

## MAGNETIC NON-EQUIVALENCE OF METHYLENE PROTONS IN DISSYMMETRIC BENZYLAMINES

### A SIMPLE METHOD OF ASSIGNMENT OF CONFIGURATION TO IDENTICALLY $\alpha, \alpha'$ -DISUBSTITUTED HETEROCYCLIC BASES<sup>1</sup>

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**Abstract**—As a result of the lack of a plane of symmetry in identically  $\alpha, \alpha'$ -*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  $\alpha, \alpha'$ -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,<sup>4</sup> 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,<sup>5</sup> and the resulting possibility of obtaining *trans* isomers as major products.<sup>6</sup>

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<sup>7</sup> and 1,3-cyclohexanedialkanoic acids,<sup>8</sup> assignment is predicted on the ready chair-chair interconversion of the *trans* isomer, rapidly averaging axial and equatorial protons to give a spectrum

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<sup>4</sup> A. Marcuse and R. Wolfenstein, *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.

<sup>5</sup> S. Siegel and B. Dmuhovsky, *J. Amer. Chem. Soc.* **84**, 3132 (1962); S. Siegel, G. V. Smith, B. Dmuhovsky, D. Dubbell and W. Halpern, *Ibid.* 3136; G. V. Smith and R. L. Burwell, Jr., *Ibid.* 925.

<sup>6</sup> J. F. Sauvage, R. H. Baker and A. S. Hussey, *J. Amer. Chem. Soc.* **83**, 3874 (1961); S. Siegel and B. Dmuhovsky, *Ibid.* **86**, 2192 (1964).

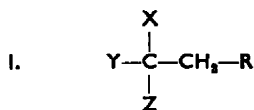
<sup>7</sup> H. Finegold and H. Kwart, *J. Org. Chem.* **27**, 2361 (1962).

<sup>8</sup> 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,<sup>9</sup> 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 pini-dine,<sup>10</sup> 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.<sup>11</sup> 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,<sup>11</sup> though it has subsequently been observed in cases in which there appears no obvious barrier to rotation,<sup>12</sup> 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.<sup>13,14</sup> Nevertheless, it has continued to be a valuable tool in the recognition of a methylene group attached to an asymmetric carbon.<sup>15</sup>



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,<sup>16</sup> sulphoxides,<sup>13,17</sup> hindered biphenyls<sup>18,19</sup> and a substituted cyclooctatetraene.<sup>20</sup>

<sup>9</sup> N. Muller and W. C. Tosch, *J. Chem. Phys.* **37**, 1167 (1962).

<sup>10</sup> R. K. Hill, T. H. Chan and J. A. Joule, *Tetrahedron* **21**, 147 (1965).

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

<sup>12</sup> 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).

<sup>13</sup> J. S. Waugh and F. A. Cotton, *J. Phys. Chem.* **65**, 562 (1961).

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

<sup>15</sup> 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).

<sup>16</sup> H. S. Finegold, *Proc. Chem. Soc.* 283 (1960).

<sup>17</sup> 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).

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

<sup>19</sup> W. L. Meyer and R. B. Meyer, *J. Amer. Chem. Soc.* **85**, 2170 (1963).

<sup>20</sup> F. A. L. Anet, A. J. R. Bourn and Y. S. Lin, *J. Amer. Chem. Soc.* **86**, 3576 (1964).

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