[CONTRIBUTION FROM THE RESEARCH LABORATORIES, HOFFMANN-LA ROCHE INC., NUTLEY 10, N. J., AND F. HOFFMANN-LA ROCHE AND CO., AG., BASLE, SWITZERLAND]

The Nuclear Magnetic Resonance Spectra of the Angular Proton in Benzo[*a*]- and Indolo[*a*]quinolizidines[1]

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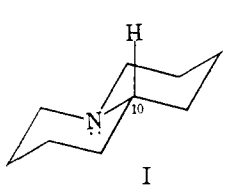
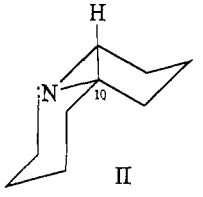
RECEIVED MARCH 19, 1964

A general method for assigning conformational structures to benzo[*a*]quinolizidines is presented with several substituted benzo[*a*]quinolizidines serving as examples. The angular proton of *trans* conformers resonates at a field higher than 6.2 τ, whereas both *cis* conformations are characterized by a downfield signal below 6.2 τ. It is possible, furthermore, to distinguish between the two alternative *cis* forms by the splitting pattern of the angular proton. In one *cis* form, the angular proton is *gauche* (ae) to one adjacent methylene proton and *trans*-diaxial to the other, and shows a quartet with small ae (J = 5 c.p.s.) and large aa (J = 11 c.p.s.) splittings, *i.e.*, roughly a 1:1:1:1 quartet. In the alternative *cis* form, the angular proton is *gauche* to both adjacent methylene protons, and shows a quartet with the inner lines close together, *i.e.*, roughly a 1:2:1 triplet, since ae and ee splittings are generally equal in magnitude.

The quinolizidine ring system is a structural feature common to many natural products. Quinolizidine itself can exist in two all-chair conformations. The preferred conformation[4] I has the two rings *trans* fused, with the hydrogen atom at C-10 *trans*-diaxial to the lone electron pair of the tertiary nitrogen atom. In the less favored conformation II, the two rings are *cis* fused, and the hydrogen atom at C-10 is *gauche* to the lone electron pair.

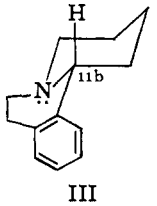


I



II

In simply substituted quinolizidines[4] or larger molecules containing a quinolizidine moiety, such as benzo[*a*]quinolizidines and indolo[*a*]quinolizidines, one *trans* form and two *cis* forms should be considered. In the two possible all-chair *cis* forms, the angular hydrogen is oriented differently with respect to the rings. In the benzo[*a*]quinolizidine (IV), the 11b-hydrogen is pseudo-equatorial to ring B and axial to ring C, whereas in V, it is pseudo-axial to ring B and equatorial to ring C.



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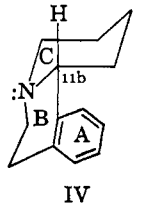
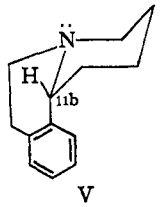


IV



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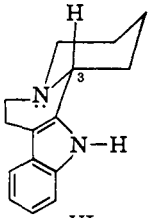
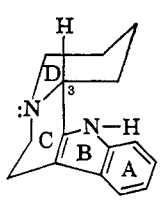
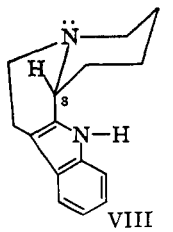


VI



VII



VIII

Similarly, in indolo[*a*]quinolizidine (VII), the 3-hydrogen is pseudo-equatorial to ring C and axial to ring D, whereas in VIII, it is pseudo-axial to ring C and equatorial to ring D.

The first spectroscopic criterion utilized to distinguish the *trans*-quinolizidines from *cis*-quinolizidines was the presence or absence of "Bohlmann bands"[5] in their infrared spectra. Solutions of *trans*-quinolizidines, in which the lone electron pair on the nitrogen is *trans*-diaxial to at least two hydrogens on adjacent carbon atoms, show prominent infrared bands between 2700 and 2800 cm.$^{-1}$. Such a relationship of the electron pair to two hydrogens is not possible in *cis*-quinolizidines, and these infrared bands are not found in their spectra. This method had been applied successfully in the structural assignment of many natural and synthetic products. In some cases, the low intensity of these bands makes the method less reliable.[6]

Katritzky and co-workers,[4] in addition to using the Bohlmann bands, have used n.m.r. to differentiate between *trans*- and *cis*-quinolizidines in the case of methyl derivatives. They observed that, in a series of N-methylquinolizidinium cations, the $^{+}$N-methyl protons of methiodides with *cis*-fused rings absorbed at lower fields than those of *trans*-fused analogs. In a series of yohimbine alkaloids,[7] the $^{+}N-CH_3$ peak in a *cis*-fused N-methylquinolizidinium system appeared near 6.5 τ, while the corresponding peak in the *trans* fused series showed up near 6.7 τ. The same relationship was also found for the heteroyohimbine alkaloid methiodides.

In another development, Rosen and Shoolery[8] observed that in the case of methyl reserpate (IX), corresponding to the partial *cis* formula VIII, the angular proton at C-3 resonated at a field lower than 6.2 τ. In methyl neoreserpate (X), corresponding to the partial *trans* formula VI, the angular proton absorbed at 6.8 τ.[9] Wenkert and co-workers[10] found

(1) Presented at the 145th National Meeting of the American Chemical Society, New York, N. Y., Sept., 1963; Abstracts of Papers, p. 21Q.

(2) Hoffmann-La Roche, Inc., Nutley 10, N. J.

(3) F. Hoffmann-La Roche and Co., AG., Basle, Switzerland.

(4) T. M. Moynehan, K. Schofield, R. A. Y. Jones, and A. R. Katritzky, *J. Chem. Soc.*, 2637 (1962); A. R. Katritzky, *Record Chem. Progr.*, **23**, 223 (1962).

(5) F. Bohlmann, *Angew. Chem.*, **69**, 641 (1957); *Chem. Ber.*, **91**, 2157 (1958); E. Wenkert and D. K. Roychaudhuri, *J. Am. Chem. Soc.*, **78**, 6417 (1956); W. E. Rosen, *Tetrahedron Letters*, 481 (1961).

(6) L. Blahaá, B. Kakáč, and J. Weichet, *Collection Czech. Chem. Commun.*, **27**, 857 (1962); T. Takemoto, Y. Kondo, and K. Kondo, *J. Pharm. Soc. Japan*, **83**, 162 (1963).

(7) M. Shamma and J. M. Richey, *J. Am. Chem. Soc.*, **85**, 2507 (1963).

(8) W. E. Rosen, *Tetrahedron Letters*, 481 (1961); W. E. Rosen and J. N. Shoolery, *J. Am. Chem. Soc.*, **83**, 4816 (1961).

(9) M. M. Robison, W. G. Pierson, R. A. Lucas, I. Hau, and R. L. Dzienian, *J. Org. Chem.*, **28**, 768 (1963).

(10) E. Wenkert, B. Wickberg, and C. L. Leicht, *J. Am. Chem. Soc.*, **83**, 5037 (1961); *Tetrahedron Letters*, 822 (1961).

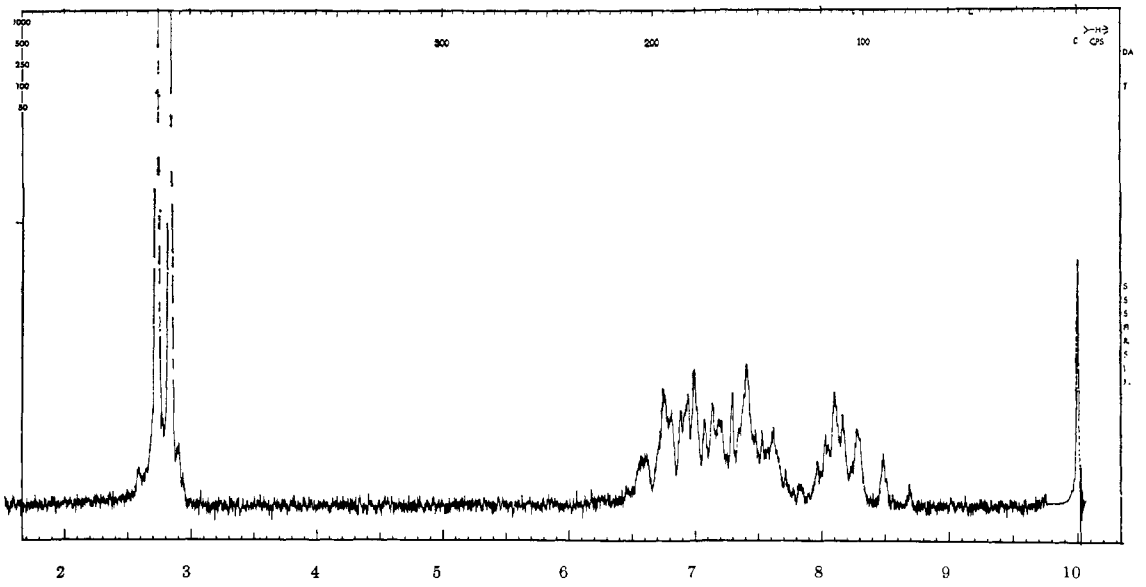
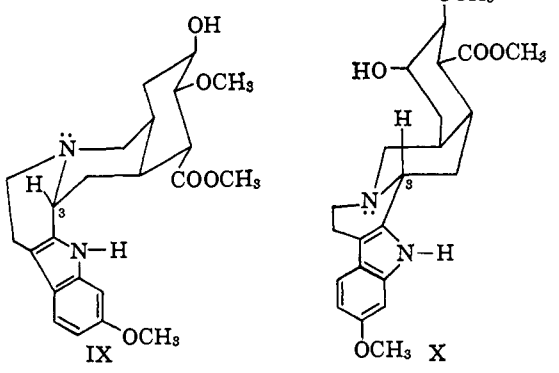


Fig. 1.—N.m.r. spectrum of *trans*-2-(*p*-chlorophenyl)-1,2,3,4,6,7-hexahydro-11bH-benzo[*a*]quinolizine (XI).

a similar difference in the n.m.r. spectra of heteroyohimbine alkaloids: 3-isoajmalicine, corresponding to the partial *cis* formula VIII, gave a signal for the C-3 proton at 5.55 τ, whereas the C-3 proton of ajmalicine, which belongs to the *trans* series VI, resonated at higher fields.

We have now found that this difference in chemical shifts for the angular proton is much more general: it also occurs in benzo[*a*]quinolizidines, and a low field signal below 6.2 τ is characteristic for both *cis* conformations. It is possible, furthermore, to distinguish between the two alternative *cis* forms by the splitting



pattern of the angular proton. The angular proton of the *cis* forms IV and VII is *gauche* (ae) to one adjacent methylene proton and *trans* diaxial (aa) to the other, and should show a quartet with small ae (J = 2–5 c.p.s.) and large aa (J = 9–12 c.p.s.)[11] splittings, *i.e.*, roughly a 1:1:1:1 quartet. In the alternative *cis* forms V and VIII, the angular proton is *gauche* to both adjacent methylene protons, and should show a quartet with the inner lines close together, *i.e.*, roughly a 1:2:1 triplet, since ea and ee splittings are, in general, equal in magnitude. Inspection of the n.m.r. spectra of the compounds shown in Chart I makes these relationships clear. The conformations shown in this chart are supported by the infrared spectra and by inspection of their molecular models.

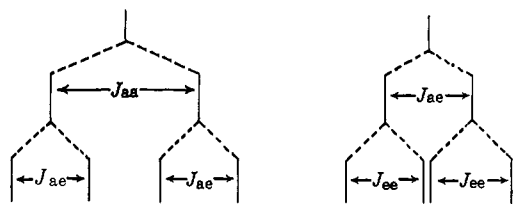
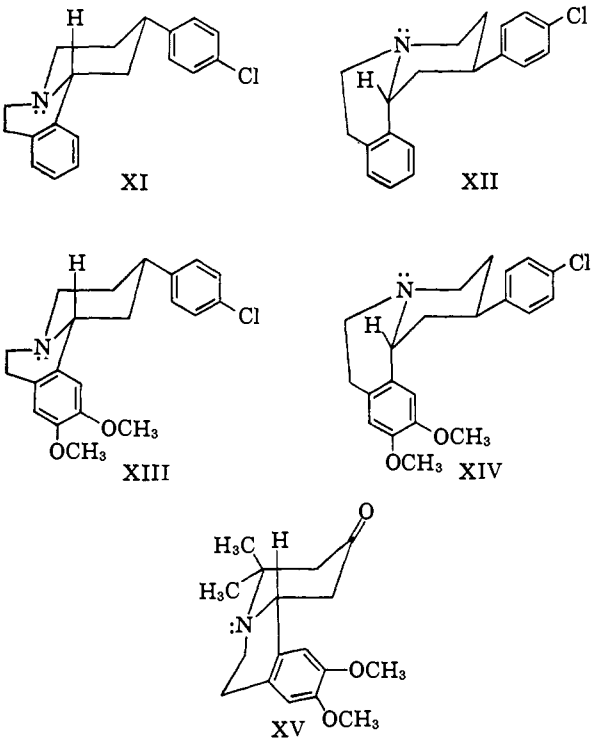


CHART I



Compounds XI and XIII show Bohlmann bands at 2755, 2805 cm.$^{-1}$ and 2755, 2795 cm.$^{-1}$, respectively. The n.m.r. spectra (Fig. 1 and 3) show no downfield one-proton signal below 6.2 τ attributable to the angular 11b-proton. These compounds are examples of the *trans* form III.

Their isomers XII and XIV show no Bohlmann bands. Compound XIV shows (Fig. 4) a downfield one-proton signal centered at 6 τ, the triplet (J = 5

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

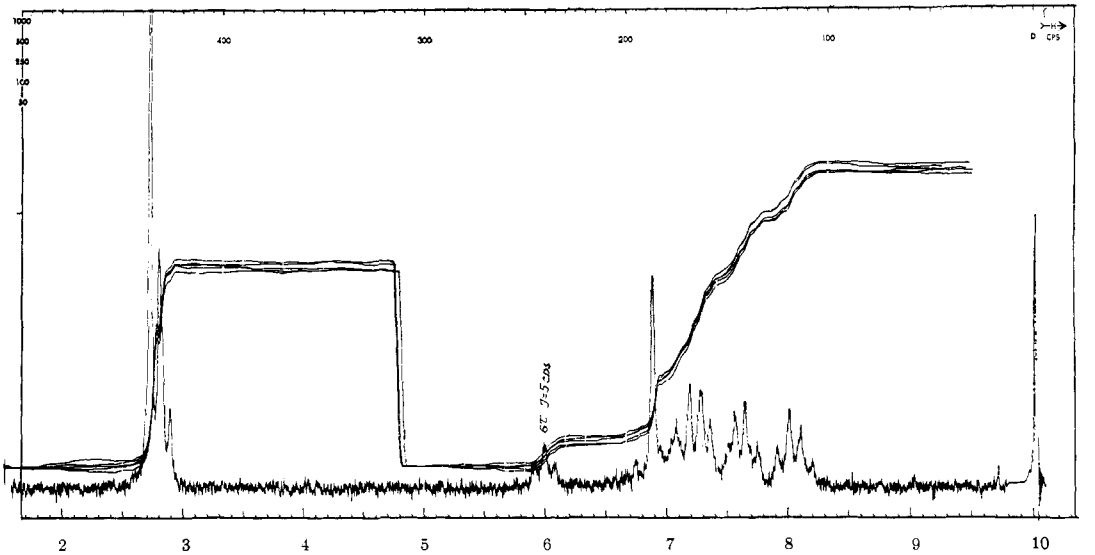


Fig. 2.—N.m.r. spectrum of *cis*-2-(*p*-chlorophenyl)-1,2,3,4,6,7-hexahydro-11bH-benzo[*a*]quinolizine (XII).

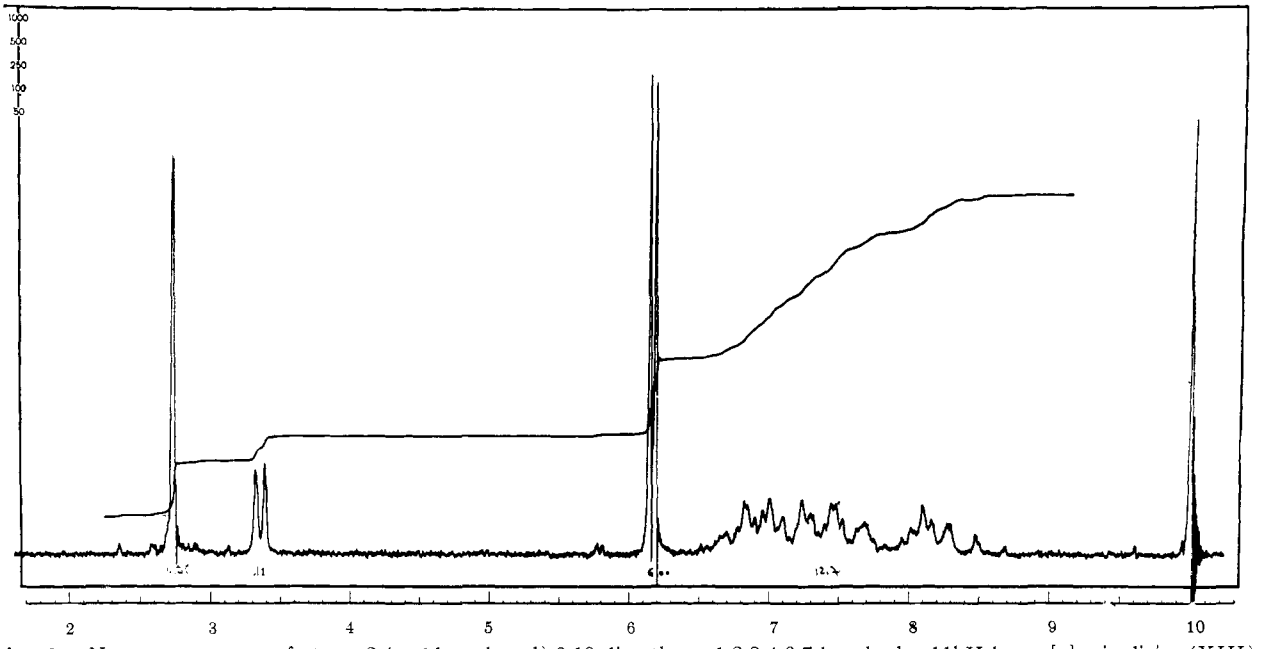


Fig. 3.—N.m.r. spectrum of *trans*-2-(*p*-chlorophenyl)-9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11bH-benzo[*a*]quinolizine (XIII).

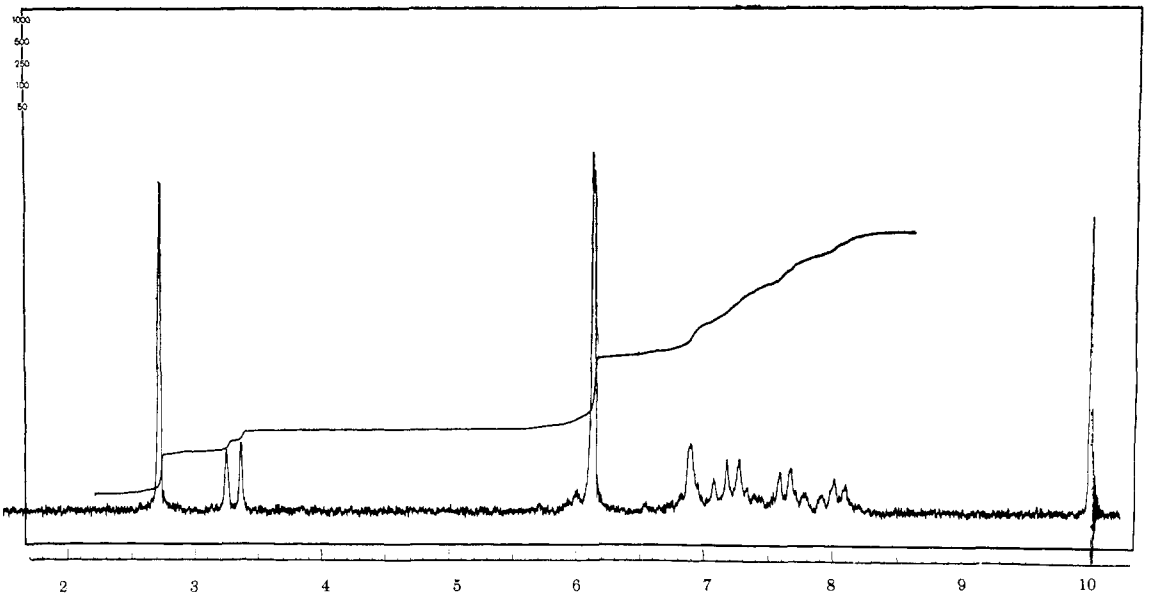


Fig. 4.—N.m.r. spectrum of *cis*-2-(*p*-chlorophenyl)-9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11bH-benzo[*a*]quinolizine (XIV).

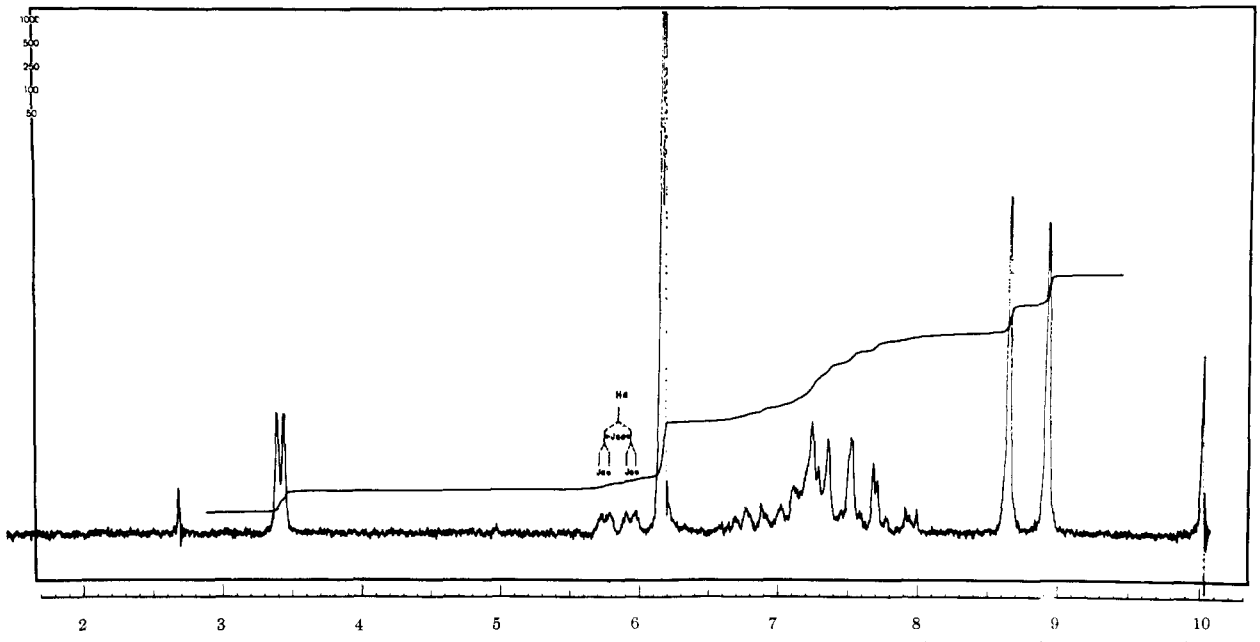


Fig. 5.—N.m.r. spectrum of 2-keto-4,4-dimethyl-9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11bH-benzo[a]quinolizine (XV).

c.p.s.) structure of which is partly masked by the peaks due to the methoxy groups. However, in the nonmethoxylated analog XII, the angular proton at C-11b appears clearly (Fig. 2) as a 1:2:1 triplet centered at 6 τ with J = 5 c.p.s. These two compounds are examples of the *cis* form V.

The ketone XV shows no Bohlmann bands. It is an example of the alternative *cis* form IV: its angular proton at C-11b gives rise to a 1:1:1:1 quartet centered at 5.85 τ with splittings J_{ae} = 5 c.p.s. and J_{aa} = 11 c.p.s. (Fig. 5).

These differences observed in the chemical shift could be largely due to the relationship of the angular proton with respect to the lone electron pair of the nitrogen. If the longitudinal magnetic susceptibility of the lone pair is larger than the transverse susceptibility, as for a carbon–carbon triple bond,[12] an angular proton *gauche* to the pair would be deshielded, whereas an angular proton *trans*-diaxial to the pair would be shielded.

(12) L. M. Jackmann, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, New York, N. Y., 1959, pp. 113–119.

Experimental

The infrared spectra were determined with solutions in chloroform, on the Beckman IR-9 spectrometer. The proton n.m.r. spectra were determined on an A-60 Varian spectrometer, with solutions in deuteriochloroform. The chemical shifts are expressed as τ units, and are referred to TMS as the internal reference. The syntheses of: *trans*-2-(*p*-chlorophenyl)-1,2,3,4,6,7-hexahydro-11bH-benzo[*a*]quinolizine (XI), *cis*-2-(*p*-chlorophenyl)-1,2,3,4,6,7-hexahydro-11bH-benzo[*a*]quinolizine (XII), *trans*-2-(*p*-chlorophenyl)-9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11bH-quinolizine (XIII) and *cis*-2-(*p*-chlorophenyl)-9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11bH-benzo[*a*]quinolizine (XIV) were reported recently by our group.[13] Compounds XIII and XIV had already been prepared by other methods.[14] The synthesis of 2-keto-4,4-dimethyl-9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11-bH-benzo[*a*]quinolizine (XV) has been reported by Beke and Szàntay.[15]

(13) H. Bruderer, M. Baumann, M. Uskoković, and A. Brossi, Abstracts, 147th National Meeting of American Chemical Society, Philadelphia, Pa., April, 1964. Complete details will be published soon in *Helv. Chim. Acta*.

(14) J. Gootjes and W. Th. Nauta, *Rec. trav. chim.*, **80**, 1223 (1961).

(15) D. Beke and C. Szàntay, *Chem. Ber.*, **95**, 2132 (1962).