

## A Nuclear Magnetic Resonance Study of the Cyclohexane Ring Conformation in Selectively Deuterated Cis Isomers of 2-Piperidino- $\alpha$ -(*p*-methoxyphenyl)cyclohexanemethanol

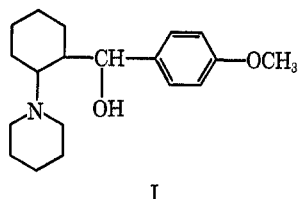
B. VERNON CHENEY\* AND LOUIS L. SKALETZKY

*Research Laboratories of The Upjohn Company, Kalamazoo, Michigan 49001*

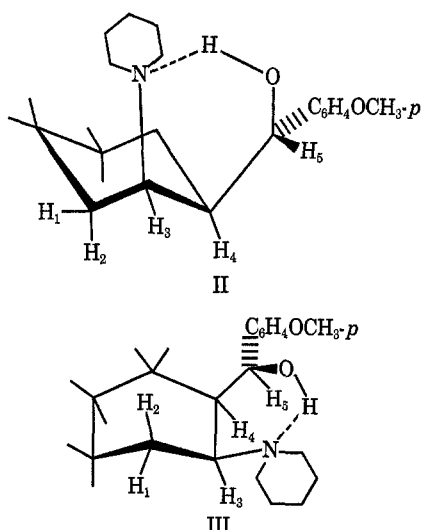
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Selectively deuterated samples of the two cis isomers of 2-piperidino- $\alpha$ -(*p*-methoxyphenyl)cyclohexanemethanol have been synthesized to allow nmr investigation of the cyclohexane ring conformation. Isotopic substitution was effected at all positions in the piperidine ring and at carbons 4–6 of the cyclohexane ring in each compound. The four remaining hydrogens on the cyclohexane ring and the side-chain carbinol hydrogen give rise to spectral bands which may be analyzed as a five-spin system using standard computer techniques. The nmr chemical shifts and proton-proton coupling constants are found to be consistent with a chair form of the ring in both cis isomers although the isomer with an axial piperidino group appears to have a somewhat flattened ring as a result of steric interactions. Differential line-broadening effects of HD couplings on ring protons in the axial *vs.* equatorial position proved to be useful in making spectral assignments and determining conformational features of the cyclohexane ring.

In an earlier paper,<sup>1</sup> Szmuszkovicz and Skaletzky reported the synthesis and stereochemical analysis of the four racemates of 2-piperidino- $\alpha$ -(*p*-methoxyphenyl)cyclohexanemethanol (I). The relative con-



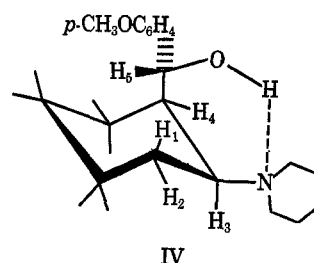
figuration and conformation of three of these alcohols were established in detail by means of various chemical transformations and spectroscopic techniques. However, in the cis-substituted cyclohexane with threo configuration of the side chain with respect to adjacent carbon (designated hereafter as *cis-A*), the conformation of the cyclohexane ring may be either a chair with an axial piperidine (II) or a twist-boat with piperidine pseudoequatorial (III). Both II and III are consistent



with the observed data which suggest a molecule with fixed conformation due to intramolecular hydrogen

bonding.<sup>2</sup> However, each structure exhibits certain unfavorable steric features that detract from the stabilizing effect of the internal hydrogen bond. The strain associated with an axial piperidine in II is expected to be considerable. While structure III permits this bulky substituent to assume a pseudoequatorial position, the cyclohexane ring takes a less advantageous skew conformation and the large groups attached to the ring tend to eclipse one another. As the evidence presented in ref 1 is in agreement with either II or III and there is some difficulty in accurately estimating the relative steric repulsions in the two systems, the present work was undertaken to investigate the cyclohexane ring conformation using more intensive nmr techniques.

Structure IV was suggested in ref 1 as the probable



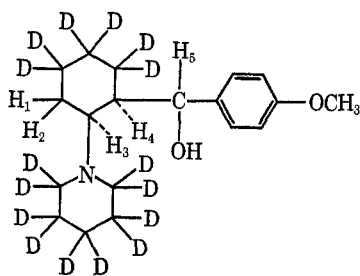
conformation of the cis isomer (*cis-B*) with erythro configuration. The ir and nmr spectra of this compound exhibit features which indicate that intramolecular hydrogen bonding imposes conformational stability in the system. Although there is a large axial substituent on the cyclohexane ring in IV which appears rather disadvantageous, steric interference between the *p*-methoxyphenyl and cyclohexane ring hydrogens is not serious. In addition, the equatorial orientation of the piperidine ring contributes greatly to the stability of the structure. For these reasons the conclusions of Szmuszkovicz and Skaletzky regarding the geometry of *cis-B* are not con-

(1) J. Szmuszkovicz and L. L. Skaletzky, *J. Org. Chem.*, **32**, 3300 (1967); see also L. L. Skaletzky, B. E. Graham, and J. Szmuszkovicz, *J. Med. Chem.*, **12**, 977 (1969).

(2) In the nmr spectrum of the compound in CDCl<sub>3</sub> solution, the OH peak is highly deshielded ( $\delta$  7.3-ppm downfield from TMS). Furthermore, infrared measurements in carbon disulfide show hydrogen-bonded hydroxyl down to infinite dilution. Thus, it may be concluded that the hydroxyl is intramolecularly hydrogen bonded to the piperidine nitrogen. Additional nmr evidence for an immobile molecular system is provided by the resonance signal of the carbinol proton (>CH\*-OH) which appears as a broad singlet in the 60-MHz spectrum of the alcohol. Since this indicates negligible coupling with the vicinal proton on the cyclohexane ring, a fixed dihedral angle of approximately 90° is predicted. Models II and III are both in accord with these observations (see ref 1 for more complete discussion).

sidered to be in doubt. However, further nmr analysis of this molecule is felt to be desirable for purposes of comparison with the results for *cis*-A.

A complete interpretation of the nmr spectrum, yielding the chemical shifts and coupling constants of all protons, would be desirable to minimize the likelihood of error in making correlations with structural features of the molecule. Unfortunately, hydrogens in the cyclohexane and piperidine rings of I give rise to broad overlapping bands which reveal little detailed line structure. Hence, there is no way to make a full analysis using presently available techniques. Since selective deuteration<sup>3-8</sup> has been used successfully in the past to simplify spectra by eliminating masking signals of protons of lesser interest, model compounds (V) of the two *cis* piperidino alcohols were synthesized in which 16 of the 20 hydrogens in the cyclohexane and piperidine rings are replaced by deuterium. In each



V

compound, the four remaining hydrogens in the cyclohexane ring and the carbinol hydrogen in the side chain give rise to spectral bands which may be analyzed as a five-spin system using standard computer techniques.<sup>9</sup> Although the existence of HD couplings is a potential source of complication in the proton resonance patterns, the small magnitude of such interactions often leads to little more than apparent line broadening so that adverse effects are minimal.<sup>10</sup> It should be noted that the effects of the HD couplings may provide useful information pertaining to the geometry of the system.

**Spectral Analysis.**—The regions of interest in the 100-MHz spectra of *cis*-A and *cis*-B are shown in the upper traces of Figures 1 and 2, respectively. In both spectra the signal of the carbinol proton ( $H_5$  in structure V) appears as a doublet approximately 5-ppm downfield from the TMS reference. Since the multiplet at  $\delta$  2.95 in Figure 1 appears in a position characteristic of an alkyl CH group bonded to an amine nitrogen, it can be ascribed to  $H_3$ . The remaining bands in the two spectra cannot be assigned with confidence by direct inspection. Hence, spin decoupling experiments were utilized to determine the assignments of the upfield signals. For example, in the spectrum of *cis*-A, ir-

radiation of  $H_5$  at 5.0 causes the multiplet at 1.56 to collapse into a broad doublet, thus indicating the position of  $H_4$ . A similar experiment with *cis*-B reveals that the pattern centered at 2.27 corresponds to  $H_4$ . With this information, the six-peak multiplet at 2.49 in Figure 2 can be assigned to  $H_3$ . The geminal hydrogens,  $H_1$  and  $H_2$ , give rise to the remaining signals in the two spectra. A sizable chemical shift difference between  $H_1$  and  $H_2$  is evident in the curve for *cis*-A, but the difference is much less in the spectrum of *cis*-B.

Using approximate chemical shifts and coupling constants obtained by inspection as initial data, a series of calculations were performed with the LAOCN3<sup>11</sup> computer program in order to produce refined values. After each computation, a plot of the theoretical spectrum was compared to the experimental curve and appropriate changes in the shifts, couplings, and line widths were made to improve the fit. Although HD couplings were not explicitly included in the calculations, adjustment of line widths compensated to a large extent for the observed effects of such interactions on the spectral bands of  $H_1$ ,  $H_2$ , and  $H_4$ . Since some of the HD splittings are partially resolved, a few slight discrepancies between the observed and calculated band shapes may be noted in Figures 1 and 2. However, the overall agreement is quite good. A list of the final nmr parameters for the two molecules is given in Table I.

TABLE I  
PROTON MAGNETIC RESONANCE DATA

Hydrogens	Chemical shifts <sup>a</sup>	Apparent line widths <sup>b</sup>	Coupling constants <sup>c,d</sup>
<i>cis</i> -A			
$H_1$	2.09	1.3	$J_{12} = -14.8$ $J_{18} = 2.0$
$H_2$	1.40	3.0	$J_{23} = 5.7$
$H_3$	2.95	0.9	$J_{34} = 4.8$
$H_4$	1.56	2.3	$J_{45} = 2.0$
$H_5$	5.00	2.0	
<i>cis</i> -B			
$H_1$	1.76	3.4	$J_{12} = -12.2$ $J_{18} = 12.3$
$H_2$	1.91	2.0	$J_{23} = 3.5$ $J_{24} = 1.0$
$H_3$	2.49	1.6	$J_{34} = 3.6$
$H_4$	2.27	2.0	$J_{45} = 10.0$
$H_5$	4.98	1.8	

<sup>a</sup> Measured in parts per million (ppm) downfield from TMS. The estimated error in the values is  $\pm 0.01$  ppm. <sup>b</sup> The values given are the theoretical line widths at half height (measured in hertz) which yield the best visual agreement with observed peak intensities. <sup>c</sup> Measured in hertz with an estimated error of  $\pm 0.1$  Hz. <sup>d</sup> In compound *cis*-A, the relative signs of  $J_{12}$ ,  $J_{18}$ , and  $J_{23}$  were established by the spin tickling method of Friedman and Gutowsky [*J. Chem. Phys.*, **45**, 3158 (1966)]. The geminal coupling was assumed to be negative in accordance with previous studies of saturated alkanes (see J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Vol. 2, Pergamon Press, New York, N. Y., 1966, pp 677-683). Generally accepted signs were chosen for compound *cis*-B.

## Discussion

Successful correlations between proton-proton coupling constants,  $J_{HH'}$ , in the system HCC'H' and

(11) S. Castellano and A. A. Bothner-By, *J. Chem. Phys.*, **41**, 3863 (1964); LAOCN3, Mellon Institute, Pittsburgh, Pa., 1966.

(3) F. A. L. Anet, *J. Amer. Chem. Soc.*, **84**, 1053 (1962).

(4) A. H. Lewin and S. Winstein, *ibid.*, **84**, 2464 (1962).

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

(6) F. A. L. Anet, M. Ahmad, and L. D. Hall, *Proc. Chem. Soc., London*, 145 (1964).

(7) E. Premuzic and L. W. Reeves, *J. Chem. Soc. (London)*, 4817 (1964).

(8) E. W. Garbisch, Jr., and M. G. Griffith, *J. Amer. Chem. Soc.*, **90**, 6543 (1968).

(9) J. D. Swalen, *Progr. Nucl. Magn. Resonance Spectrosc.*, **1**, 205 (1966).

(10) Although the effects of HD couplings may be removed by double irradiation, this technique was not employed in the present case because of a lack of the necessary heteronuclear decoupling equipment.

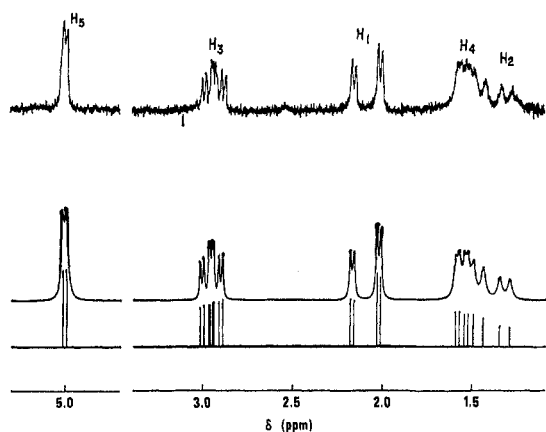


Figure 1.—Upper trace: 100-MHz spectrum of partially deuterated *cis*-A in 0.01 *M* CDCl<sub>3</sub> solution. Lower trace: plot of calculated spectrum with adjusted line widths to compensate for broadening effects of HD interactions.

dihedral angles,  $\phi_{HH'}$ , have often been made using relationships of the form<sup>12</sup>

$$J_{HH'}^{\text{vic}} = A \cos^2 \phi_{HH'} + B \cos \phi_{HH'} \quad (1)$$

where the coefficients  $A$  and  $B$  depend upon the CC separation, the CCH bond angles, and the ionic effects of other substituents on the carbons.<sup>13</sup> Relative differences in bond lengths and bond angles in the cyclohexane rings of the two *cis* isomers under consideration are expected to be minimal on account of the constraints of the cyclic system. However, previous studies<sup>14–16</sup> have indicated that changing the positions of bulky ring substituents does alter the ring geometry somewhat causing differences in the coefficients  $A$  and  $B$  of eq 1. The resultant uncertainty in predicting dihedral angles from observed vicinal couplings is roughly  $\pm 20\%$ . Nevertheless, eq 1 provides a useful basis from which to draw qualitative conclusions regarding ring geometry. For the purpose of making order-of-magnitude comparisons, consider the relationship with  $A = 13$  Hz and  $B = 0$  which are similar to the coefficients given by Garbisch and Griffith<sup>8</sup> for cyclohexane. If distortions of the ring from a perfect chair form are neglected, we obtain the following possible vicinal coupling constants between protons in various ring configurations:  $J_{aa} = 13$  Hz and  $J_{ae} = J_{ee} = 3.2$  Hz. For a perfect boat form, the vicinal proton–proton couplings are  $J_{aa'} = J_{a'a'} = J_{e'e'} = 13$  Hz and  $J_{ae'} = J_{ae} = J_{ee'} = J_{a'e'} = 3.2$  Hz, where  $a$  denotes the flag hydrogen,  $e$  the bowsprit,  $a'$  indicates a pseudoaxial hydrogen, and  $e'$  a pseudoequatorial hydrogen. Although the eclipsed interactions associated with the boat form make this conformation highly unlikely, some twisting of the ring would reduce the repulsions considerably. The flexible nature of the boat form allows such skewing without undue distortion of bond lengths and angles in the ring. Variations in the vicinal coupling constants due to deviations of the dihedral angles from those of a perfect boat conformation may be predicted qualitatively using eq 1.

(12) M. Barfield and D. M. Grant, *Advan. Magn. Resonance*, **1**, 149 (1965).

(13) M. Karplus, *J. Amer. Chem. Soc.*, **85**, 2870 (1963).

(14) R. U. Lemieux and J. W. Lown, *Tetrahedron Lett.*, 1229 (1963).

(15) F. A. L. Anet, R. A. B. Bannard, and L. O. Hall, *Can. J. Chem.*, **41**, 2331 (1963).

(16) F. A. L. Anet, *J. Amer. Chem. Soc.*, **84**, 1053 (1962).

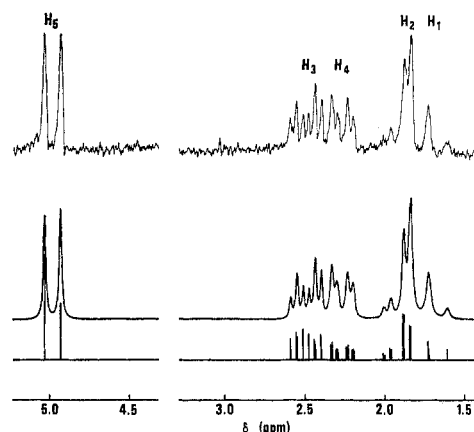


Figure 2.—Upper trace: time-averaged 100-MHz spectrum of partially deuterated *cis*-B in 0.001 *M* CDCl<sub>3</sub> solution. The spectrum was drawn after 265 scans on the Varian C-1024 CAT. Lower trace: plot of calculated spectrum with adjusted line widths to compensate for effects of HD couplings.

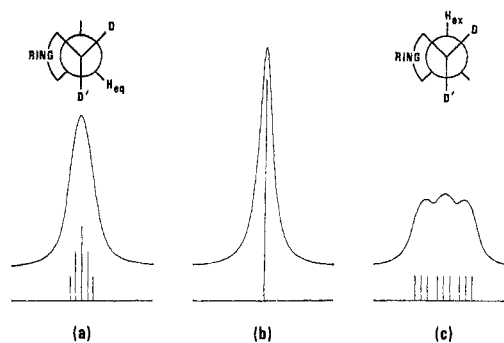


Figure 3.—Schematic representations of first-order perturbing effects of an adjacent CD<sub>2</sub> group on a proton spectral line when (a) H is equatorial in the cyclohexane ring, (b) the HD interactions are decoupled by irradiating the deuterium nuclei, and (c) H is axial.

The effects of the vicinal proton–deuterium coupling constants also provide a source of conformational data. It is possible to estimate the magnitude of  $J_{HD}^{\text{vic}}$  from the coupling  $J_{HH'}^{\text{vic}}$  in the corresponding system where H' replaces D by using the expression

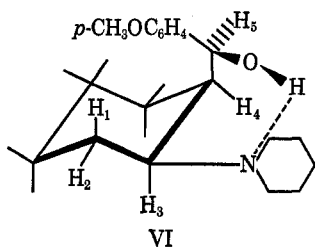
$$J_{HD}^{\text{vic}} = \frac{\gamma_D}{\gamma_H} J_{HH'}^{\text{vic}} = 0.1535 J_{HH'}^{\text{vic}} \quad (2)$$

where  $\gamma_D$  and  $\gamma_H$  are the respective magnetogyric ratios of the isotopes. As  $\gamma_D$  is less than one-sixth of  $\gamma_H$ , the splittings due to vicinal deuterium atoms in a saturated molecule generally will be no more than 2 Hz. This fact, combined with complex resonance patterns resulting from the deuterium magnetic quantum number  $I_D = 1$ , often leads to unresolved splittings and apparent line broadening in the proton spectrum. As shown in the schematic drawings of Figure 3, the effect of an adjacent CD<sub>2</sub> group on the spectral lines of a given hydrogen depends greatly on the position of the hydrogen. Although the HD couplings lead to significant line broadening when H is equatorial, an even wider pattern with some resolution of the component lines may result if H is axial. The apparent line widths of H<sub>1</sub>, H<sub>2</sub>, and H<sub>4</sub> in the partially deuterated *cis* piperidino alcohols clearly show these effects.

It is of interest to examine the experimental nmr data for compound *cis*-B in light of the foregoing observations. H<sub>3</sub> experiences one large axial–axial cou-

pling and two smaller axial-equatorial interactions in accord with the requirements of structure IV. Furthermore, the signals corresponding to the axial  $H_1$  are  $\sim 1.4$ -Hz wider than those of the equatorial hydrogens,  $H_2$  and  $H_4$ . The signals of  $H_3$  and  $H_5$ , which experience no significant HD coupling, are much narrower as expected. An interesting item is the existence of long-range coupling between the equatorial hydrogens  $H_2$  and  $H_4$  in agreement with previous observations on various saturated six-membered-ring compounds.<sup>17</sup> The observed value of  $J_{45}$  is also consistent with IV in that it could correspond to a dihedral angle  $\phi_{45} \approx 150^\circ$ , thus facilitating formation of an internal hydrogen bond between the hydroxyl group and the piperidino nitrogen.

The vicinal couplings exhibited by  $H_3$  in compound *cis*-A do not agree well with the theoretical values for either a perfect chair or a boat conformation of the cyclohexane ring. A possible explanation for the disagreement could be the existence of an equilibrium between II and its inverted isomer VI. However, there



is an axial-axial relationship between  $H_1$  and  $H_3$  in VI which would contribute a sizable amount to the observed value of  $J_{13}$  if this isomer were present to a significant degree. Since the actual value of  $J_{13}$  is much too small in *cis*-A to allow for any contribution from VI, it is concluded that the presence of this structure may be discounted.<sup>18</sup> As the foregoing explanation for the disagreement must be discarded, it might be argued that the assumed magnitudes of the terms  $A$  and  $B$  used in eq 1 to obtain the theoretical couplings are exceptionally poor for this case. However, the relation yields satisfactory correlations for compound *cis*-B and severe distortions of the cyclohexane ring in *cis*-A would be required to alter the values of  $A$  and  $B$  sufficiently to produce the observed shifts. Hence, it is felt that the coupling constants mainly reflect changes in the dihedral angles resulting from a slight cyclohexane ring deformation.

One possibility that may be ruled out is a twist-boat conformation similar to that of structure III with  $H_1$  as bowsprit,  $H_2$  in the flag position, and the remaining ring hydrogens,  $H_3$  and  $H_4$ , in pseudoaxial positions. The fact that  $J_{23}$  and  $J_{34}$  are larger than  $J_{13}$  is consistent with this assignment. In order to obtain theoretical couplings of the magnitude observed, eq 1 requires dihedral angles of the order  $\phi_{13} \approx 70^\circ$ ,  $\phi_{23} \approx 130^\circ$ , and  $\phi_{34} \approx 50^\circ$ . However, these angles are not mutually compatible since pseudorotation of the boat in a direction which yields qualitatively correct values for  $\phi_{23}$  and  $\phi_{34}$  simultaneously gives  $\phi_{13} \approx 10^\circ$  ( $J_{13} \approx 12.7$  Hz).

(17) A. Rassat, C. W. Jefford, J. M. Lehn, and B. Waegell, *Tetrahedron Lett.*, No. 5, 233 (1964).

(18) This is in agreement with the conclusions given in ref 1 which eliminated structure VI on the basis of severe steric interactions between the aromatic and cyclohexane rings.

Furthermore, the pseudorotation would almost restore the ring to a perfect boat with the piperidino group in pseudoaxial position which is indeed a highly unfavorable arrangement. As a second possibility, the cyclohexane ring could assume a slightly distorted chair conformation appearing much like structure II. With this arrangement  $H_1$  and  $H_3$  are designated as equatorial hydrogens while  $H_2$  and  $H_4$  are assigned to axial positions. In this case, the approximate dihedral angles predicted by eq 1 would be  $\phi_{13} \approx 70^\circ$ ,  $\phi_{23} \approx 50^\circ$ , and  $\phi_{34} \approx 50^\circ$ . These angles correspond well with the results expected for a flattened chair in which the stress associated with an axial piperidino group has been relieved somewhat by tipping the group away from the ring center. The value of  $J_{45}$  does not appear to be of consequence in deciding between the two possible *cis*-A structures. It corresponds to a dihedral angle,  $\phi_{45} \approx 70^\circ$ , which permits formation of an internal hydrogen bond in both cases.

A summary of the conclusions drawn from the vicinal coupling data is given in Table II. Omitted from the

TABLE II  
RELATIONSHIPS BETWEEN VICINAL COUPLING  
CONSTANTS AND MOLECULAR GEOMETRY IN *cis*-A AND *cis*-B

Compd	H,H'	$J_{HH'}^{vic}$ , Hz	$\phi_{HH'}$ , <sup>a</sup> degrees	Con- figuration	Suggested cyclohexane ring conformation
<i>cis</i> -A	$H_1, H_3$	2.0	70	ee	Slightly flat- tened chair
	$H_2, H_3$	5.7	50	ae	
	$H_3, H_4$	4.8	50	ea	
	$H_4, H_5$	2.0	70	Gauche	
<i>cis</i> -B	$H_1, H_3$	12.3	170	aa	Chair
	$H_2, H_3$	3.5	60	ea	
	$H_3, H_4$	3.6	60	ae	
	$H_4, H_5$	10.0	150	Trans	

<sup>a</sup> In accordance with the approximate nature of eq 1, the dihedral angles are given to the nearest  $10^\circ$  for the purpose of indicating orders of magnitude. Although there are two possible angles for each coupling, only those combinations consistent with the geometric requirements of cyclohexane ring are reported.

table are those sets of dihedral angles which correspond to boat forms of the cyclohexane ring with bulky substituents in flag or pseudoaxial positions. Such structures are considered highly unlikely on steric grounds. Although the vicinal proton-proton coupling constants seem to be in accord with a flattened chair conformation for the *cis*-A ring, the approximate nature of the correlation makes it imperative to investigate the remaining nmr data for corroborative or contradictory evidence.

In compound *cis*-A, the signals of  $H_1$ ,  $H_2$ , and  $H_4$  display the expected line-broadening effects of HD coupling. The relative line widths are also consistent with the assigned configurations of the three hydrogens in the deformed chair structure. It is interesting to note that the line widths in the  $H_2$  multiplet are considerably broader than the lines of the other axial hydrogen  $H_4$  while the equatorial  $H_1$  signals are surprisingly narrow. These data suggest that the HD dihedral angles are reflecting the changes associated with flattening of the cyclohexane ring.

According to Pople and Bothner-By,<sup>19</sup> the magnitude of the geminal coupling constant in a methylene group is sensitive to the relative configuration of an electronegative substituent, X, on an adjacent carbon. The

(19) J. A. Pople and A. A. Bothner-By, *J. Chem. Phys.*, **42**, 1330 (1965).

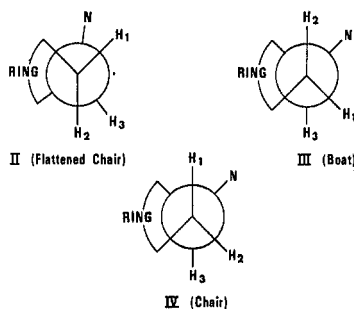


Figure 4.—Relative configurations of  $H_1$ ,  $H_2$ ,  $H_3$ , and  $N$  in structures II, III, and IV. The projection view in each case is down the bond connecting the carbon on which  $H_1$  and  $H_2$  are located with the carbon to which  $H_3$  and the piperidino group are attached.

theory predicts an algebraic decrease in  $J_{HH}^{gem}$  when the electron-withdrawing atom or group is trans to one of the  $CH_2$  hydrogens. If both hydrogens are gauche to X, a small positive contribution to the geminal coupling is expected. It is, therefore, possible to qualitatively account for the observed 2.5-Hz difference in  $J_{12}$  between compounds *cis-A* and *cis-B* on the basis of the relative configurations of  $H_1$ ,  $H_2$ , and the piperidino nitrogen. The diagrams of Figure 4 show that  $H_1$  and  $H_2$  are both gauche to  $N$  in structures III and IV. Hence, if *cis-A* were similar to III, the experimental value for  $J_{12}$  would be expected to differ negligibly from the corresponding coupling in *cis-B*. It is noted that  $H_2$  and  $N$  would be nearly trans in the flattened chair. As this would give rise to a negative contribution to  $J_{12}$ , the observed difference in the geminal couplings follows from the theory and gives additional support to the proposal that *cis-A* has structure II.<sup>20</sup>

In the absence of shielding effects from sources external to the cyclohexane ring, it has been found that axial hydrogens exhibit resonance signals approximately 0.5-ppm upfield from equatorial hydrogens if the ring adopts the chair form and does not undergo rapid conformational interconversion.<sup>21</sup> With substituted cyclohexanes, the relative shifts of the ring hydrogens may be greatly altered or even reversed by the magnetic shielding effects of the attached groups. In both *cis-A* and *cis-B*, the ring substituents should give rise to significant shifts as a result of electronegativity differences, magnetic anisotropy, and steric interactions. In order to determine whether the chemical shifts of ring hydrogens in *cis-A* exhibit unusual features not in accord with the proposed structure II, the resonance position of each hydrogen may be compared with that of its identically numbered, but oppositely oriented, counterpart in *cis-B*. The resulting chemical shift differences listed in Table III demonstrate in every case that the equatorial hydrogen resonates at lower field than the corresponding axial hydrogen. However, the wide variation in the quantity  $\delta_e - \delta_a$  indicates that the ring substituents do exert significant long-range shielding effects in the two compounds. Nevertheless, the observed chemical shifts are quite compatible with the proposed structure II for compound *cis-A*.

(20) Widening of the C-CH<sub>2</sub>-C angle in the cyclohexane ring also yields a negative contribution to  $J_{12}$  [see R. Cahill, R. C. Cookson, and T. A. Crabb, *Tetrahedron*, **25**, 4711 (1969)]. A slight widening of this angle should accompany flattening of the cyclohexane ring.

(21) F. A. Bovey, F. P. Hood, E. W. Anderson, and R. L. Kornegay, *Proc. Chem. Soc.*, 418 (1964).

TABLE III  
COMPARISON OF CHEMICAL SHIFTS EXHIBITED BY  
CORRESPONDING RING HYDROGENS  
IN *cis-A* AND *cis-B*

Hydrogen	—Ring configuration—		$\delta_e - \delta_a$ , ppm
	II	IV	
$H_1$	e	a	0.33
$H_2$	a	e	0.51
$H_3$	e	a	0.46
$H_4$	a	e	0.71

In summary, analysis of the nmr data obtained from the selectively deuterated *cis* 1,3-piperidino alcohols (V) leads to the conclusion that the cyclohexane ring possesses a chair conformation in both isomers. The evidence best fits a slightly flattened chair for compound *cis-A* in which the bulky piperidino group assumes an axial position.<sup>22</sup>

### Experimental Section

The synthesis of the deuterated *cis-A* and *cis-B* isomers V was based on the previously described preparation of this class of compound.<sup>1</sup>

2-(*p*-Methoxybenzoyl)cyclohexanone-3,3,4,4,5,5-*d*<sub>6</sub>.—Cyclohexanone-3,3,4,4,5,5-*d*<sub>6</sub> was synthesized from cyclohexanone-*d*<sub>10</sub> (Merck and Co.) in a manner analogous to that described by Anet<sup>23</sup> for the preparation of cyclohexanone-2,2,6,6-*d*<sub>4</sub>. The presence of a molecular ion at *m/e* 104 confirmed the isotopic composition.

The pyrrolidine enamine of cyclohexanone-3,3,4,4,5,5-*d*<sub>6</sub> was prepared from 0.5 g (0.0048 mol) of cyclohexanone-3,3,4,4,5,5-*d*<sub>6</sub> and 2 g of distilled pyrrolidine in 100 ml of dry benzene at reflux for 2 hr using a Soxhlet with an extraction thimble containing 10 g of Linde Molecular Sieves No. 4A. The benzene was evaporated and the oil residue dissolved in 16 ml of chloroform (purified by passage through Woelm neutral alumina, activity I).

A solution of 0.86 g (0.00504 mol) of *p*-anisoyl chloride in 1 ml of purified chloroform was added over 4 min to the above chloroform solution and 0.5 g (0.00495 mol) of distilled triethylamine in a nitrogen atmosphere at 0–5°. The reaction was stirred for 1 hr at 0–10° and then for 16 hr at room temperature. Work-up in the usual way gave 0.439 g (38.5%) of the keto-enol forms, mp 64–80°. In a subsequent run the yield of product was 49%. The mass spectrum showed a molecular ion at 238 (calcd 238).

*cis-A*-(2-Piperidino)- $\alpha$ -(*p*-methoxyphenyl)cyclohexanemethanol-*d*<sub>16</sub>.—Piperidine-*d*<sub>10</sub> (NH) was prepared by equilibration of 0.500 g of piperidine-*d*<sub>11</sub> (Merck and Co.) with 0.5 ml of water and 5 mg of *p*-toluenesulfonic acid monohydrate in toluene in a stoppered round-bottomed flask. The toluene layer was dried by stirring over 3 g of Linde Molecular Sieves No. 4A for 30 min. This drying procedure was repeated with 3 g of fresh molecular sieves. The toluene layer was combined with toluene washings of the molecular sieves and filtered (gravity) into a 30-ml round-bottomed flask fitted with a 10-ml-capacity Soxhlet and an extraction thimble containing 1.5 g of fresh molecular sieves.

To the toluene solution was added 10 mg of *p*-toluenesulfonic acid monohydrate and 0.238 g (0.001 mol) of 2-(*p*-methoxybenzoyl)cyclohexanone-3,3,4,4,5,5-*d*<sub>6</sub>; the solution was heated at reflux under nitrogen for 16 hr. The toluene was evaporated *in vacuo*. The enamine was dissolved in 25 ml of dry ethanol and hydrogenated in the presence of 0.10 g of platinum oxide for 21 hr at an initial pressure of 50 psi. The solvent was evaporated and the residue dissolved in 15 ml of ether which was extracted with five 5-ml portions of 10% acetic acid. The acetic acid layer was cooled and then basified with 20% sodium hydroxide. The resulting oil was extracted into ether and the dried ether layer evaporated to 0.26 g of oil. The hydrochloride was prepared and crystallized from methanol-ether, 0.242 g (68%), mp 238–238.5°.

(22) It is of interest to note that in the case of the hydrochloride of *cis-A* (V HCl) in D<sub>2</sub>O where intramolecular hydrogen bonding may play a minor role, nmr analysis indicates that the piperidino group adopts the more stable equatorial position.

(23) F. A. L. Anet, *Can. J. Chem.*, **39**, 2262 (1961).

The mass spectrum indicated  $d_{16}$  ( $m/e$  319) and a minor quantity of  $d_{15}$  ( $m/e$  318). A sample of the hydrochloride was converted to the free base and purified by silica gel chromatography eluting with methanol-methylene chloride mixtures.

*cis*-B, 2-Piperidino- $\alpha$ -(*p*-methoxyphenyl)cyclohexanemethanol- $d_{16}$ .—A sample of *cis*-A free base was isomerized with tri-

fluoroacetic acid as previously described.<sup>1</sup> The crude product was purified by silica gel chromatography and crystallization from ether ( $-20^\circ$ ), mp 133–135°. The mass spectrum was the same as the spectrum of the *cis*-A isomer.

Registry No.—*cis*-A, 13724-43-1; *cis*-B, 13724-46-4.

## A Synthesis of Dihydrothiopyran-3-ones. The Intramolecular Cyclization of Allylthioglycolic Acid Chlorides

KIKUMASA SATO,\* SEIICHI INOUE, AND KEIICHI KONDO

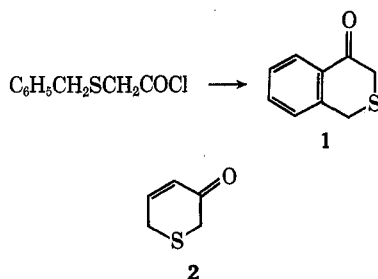
Department of Applied Chemistry, Faculty of Engineering, Yokohama National University, Minami-ku, Yokohama, Japan

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Intramolecular cyclization of allylthioglycolic acid chloride effected by aluminum chloride gave two products, 3,4-dihydro-2*H*-thiopyran-3-one and 3,6-dihydro-2*H*-thiopyran-3-one. Under similar conditions 3-methyl-, 2-methyl-, and 3,3-dimethylallylthioglycolic acid chloride produced 4-methyl- and 5-methyl-3,6-dihydro-2*H*-thiopyran-3-one and 4-isopropylidene-tetrahydrothiophen-3-one, respectively. The substituent effects on the directionality of cyclization are discussed.

While the chemistry of thiopyrones have been widely investigated, little is known about the synthesis and chemical behavior of the isomeric thiopyran-3-one system. In the course of our study on the intramolecular cyclization of compounds containing heteroatoms, we are interested in thiopyran-3-ones, and we have now developed a novel and versatile synthesis for 3,6-dihydrothiopyran-3-ones bearing substituents on the ring.

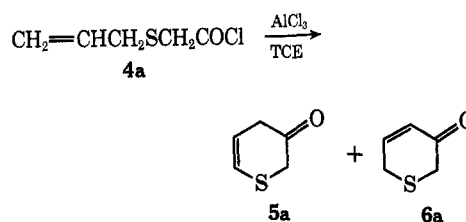
The cyclization of benzylthioglycolic acid chloride reportedly produces isothiochromanone-4 (1).<sup>1</sup> Analogous formation of the parent thiopyranone 2 has not



been reported.<sup>2</sup> We report here successful cyclization of allylthioglycolic acid chlorides to the previously unknown thiopyranone.

Allylthioglycolic acid (3a)<sup>3</sup> was synthesized in 82% yield by the reaction of allyl chloride with thioglycolic acid in aqueous sodium hydroxide solution. The acid was then converted into the acid chloride 4a in 89% yield by the reaction with thionyl chloride. Treatment of acid chloride 4a with aluminum chloride in 1,1,2,2-tetrachloroethane (TCE) at 50–55° gave 5a and 6a in a ratio of 53:47.

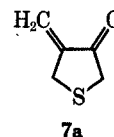
The structure of the lower boiling compound 5a, 3,4-dihydro-2*H*-thiopyran-3-one, was suggested by a combination of spectral data: ir 1710, 960, and 655  $cm^{-1}$ ; uv 221 and 242  $\mu$  ( $\alpha,\beta$ -unsaturated sulfide); nmr two methylene groups at  $\delta$  3.23 and 2.97 ppm, and



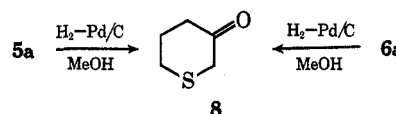
two olefinic protons at  $\delta$  5.83 and 6.25 ppm (each double triplet).

Another higher boiling product 6a, 3,6-dihydro-2*H*-thiopyran-3-one, was characterized by a carbonyl band at 1670  $cm^{-1}$  and uv absorption maximum at 234  $m\mu$ , suggesting the presence of a  $CH=CHCO$  unit. The nmr spectrum of 6a showed signals of two olefinic protons at  $\delta$  5.89 and 6.90 ppm (each double triplet), as well as two methylene groups at  $\delta$  3.20 and 3.21 ppm.

Cyclization of 4a would be expected to lead to 3,6-dihydro-2*H*-thiopyran-3-one (6a), to 3,4-dihydro-2*H*-thiopyran-3-one (5a), or to 4-methylenetetrahydrothiophen-3-one (7a). The third possible product 7a was



not formed, since the ir spectra of products, especially that of the higher boiling material having a conjugated carbonyl function, showed no absorption of a methylene group at ca. 890  $cm^{-1}$  or somewhat higher region,<sup>4</sup> and nmr pattern of olefinic proton signals of products is characteristic as a *cis*-disubstituted olefin rather than an *exo* methylene system (7a). The assignment of a thiopyran-3-one skeleton to our products was ultimately confirmed by catalytic reduction of 5a and 6a to the known ketone 8.<sup>5</sup>



(1) (a) R. Lesser and A. Mehrländer, *Ber., B.*, **56**, 1642 (1932); (b) P. Cagniant and M. P. Cagniant, *Bull. Soc. Chim. Fr.*, 1998 (1959).

(2) Quite recently W. C. Lumma, Jr., and G. A. Berchtold [*J. Org. Chem.*, **34**, 1566 (1969)] have independently reported the synthesis and photochemistry of 5-methyl-3,6-dihydro-2*H*-thiopyran-3-one.

(3) (a) E. Larsson and B. O. Osberg, *Acta Chem. Scand.*, **14**, 768 (1960); (b) E. Larsson, *Ber.*, **63**, 1347 (1930).

(4) L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," Wiley, New York, N. Y., 1958, p 51.

(5) (a) N. J. Leonard and J. Figueras, Jr., *J. Amer. Chem. Soc.*, **74**, 917 (1952); (b) E. A. Fehnel, *ibid.*, **74**, 1569 (1952).