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## The Reaction of *trans*-2-Aminocyclohexanol with Formaldehyde

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From a study of the geminal coupling constants for  $\text{-O-CH}_2\text{-N-}$  protons structure II has been assigned to the product of the reaction between *trans*-2-aminocyclohexanol and formaldehyde. The previously proposed structure I is shown to be incorrect.

Structure I has been proposed (1,2) for the product  $\text{C}_{15}\text{H}_{24}\text{O}_3\text{N}_2$  m. p. 157-158° obtained from the reaction between *trans*-2-aminocyclohexanol and formaldehyde. On the basis of infrared evidence, Gil-Av (3) ruled out the presence of an oxazolidine ring in this compound since only a single peak ( $\nu$  max 1127  $\text{cm}^{-1}$ ) was present in the normally complex 1060-1190  $\text{cm}^{-1}$  region of oxazolidines (4) but no alternative structure was proposed. Crandall and van Hoozer (2) discounted the infrared data and quoted the N.M.R. spectrum of the product as evidence for structure I.

The N.M.R. spectrum ( $\text{CCl}_4$ ) shows a singlet at 5.85  $\tau$  (2 protons) which has been assigned to the N- $\text{CH}_2\text{-N}$  protons and a quartet centered at 5.88  $\tau$  (4 protons) assigned to the O- $\text{CH}_2\text{-N}$  protons.

We have re-examined the N.M.R. spectrum of the compound and find that the geminal coupling constant ( $J$ ) (5) for the O- $\text{CH}_2\text{-N}$  protons is (-)11.5 c.p.s. This would appear to be too negative for the methylene protons situated between oxygen and nitrogen in an oxazolidine ring (6).

We therefore prepared some oxazolidines of the type III by reaction of primary amines with cyclohexene oxide followed by treatment of the resultant aminoalcohol with formaldehyde, and measured the value of  $J$  for the O- $\text{CH}_2\text{-N}$  methylene protons. As is seen from Table I,  $J$  was (-)2.5 c.p.s. for the compounds studied. Furthermore, a value of (-)2.5 c.p.s. for a compound of the partial structure IV has been recorded in the literature (7).

These compounds (III) also showed the characteristic multiple absorptions in the 1060-1190  $\text{cm}^{-1}$  region of their infrared spectra. Since structure I is therefore untenable we propose structure II.

In compounds III and, therefore, a compound of structure I, a value of  $J$  in the region of (-)2.5 c.p.s. is expected since models indicate a near eclipsing relationship between both the lone pairs on

oxygen and the adjacent C-H bonds of the methylene group. Thus, transfer of electrons should occur into the antisymmetric  $\text{CH}_2$  molecular orbital giving a positive contribution to  $J$  (8). In 1,3-oxazines where the lone pairs of electrons are in an axial-equatorial relationship with the C-H bonds situated between the heteroatoms,  $J$  is more negative than in the oxazolidines and has been found to vary from -8 to -10 c.p.s. (6).

In structure II the O- $\text{CH}_2\text{-N}$  protons are in a seven-membered ring and a Dreiding model of the most favourable conformation, Fig. I (9), shows the dihedral angle between the C- $\text{H}_A$  (C- $\text{H}_A'$ ) bond and one of the oxygen lone pairs to be approximately 28°, the other lone pair making the same angle with the C-N bond. Transfer of electrons from the oxygen lone pairs into the methylene group might then be expected to be small and the observed value of  $J$  of (-)11.5, slightly more negative than that observed in six-membered ring heterocycles, is in accord with this. Similar arguments apply to the lone pair on nitrogen, but this gives rise to smaller effects (6) than oxygen.

The low field signals of the O- $\text{CH}_2\text{-N}$  quartet are assigned to  $\text{H}_A$  and  $\text{H}_A'$  since these are in pseudo-equatorial positions and therefore absorb at lower field than the pseudo-axially situated  $\text{H}_B$  and  $\text{H}_B'$ . Examination of the N.M.R. spectra shows that  $\text{H}_A$  and  $\text{H}_A'$  are coupled to the N- $\text{CH}_2\text{-N}$  protons since the signals arising from these appear as triplets ( $J = 0.9$  c.p.s.). The long range coupling in this compound is therefore added evidence in support of the proposed structure as this type of coupling between equatorial protons in *N*-heterocycles is well known.

The chemical evidence quoted by the previous workers (1,2) as evidence for I is also in perfect agreement with structure II.

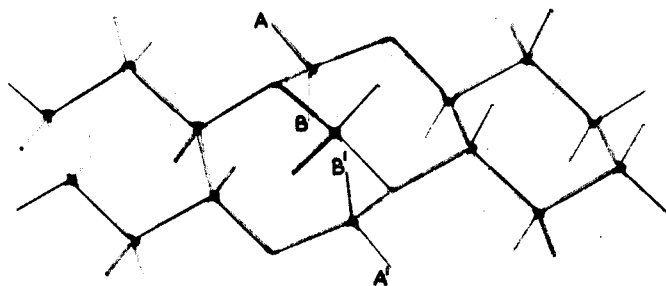


Figure 1

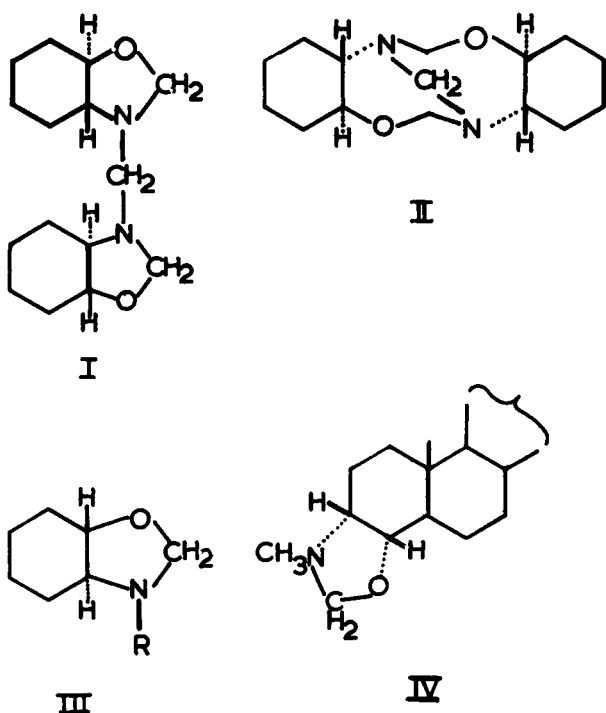


TABLE I

| Compound           | Solvent                       | J (c.p.s.) | Chemical Shifts ( $\tau$ )<br>of -O-CH <sub>2</sub> -N- protons |      |
|--------------------|-------------------------------|------------|---|------|
| III R = phenyl     | CCl <sub>4</sub>              | - 2.5      | 4.99  | 5.30 |
| III R = cyclohexyl | CCl <sub>4</sub>              | - 2.5      | 5.50  | 5.76 |
| III R = benzyl     | CCl <sub>4</sub>              | - 2.5      | 5.45  | 6.03 |
| II                 | CCl <sub>4</sub>              | -11.5      | 5.72  | 6.05 |
| II                 | CDCl <sub>3</sub>             | -11.6      | 5.54  | 5.88 |
| II                 | C <sub>6</sub> H <sub>6</sub> | -11.6      | 5.54  | 6.02 |

## EXPERIMENTAL

The N.M.R. spectra were recorded on a Perkin-Elmer R10 60 Mc. spectrometer using tetramethylsilane as internal reference and the infrared spectra were recorded on a Perkin-Elmer 237 spectrometer.

## Compound II (10).

This was prepared following the method of Crandall and van Hoozer (2).

## Compound III (R = Benzyl).

A mixture of benzylamine (21.4 g., 0.2 mole) and cyclohexene oxide (19.6 g., 0.2 mole) was boiled under reflux for 16 hours, cooled and then shaken with 36% formaldehyde solution (21 ml., 0.25 mole). The mixture was extracted several times with ether and the ethereal solution washed with 10% sodium hydroxide solution and water and then dried over sodium sulphate. The liquid which remained after removal of the ether was distilled under vacuum and the fraction b.p. 98-100° at 0.15 mm. Hg. collected. Yield 34 g.  $n_D^{20}$  1.5385  $\nu(\text{CCl}_4)$  1070, 1078, 1093, 1118 and 1170  $\text{cm}^{-1}$ . (Found: C, 77.66; H, 8.67; N, 6.72. C<sub>14</sub>H<sub>19</sub>NO requires C, 77.38; H, 8.81; N, 6.45.)

## Compound III (R = Cyclohexyl).

This was prepared as described above from a mixture of cyclohexylamine (19.8 g., 0.2 mole) and cyclohexene oxide (19.6 g., 0.2 mole). The fraction b.p. 82-83°/0.15 mm. was collected. Yield 33.0 g.  $n_D^{20}$  1.5022  $\nu(\text{CCl}_4)$  1068, 1078, 1090, 1113, 1135, 1172 and 1185  $\text{cm}^{-1}$ . (Found: C, 74.47; H, 10.93. C<sub>13</sub>H<sub>20</sub>NO requires C, 74.49; H, 11.08.)

## Compound III (R = Phenyl).

The compound was prepared by boiling a mixture of aniline (18.8 g., 0.2 mole) and cyclohexene oxide (19.6 g.) under reflux for 3 hours. The mixture was cooled, treated with formaldehyde and worked up as before. The semi-solid product obtained after removal of the ether was filtered to remove starting materials (the reaction time was probably too short) and the solid residue (10 g.) was recrystallised from methanol as white needles m.p. 67-68°. Yield 7 g.  $\nu(\text{CCl}_4)$  1070, 1097, 1135, 1142, 1174 and 1186  $\text{cm}^{-1}$ . (Found: C, 76.58; H, 8.25; N, 7.19. C<sub>13</sub>H<sub>17</sub>NO requires C, 76.81; H, 8.43; N, 6.89.)

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- (5) J, the geminal coupling constant for the O-CH<sub>2</sub>-N protons, has been assumed to be negative.
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- (8) J. A. Pople and A. A. Bothner-By, *J. Chem. Phys.*, 42, 1339 (1965).
- (9) Although it may not be apparent from Fig. 1 the probable conformation of II has an axis of symmetry which passes through the 19-carbon atom. Thus, the protons on this carbon atom are equivalent and similarly the methylene groups at C-2 and C-11 are in identical environments.
- (10) This compound may be named 1,10-diaza-3,12-dioxatetracyclo-[8, 8, 1, 0<sup>4</sup>, 9<sup>0,10</sup>, 18]nonadecane.

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