the shift of H_8 is unaffected by the benzyl group. A similar argument applies to the shifts of methoxy$_7$.

The stereochemistry of compounds **3** and **4** at C_1 may be inferred from the shifts for H_1 in **3**, **4**, and **5**.



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(6) C. E. Johnson, Jr., and F. A. Bovey, *J. Chem. Phys.*, **29**, 1012 (1958).

(7) C. E. Johnson, Jr., and F. A. Bovey, "Table of Chemical Shifts Arising from Diamagnetic Aromatic Rings," Minnesota Mining and Manufacturing Co., St. Paul, Minn., 1958.

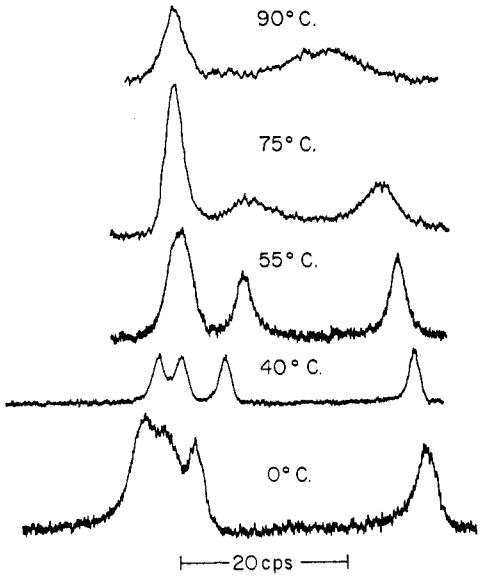
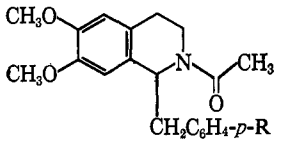


Figure 3. Nmr line shapes for H_5 and H_8 in mixtures of **4a** and **4b** at different temperatures, solvent $CDCl_3$.

From models it is clear that H_1 in **5** is axial, the observed shift being τ 5.25. Thus the H_1 shifts in Table II listed under species **a** represent axial hydrogens whereas those under **b** are equatorial.

Table II. Chemical Shifts, τ Scale, $CDCl_3$, 34°



Species	R	1-H	5-H	8-H	6-OCH_3	7-OCH_3	CCH_3
a	H	5.18	3.37	3.41	6.15	6.22	8.40
b	H	4.35	3.52	3.89	6.18	6.45	7.89
a	OCH_3	5.23	3.39	3.42	6.18	6.25	8.39
b	OCH_3	4.40	3.50	3.72	6.20	6.42	7.90
a	OBz	5.23	3.40	3.45	6.18	6.25	8.39
b	OBz	4.40	3.52	3.85	6.21	6.45	7.91

In compounds **3**, **4**, and **5**, the chemical shifts of the acetyl methyls (around τ 7.8) lie close to that in N,N-dimethylacetamide, τ 7.88.[8] On the other hand among the 1-benzyl-2-acetyl compounds listed in Table II, each sample shows one acetyl resonance in the normal region, τ 7.8, whereas the other one is *more shielded*, τ 8.6.

Taken together these data show that for each of the 1-benzyl-2-acetyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinolines studied one of the resonances owing to H_8 and acetyl is shielded by the benzyl group.

In principle one might expect to find four isomers for **4** due to the equatorial–axial conformation of C_1 and *cis–trans* isomerism involving the acetyl group. Actually only two species are resolved in the nmr spectrum of **4**.[9]

(8) G. V. D. Tiers, Tables of Chemical Shift Values, Minnesota Mining and Manufacturing Co., St. Paul, Minn., 1958.

(9) It is still possible that accidental degeneracy of chemical shifts renders some species unresolvable.

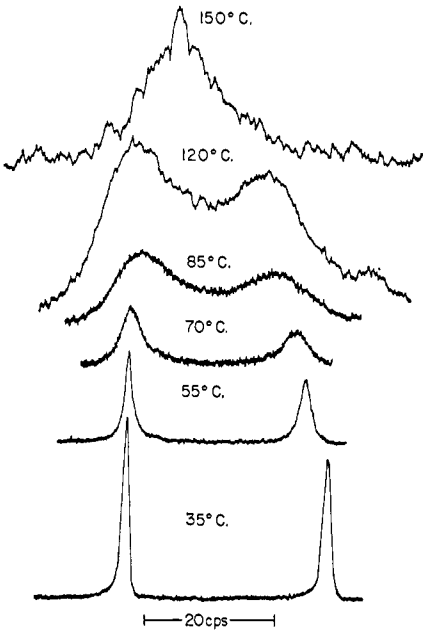


Figure 4. Nmr line shapes for acetyl hydrogens in **4a** + **4b** at different temperatures.

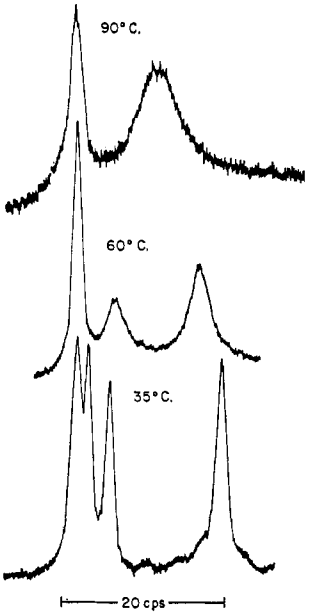


Figure 5. Methoxy resonance of **4a** + **4b** at different temperatures.

Inspection of models indicates that the only structure for **3** compatible with shielding at H_8 and acetyl is that with H_1 axial and acetyl methyl *cis* to the benzyl group, **a**. A rocking motion of the benzyl group would bring about the extra shielding (due to the benzyl ring current) described above. In the second species labeled **b**, H_1 is equatorial, and the position of the acetyl methyl cannot be specified.

Assuming that **4** exists as an approximately equal mixture of two species, **a** and **b**, it should be possible to average the shifts between them by rapid inversion at C_1. This is indeed the case for, with increasing temperature, the resonances for the different hydrogens assigned to **4a** and **b** coalesce to single lines by 120°. Figures 3 and 4 depicit the aryl and acetyl resonances

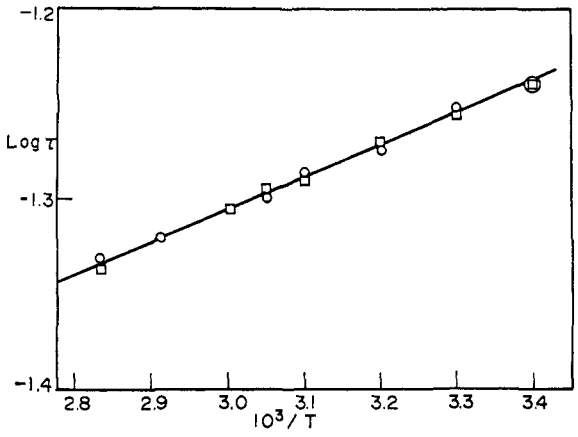


Figure 6. Arrhenius plot for exchange, **4a** ⇌ **4b**: □, acetyl resonance; ○, aryl resonance.

for **4a** and **b** as a function of temperature. The acetyl lines broaden and move together with increasing temperature, as do the lines for H_5 and H_8. Similar effects are seen in the methoxy absorption (Figure 5). The multiplet for ring C which spans 20 Hz at 0° narrows to ~1 Hz by 90°. Finally the resonances for H_1 broaden and move together but do not completely average out.

The acetyl and aromatic hydrogen line shapes in Figures 1 and 2 were employed to calculate the mean lifetime between successive exchanges of a hydrogen between different environments.[10] At each temperature the values of τ obtained from the acetyl and aromatic line shapes are very similar. The Arrhenius plot in Figure 6 yields an activation energy of 7.8 ± 0.4 kcal.

Evidently the changes for the aromatic and acetyl line shapes described above must result from the same process. It is tentatively concluded that inversion at C_1 brings about the temperature behavior reported here.

In summary, the compounds listed in Table II exist in two forms and interconversion rates between them have been measured with the nmr line-shape method.

(10) (a) H. S. Gutowsky and A. Saika, *J. Chem. Phys.*, **21**, 279 (1953); H. S. Gutowsky and C. H. Holm, *ibid.*, **21**, 1688 (1953). (b) We have employed a treatment for an unequal doublet 100/80. It is recognized that the isomer ratio may vary with temperature; however, altering it by 10% in either direction changes ΔE by less than 4%, within our experimental error. The line shapes for H_1 and the methoxy groups were not sufficiently reproducible to use for rate measurements.

Experimental Section

Compounds. The compounds used in this research were synthesized by Dr. K. Buck.[11]

Nmr Spectra. All nmr spectra were determined with a Varian A-60 nmr spectrometer equipped with a variable-temperature probe.

Acknowledgment. This research was supported by a Public Health Service Fellowship from the National Institute of General Medical Sciences (D. R. D.) and grants from the National Institute of Neurological Diseases and Blindness (NB 04529) and the National Institute of General Medical Sciences (GM-08686-03).

(11) K. Buck, Ph.D. Thesis, The Ohio State University, Columbus, Ohio, 1966. We thank Dr. Buck for making these compounds available to us.

Quinazolines and 1,4-Benzodiazepines. XXXIII. Three Tautomeric Forms of the Benzodiazepine Ring System[1]

George F. Field, William J. Zally, and Leo H. Sternbach

Contribution from the Chemical Research Department, Hoffmann-La Roche Inc., Nutley, New Jersey 07110. *Received September 16, 1966*

Abstract: The reaction of 6-chloro-2-chloromethyl-1,2-dihydro-4-phenylquinazoline 3-oxides (**1**) with base gives either the 1,3-dihydro-2H-azirino[1,2-*a*]quinazoline 4-oxides (**4**) which are valence isomeric with the unknown 2H-1,4-benzodiazepine 4-oxide ring system or a 3H-1,4-benzodiazepine 4-oxide (**7**). The effect of substituents in the 2 position as well as solvent on the course of the reaction is discussed. The 2H isomers **4** are readily isomerized to 5H-1,4-benzodiazepine 4-oxides (**5**).

The properties of the heterocyclic congeners of tropilidene are of interest, and considerable attention has been devoted to the synthesis of these compounds.[2] An entry into this area of chemistry which deserves more extensive exploitation is the ring expansion of dihydro derivatives of aromatic heterocycles bearing a chloromethyl group.[3] An easily accessible set of such dihydro derivatives is the 2-chloromethyl-1,2-dihydroquinazoline 3-oxides (**1**) which are obtained by condensation of 2-amino-5-chlorobenzophenone *anti*-oxime with α-chloro aldehydes or α-chloro ketones.[4]

(1) A part of this work has been reported in preliminary form: paper XXXI, G. F. Field, W. J. Zally, and L. H. Sternbach, *Tetrahedron Letters*, 2609 (1966); paper XXXII, R. Ian Fryer, B. Brust, J. V. Earley, and L. H. Sternbach, *J. Chem. Soc.*, in press.

(2) F. D. Marsh and H. E. Simmons, *J. Am. Chem. Soc.*, **87**, 3529 (1965); R. J. Colter and W. F. Beach, *J. Org. Chem.*, **29**, 751 (1964); L. A. Paquette, *J. Am. Chem. Soc.*, **85**, 3288 (1963); G. Maier, *Chem. Ber.*, **98**, 2438 (1965); E. Vogel, W. A. Böll, and H. Günther, *Tetrahedron Letters*, 609 (1965); J. A. Moore and J. Binkert, *J. Am. Chem. Soc.*, **81**, 6029 (1959); W. von E. Doering and R. A. Odum, *Tetrahedron*, **22**, 81 (1966); F. Johnson and W. A. Nasutavicus, *J. Heterocyclic Chem.*, **2**, 26 (1965).

(3) The ring enlargement of 4-chloromethyl-1,4-dihydropyridines has been studied. See R. F. Childs and A. W. Johnson, *Chem. Commun.*, 95 (1965); M. Andersen and A. W. Johnson, *J. Chem. Soc.*, 2411 (1965), and earlier papers.

(4) *Cf.* G. F. Field, W. J. Zally, and L. H. Sternbach, *J. Org. Chem.*, **30**, 3957 (1965).