Tetrahedron, 1965, Vol. 21, pp. 2015 to 2019. Pergamon Press Ltd. Printed in Northern Ireland

MAGNETIC NON-EQUIVALENCE OF METHYLENE PROTONS IN DISSYMMETRIC BENZYLAMINES

A SIMPLE METHOD OF ASSIGNMENT OF CONFIGURATION TO IDENTICALLY α,α'-DISUBSTITUTED HETEROCYCLIC BASES[1]

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(*Received* 9 *February* 1965)

Abstract—As a result of the lack of a plane of symmetry in identically α,α'-*trans*-disubstituted heterocyclic amines, the methylene protons of their N-benzyl derivatives are stereochemically and magnetically non-equivalent. The resultant splitting in the NMR spectrum enables an easy differentiation between *cis* and *trans* isomers.

CLASSICALLY, the assignment of configuration to the *cis* and *trans* isomers of identically α,α'-disubstituted heterocyclic bases (e.g., 2,6-dimethylpiperidine) has been based on resolution of the *trans* isomer into its optical antipodes. This method, even when successful, is often tedious, is unsatisfactory in those cases in which the *trans* isomer does not form crystalline, separable salts with the resolving acid,[4] and fails if only the *cis* isomer is available. An alternate method is to assign the *cis* configuration to the major product of catalytic hydrogenation of the corresponding aromatic amine (pyridine or pyrrole). Assignments made on this basis cannot be considered completely reliable, due to the stepwise nature of addition of hydrogen, the isomerization of intermediate olefins on the catalyst,[5] and the resulting possibility of obtaining *trans* isomers as major products.[6]

The stereochemistry of a number of six-membered rings has been attacked successfully by NMR spectroscopy in recent years. In applying this technique to the study of 1,3-disubstituted cyclohexanes, e.g., 1,3-cyclohexanediols[7] and 1,3-cyclohexanedialkanoic acids,[8] assignment is predicted on the ready chair–chair interconversion of the *trans* isomer, rapidly averaging axial and equatorial protons to give a spectrum

[1] This work was supported in part by a research grant (GM-06568) from the Public Health Service, to whom the authors express their gratitude.
[2] Alfred P. Sloan Foundation Research Fellow.
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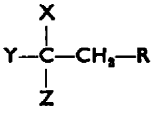
[4] A. Marcuse and R. Wolffenstein, *Ber. Dtsch. Chem. Ges.* **32**, 2525 (1899), were unable to assign configurations to the 2,6-dimethylpiperidines when the tartrate of one isomer failed to crystallize and the other tartrate could not be resolved.
[5] S. Siegel and B. Dmuchovsky, *J. Amer. Chem. Soc.* **84**, 3132 (1962); S. Siegel, G. V. Smith, B. Dmuchovsky, D. Dubbell and W. Halpern, *Ibid.* 3136; G. V. Smith and R. L. Burwell, Jr., *Ibid.* 925.
[6] J. F. Sauvage, R. H. Baker and A. S. Hussey, *J. Amer. Chem. Soc.* **83**, 3874 (1961); S. Siegel and B. Dmuchovsky, *Ibid*, **86**, 2192 (1964).
[7] H. Finegold and H. Kwart, *J. Org. Chem.* **27**, 2361 (1962).
[8] T. L. Westman, R. Paredes and W. S. Brey, Jr., *J. Org. Chem.* **28**, 3512 (1963).

with one or more comparatively sharp peaks or multiplets; the higher barrier to inversion (from diequatorial to diaxial substituents) in the *cis* isomer results in spreading of the NMR bands for the ring protons over a broad region. Thus, by comparing the relative sharpness of the bands of the two isomers, it may be possible to distinguish *cis* from *trans*. Muller and Tosch,[9] in their studies on dimethylcyclohexanes, cautioned, however, that the appearance of a relatively narrow region of ring proton resonance does not necessarily imply rapid ring inversion.

During the course of our investigation of the stereochemistry of the alkaloid pinidine,[10] it became necessary to make unambiguous assignments of configuration to *cis* and *trans* 2,6-dimethylpiperidines. Our approach to the solution of this problem is based on the effect of the symmetry properties of the two isomers on their NMR spectra, and offers a general solution for stereochemical problems of this kind.

It has been recognized for some time that the two protons of a methylene group adjacent to an asymmetrically substituted carbon (I) are magnetically non-equivalent, and consequently split each other in the NMR spectrum.[11] Nair and Roberts called specific attention to this phenomenon and pointed out that it offered a simple way of detecting the grouping (I) without resorting to optical resolution. The phenomenon was first attributed to restricted rotation,[11] though it has subsequently been observed in cases in which there appears no obvious barrier to rotation,[12] and it has since been pointed out that the magnetic non-equivalence of the methylene protons is an inherent property of the system, regardless of free rotation or conformational isomerism.[13,14] Nevertheless, it has continued to be a valuable tool in the recognition of a methylene group attached to an asymmetric carbon.[15]

I.



That this phenomenon is not restricted to asymmetric carbon, but exhibited by methylenes adjacent to *any* dissymmetric moiety, is shown by the NMR spectra of sulphites,[16] sulphoxides,[13,17] hindered biphenyls[18,19] and a substituted cyclooctatetraene.[20]

[9] N. Muller and W. C. Tosch, *J. Chem. Phys.* **37**, 1167 (1962).

[10] R. K. Hill, T. H. Chan and J. A. Joule, *Tetrahedron* **21**, 147 (1965).

[11a] J. J. Drysdale and W. D. Phillips, *J. Amer. Chem. Soc.* **79**, 319 (1957); [b] P. M. Nair and J. D. Roberts, *Ibid.* 4565.

[12] For a striking recent example, see J. C. Randall, J. J. McLeskey, III, P. Smith and M. E. Hobbs, *J. Amer. Chem. Soc.* **86**, 3229 (1964).

[13] J. S. Waugh and F. A. Cotton, *J. Phys. Chem.* **65**, 562 (1961).

[14] For recent studies, [a] E. I. Snyder, *J. Amer. Chem. Soc.* **85**, 2624 (1963); [b] G. M. Whitesides, D. Holtz and J. D. Roberts, *Ibid.* **86**, 2628 (1964).

[15] For recent examples, see D. Jung and A. A. Bothner-By, *J. Amer. Chem. Soc.* **86**, 4025 (1964); P. J. Kropp, *Ibid.* 4056; G. Fraenkel, D. T. Dix and D. G. Adams, *Tetrahedron Letters* 3155 (1964).

[16] H. S. Finegold, *Proc. Chem. Soc.* 283 (1960).

[17] T. D. Coyle and F. G. A. Stone, *J. Amer. Chem. Soc.* **83**, 4138 (1961); K. Mislow, A. L. Ternay, Jr., and J. T. Melillo, *Ibid.* **85**, 2329 (1963).

[18] K. Mislow, M. A. W. Glass, H. B. Hopps, E. Simon and G. H. Wahl, Jr., *J. Amer. Chem. Soc.* **86**, 1710 (1964).

[19] W. L. Meyer and R. B. Meyer, *J. Amer. Chem. Soc.* **85**, 2170 (1963).

[20] F. A. L. Anet, A. J. R. Bourn and Y. S. Lin, *J. Amer. Chem. Soc.* **86**, 3576 (1964).

It seemed apparent that symmetrically *trans*-disubstituted heterocyclic bases could also serve as the dissymmetric moiety in shielding the protons of an attached methylene, and accordingly we examined the NMR spectra of the N-benzyl derivatives of the 2,6-dimethylpiperidines and related compounds. The spectra of the N-benzyldimethylpiperidines are shown in Fig. 1. In accord with these expectations, the benzyl methylene region of the *trans* isomer (II) appears as an AB quartet, centered at 6·37 τ, with

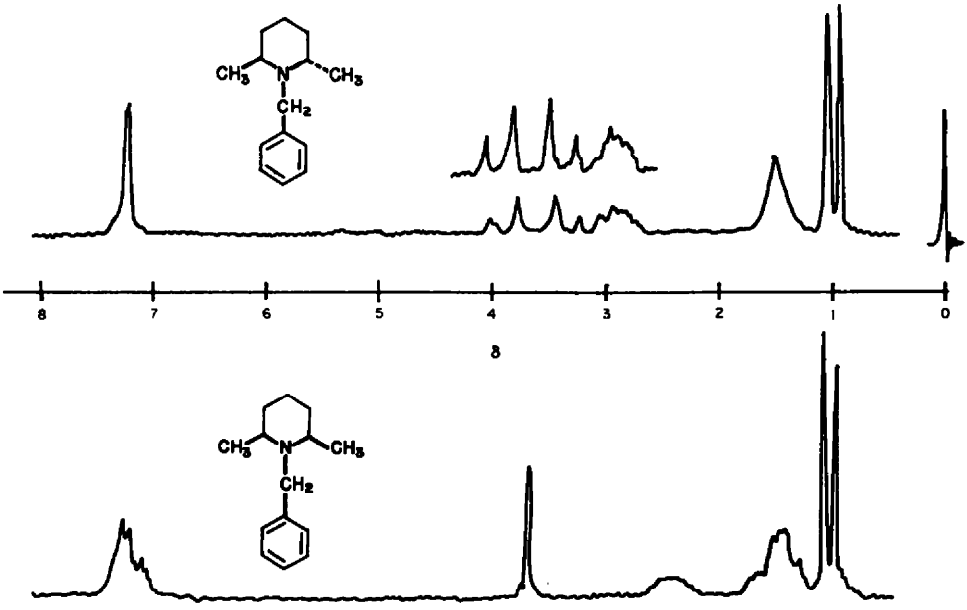
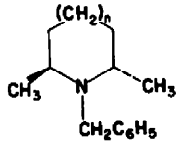


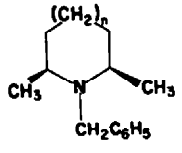
FIG. 1. NMR spectra of *cis* and *trans*-N-benzyl-2,6-dimethylpiperidines.

a coupling constant of 14 c/s. The methylene protons are clearly non-equivalent, in contrast to the situation in the *cis* isomer (III), in which the methylene appears as a sharp singlet at 6·30 τ. This simple and unambiguous assignment of configuration confirms that made by optical resolution of derivatives of the *trans* isomer.[10,21]

The two isomeric 2,5-dimethylpyrrolidines have been prepared by Overberger *et al.*,[22] and configurations tentatively assigned on the basis that catalytic hydrogenation of 2,5-dimethylpyrrole gives the *cis* isomer. Our NMR studies on the N-benzyl derivatives bear out this conclusion: the presumed *cis* isomer (IV) shows a sharp methylene singlet at 6·59 τ, while the *trans* isomer (V) displays an AB quartet, centered at 6·59 τ, J = 13·2 c/s.



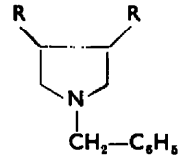
II. n = 1
V. n = 0



III. n = 1
IV. n = 0

[21] R. Lukeš and J. Jizba, *Coll. Czech. Chem. Comm.* 19, 930 (1954).
[22] C. G. Overberger, L. C. Palmer, B. S. Marks and N. R. Byrd, *J. Amer. Chem. Soc.* 77, 4100 (1955).

This simple method of determination of configuration should be applicable, in principle, to any symmetrically disubstituted heterocyclic base. The substituents should be such that the ring methine and methylene proton absorption does not overlap with the N—CH_2—X methylene region. A series of *trans*-3,4-disubstituted pyrrolidines (VI) was examined, but gave disappointing results; the N-benzyl methylene



VI a. R = CH_3
b. R = C_2H_5
c. R = C_6H_5

showed no signs of splitting (Table 1). Apparently, the asymmetry at the β-carbon atoms is too far removed from the benzylic methylene protons to perturb their magnetic environment. It has previously been observed that stereochemically non-equivalent protons may fail to show observable magnetic non-equivalence, and that the phenomenon may be solvent-dependent.[18] Only a positive observation of the AB quartet pattern of the methylene protons can establish their proximity to a dissymmetric grouping.

TABLE 1. BENZYLIC METHYLENE PROTON MAGNETIC RESONANCE SPECTRA

Compound	Solvent	τ	J (c/s)	$\Delta\nu$* (c/s)	Half-width† (c/s)
II	CCl_4	6·37	14·4	31·3	
III	CCl_4	6·30	—	—	
IV	CCl_4	6·59	—	—	
V	CCl_4	6·59	13·2	21·3	
VIa	CCl_4	6·49			1·5
	C_6H_6	6·50			1·8
VIb	CCl_4	6·41			1·5
	C_6H_6	6·41			1·5
	CS_2	6·62			1·8
	$C_6H_5NO_2$	6·46			1·7
	C_5H_5N	6·52			1·6
	$(CH_3)_2SO$	6·56			1·8
VIc	C_5H_5N	5·42			2·6
	CH_3CN	5·79			4·0
	$C_6H_5NO_2$	5·17			5·3

* Relative chemical shift of the methylene protons.

† Line width measured at half-height of the band. In all cases, line-width of the reference $(CH_3)_4Si$ band is between 1·2–1·5 c/s.

EXPERIMENTAL[23]

cis- *and* trans-N-*Benzyl*-2,6-*dimethylpiperidines* (II *and* III). The *cis* and *trans* isomers of 2,6-dimethylpiperidine were prepared by Na–EtOH reduction of 2,6-lutidine.[4] The preparation of the N-benzyl derivatives has been described elsewhere.[10]

cis- *and* trans-2,5-*Dimethylpyrrolidine*. A mixture of *cis*- and *trans*-1-amino-2,5-dimethylpyrrolidine was synthesized by the method of Overberger *et al.*[22] and separated by distillation through a spinning

[23] M.ps were determined in capillaries, and are uncorrected. NMR spectra were measured on a Varian A-60 spectrometer, with tetramethylsilane as an internal standard.

band column into the two isomers: *cis*, b.p. 42° (19 mm), picrate m.p. 155–156° (reported b.p. 60–61° (40 mm), picrate m.p. 154–156°); *trans*, b.p. 54° (19 mm), picrate m.p. 165–166° (reported b.p. 56° (20 mm), picrate m.p. 162–164°). Catalytic hydrogenolysis of the 1-amino compounds, again following the procedure of Overberger,[23] gave the corresponding dimethylpyrrolidines, isolated as their hydrochlorides.

cis-2,5-Dimethylpyrrolidine hydrochloride had m.p. 202–203° (from EtOH–ether). (Found: C, 52·86; H, 10·34; N, 10·30; Cl, 26·38. Calc. for $C_6H_{14}NCl$: C, 53·13; H, 10·40; N, 10·33; Cl, 26·14%.)

The *picrate* was prepared from the hydrochloride and melted at 116–118° after recrystallization from benzene (reported m.p.[24] 117–118°; m.p.[25] 120–121°).

trans-2,5-Dimethylpyrrolidine hydrochloride, after recrystallization from EtOH–ether, m.p. 187–188°. (Found: C, 52·83; H, 10·48; N, 10·36%.)

The *picrate*, prepared from the hydrochloride, melted at 126–127° (lit.[25] m.p. 130–131°) after recrystallization from benzene.

N-*Benzoyl*-cis-2,5-*dimethylpyrrolidine*. This was prepared by benzoylation of the *cis* amine hydrochloride with benzoyl chloride and NaOH aq. The colourless oil failed to crystallize and was purified by chromatography over alumina. (Found: C, 76·68; H, 8·66; N, 7·14. Calc. for $C_{13}H_{17}NO$: C, 76·81; H, 8·43; N, 6·89%.)

N-*Benzoyl*-trans-2,5-*dimethylpyrrolidine*. Prepared as described for the *cis* isomer, m.p. 85–86°. (Found: C, 76·81; H, 8·48; N, 6·81%.)

N-*Benzyl*-cis-2,5-*dimethylpyrrolidine* (IV). The base was prepared by LAH reduction of the benzoyl compound in ether. The *hydrochloride*, m.p. 196–197° was recrystallized from ethyl acetate. (Found: N, 6·10. Calc. for $C_{13}H_{20}NCl$: N, 6·20%.)

The *picrate* melted at 108–110° (ethanol–water). (Found: C, 54·68; H, 5·44; N, 13·56. Calc. for $C_{19}H_{22}N_4O_7$: C, 54·54; H, 5·30; N, 13·39%.)

N-*Benzyl*-trans-2,5-*dimethylpyrrolidine* (V). Prepared in the same manner as the *cis* compound; the *hydrochloride*, m.p. 152–153° after recrystallization from ethyl acetate. (Found: N, 6·00%.)

The *picrate* melted at 129–130° (ethanol–water). (Found: C, 54·54; H, 5·49; N, 13·16%.)

N-*Benzyl*-trans-3,4-*dimethylpyrrolidine* (VIa). The base was prepared in the same manner as described above, by LAH reduction of the N-benzoyl derivative of *trans*-3,4-dimethylpyrrolidine.[25] The *reineckate* was recrystallized twice from dil. EtOH, m.p. 149° (dec). (Found: C, 40·12; H, 5·29; Cr, 10·77. Calc. for $C_{17}H_{26}N_7S_4Cr$: C, 40·13; H, 5·15; Cr, 10·23%.)

N-*Benzyl*-trans-3,4-*diethyl-pyrrolidione*-2,5. A solution of racemic α,β-diethylsuccinic acid[26] (10 g) in 25 ml benzylamine was refluxed for 30 min, then distilled. The imide (10 g) was collected at 329–332°, and purified by redistillation, b.p. 164° (3·5 mm). (Found: C, 73·44; H, 7·85; N, 5·80. Calc. for $C_{15}H_{19}NO_2$: C, 73·44; H, 7·81; N, 5·71%.)

N-*Benzyl*-trans-3,4-*diethylpyrrolidine* (VIb). The base was prepared from the above imide by reduction with LAH in ether. The *reineckate* melted at 112–114° (dec) after two recrystallizations from dil. EtOH. (Found: C, 41·96; H, 5·81; Cr, 9·82. Calc. for $C_{19}H_{30}N_7S_4Cr$: C, 42·51; H, 5·63; Cr, 9·69%.)

N-*Benzyl*-3,4-*diphenylpyrrolidine*[27] (VIc) was kindly supplied by Dr. N. Sperber of the Schering Corporation.

[24] A. P. Terent'ev and M. A. Volodina, *Dokl. Akad. Nauk, S.S.S.R.* **88**, 845 (1953); *Chem. Abstr.* **48**, 3338 (1954).

[25] G. E. McCasland and S. Proskow, *J. Amer. Chem. Soc.* **76**, 6087 (1954). We are indebted to Prof. McCasland for kindly furnishing us with samples of the *cis* and *trans*-amines.

[26] E. Berner and R. Leonardsen, *Liebigs Ann.* **538**, 1 (1939).

[27] F. J. Villiani and N. Sperber, U.S. Patent 2,852,526; *Chem. Abstr.* **53**, 8164 (1959). Its stereochemistry is unspecified.