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DETERMINATION OF THE CONFORMATIONS OF EPIMERIC 2,3-DIPHENYL-3-AMINO-1-PROPANOLS

SIMPLIFIED ABCX NMR SPECTRA[1]

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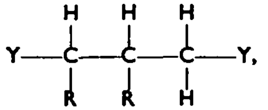
Abstract—The ^1H NMR spectra of 2,3-substituted propanes in which both terminal carbon atoms are directly bonded to electronegative elements (Y):

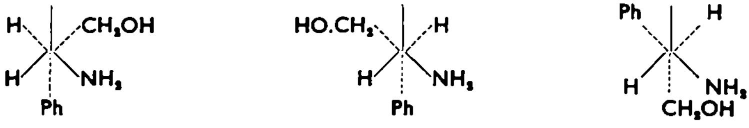


$$Y-\overset{H}{\underset{R}{C}}-\overset{H}{\underset{R}{C}}-\overset{H}{\underset{H}{C}}-Y,$$

have been analysed. The spectra are of the ABCX type with $J_{AC} \approx J_{BC} \approx 0$. The conformations of the epimeric 2,3-diphenyl-3-amino-1-propanols and their cyclized products have been determined by comparing the calculated vicinal proton-proton coupling constants with those usually found in conformational studies.

INTRODUCTION

In a previous paper[5] the stereo-specific behaviour of the epimeric 2,3-diphenyl-3-amino-1-propanols towards *p*-nitrobenzaldehyde was reported. This cyclization was accompanied by a very slight change in optical rotation of the *threo* form as contrasted with the considerable shift in the case of *erythro* form. This striking difference was interpreted in terms of the preferred conformations I and II:—



I (*Threo*) II (*Erythro*) III (*Threo*)

Fig. 1

The predictions of conformational analysis would suggest the prevalance of *trans* phenyl groups in both cases. Accordingly, a gauche orientation of the hydroxymethyl and amino groups in the *threo* form (I) and a *trans* orientation of these functional

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[5] G. Fodor, J. Stefanovsky and B. Kurtev, *Chem. Ber.* **98**, 705 (1965).

groups in the *erythro* form (II) has been expected. All this seems to be consistent with the results from both stereospecific cyclization and changes in optical rotation connected with it.

Also the IR spectra of the N,N-dimethyl derivatives show no free OH absorption in the *threo* form but a considerable amount in the *erythro* form. The IR spectra of the unmethylated amino-alcohols however showed little difference between the relative amounts of free and bonded OH groups. However, a second *threo* form is possible which has a gauche orientation of the two reacting groups and a gauche orientation of the phenyl groups (III). This conformation appears not unlikely since it would involve a diequatorial arrangement of the two phenyl groups in the transition state of the cyclization reaction.

In the *threo* forms the dihedral angle between the secondary hydrogen atoms on C_2 and C_3 would be about 60° with the phenyl groups *trans* (I) and about 180° with them gauche (III). In the *erythro* form the dihedral angle for the same hydrogen atoms would be about 180° with the phenyl groups *trans* (II).

This NMR investigation was undertaken for two reasons: (i) to confirm the structure of the *erythro* form and (ii) to assign the structure of the *threo* form to I or III or perhaps a mixture of both.

Analysis of the NMR Spectra of the Parent Aminoalcohols, their N,N-*dimethyl Derivatives and Cyclized Products*

A. *General appearance of the spectra* (Fig. 2)

The NMR spectra of both epimers of 2,3-diphenyl-3-amino-1-propanol and 2,3-diphenyl-3-N,N-dimethylamino-1-propanol,[6] together with the *cis* and *trans* forms of 4,5-diphenyl-tetra-hydro-1,3-oxazinone-2 and 2-(*p*-nitrophenyl)-4,5-diphenyl-tetrahydro-1,3-oxazine were measured as deuterochloroform solutions at 60 Mc/s at room temperature (Varian A-60 spectrometer). Each of the amino-propanols gave a single peak for the OH/NH_2 protons due to exchange. These peaks, like those of the N,N-dimethylamino-propanols were markedly concentration dependent and could easily be removed by deuteration. Apart from the peaks due to the phenyl protons and the singlet peaks due to the protons on C_2 of the 2-(*p*-nitrophenyl)-4,5-diphenyl-tetrahydro-1,3-oxazines, the remaining peaks in the spectra were in the region $\tau = 5{\cdot}0$–$7{\cdot}5$ ppm and consisted of peaks due to the four hydrogen atoms attached to saturated carbon atoms.

The two methylene protons would not be expected to be magnetically equivalent in the oxazines due to the lack of symmetry nor in the acyclic compounds due to the proximity of two asymmetric centres.[7] The methylene and N—C(Ph)-protons would be expected to be more deshielded than the other proton.[8] So for each compound an ABCD spectrum would be expected, which should approximate to an ABCX spectrum due to the deshielding effects. However, these spectra would be considerably simpler than in the general case because coupling constants between protons separated by more than three bonds are practically zero[8] (e.g. J_{AC} and J_{BC} in Fig. 3).

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[6] For preparative details see A. Orahovats, *Monatsh.* In press.

[7] G. M. Whitesides, D. Holtz and J. D. Roberts, *J. Amer. Chem. Soc.* **86**, 2628 (1964), and Refs. therein.

[8] L. M. Jackman, *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry.* Pergamon Press, London (1959).

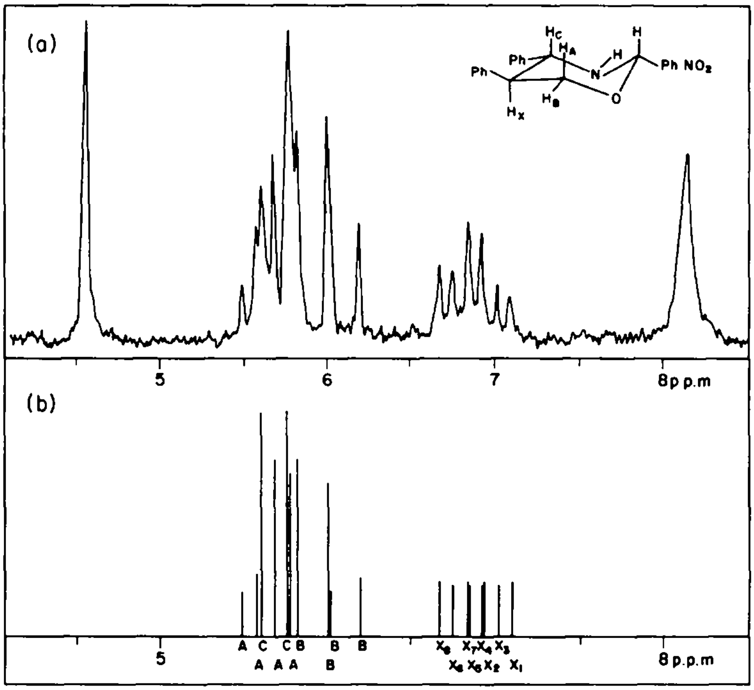
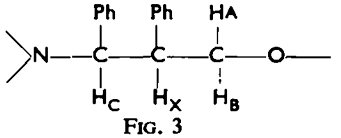


FIG. 2. Experimental and Calculated 60 Mc/s ^{1}H NMR spectra of *trans*-2-(*p*-nitro phenyl)-4,5-diphenyl-tetrahydro-1,3-oxazine, ca. 10% w/v in $CDCl_3$: (a) experimental (b) calculated.

Under these conditions the sizes of the submatrices of the ABCD Hamiltonian remain unchanged,[9] which does not allow analytical solutions of the transition energies to be obtained. However, the ABCX Hamiltonian is considerably simplified.

B. *ABCX NMR spectra*

The ABCX system has been described previously by Banwell and Sheppard.[10] The two 3 × 3 submatrices of the Hamiltonian become two 1 × 1 and two 2 × 2 (because $J_{AC} \approx J_{BC} \approx 0$), which allows analytical solutions of all the eigenvalues and transition energies. If we represent the relevant portion of the molecules under discussion as in Fig. 3:



$$>N-\overset{Ph}{\underset{H_C}{C}}-\overset{Ph}{\underset{H_X}{C}}-\overset{H_A}{\underset{H_B}{C}}-O-$$

FIG. 3

it can be shown that the two simplified ABC-type spectra, one for each spin of the X nucleus, both consist of an AB-type quartet which gives $|J_{AB}|$, and a C singlet. The separations between the lines of the two ABC-type spectra give $|J_{AX}|$, $|J_{BX}|$, and $|J_{AB}|$, together with the relative signs of J_{AX} and J_{BX}. This may be considered to be the superposition of the AB part of an ABX and the C part of a CX spectrum.

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[9] J. A. Pople, W. G. Schneider and H. J. Bernstein, *High-resolution Nuclear Magnetic Resonance*. McGraw-Hill, New York (1959).

[10] C. N. Banwell and N. Sheppard, *Proc. Roy. Soc.* A263, 136 (1961).

Under the same conditions the frequencies of the eight X transitions and the four ABX combination transitions with non-zero intensities are symmetrically placed about ν_X, their frequencies and intensities being given in Table 1. The two ABX combination transitions between unperturbed states, together with the six ABC, the six BCX, and the six ACX combination transitions are forbidden.

Table 1. X and ABX combination transitions of the simplified ABCX system

No.	Transition*	Origin	Energy	Relative intensity
1	$\alpha\alpha\alpha\beta \rightarrow \alpha\alpha\alpha\alpha$	X	$\nu_X + \frac{1}{2}(J_{AX} + J_{BX} + J_{CX})$	1
2	$\alpha\alpha\beta\beta \rightarrow \alpha\alpha\beta\alpha$	X	$\nu_X + \frac{1}{2}(J_{AX} + J_{BX} - J_{CX})$	1
3	$\alpha\beta\alpha\beta' \rightarrow \alpha\beta\alpha\alpha'$	X	$\nu_X + \frac{1}{2}J_{CX} + D_+ - D_-$	$\cos^2(\phi_+ - \phi_-)$
4	$\beta\alpha\alpha\beta' \rightarrow \beta\alpha\alpha\alpha'$	X	$\nu_X + \frac{1}{2}J_{CX} - D_+ + D_-$	$\cos^2(\phi_+ - \phi_-)$
5	$\alpha\beta\beta\beta' \rightarrow \alpha\beta\beta\alpha'$	X	$\nu_X - \frac{1}{2}J_{CX} + D_+ - D_-$	$\cos^2(\phi_+ - \phi_-)$
6	$\beta\alpha\beta\beta' \rightarrow \beta\alpha\beta\alpha'$	X	$\nu_X - \frac{1}{2}J_{CX} - D_+ + D_-$	$\cos^2(\phi_+ - \phi_-)$
7	$\beta\beta\alpha\beta \rightarrow \beta\beta\alpha\alpha$	X	$\nu_X - \frac{1}{2}(J_{AX} + J_{BX} - J_{CX})$	1
8	$\beta\beta\beta\beta \rightarrow \beta\beta\beta\alpha$	X	$\nu_X - \frac{1}{2}(J_{AX} + J_{BX} + J_{CX})$	1
9	$\beta\alpha\alpha\beta' \rightarrow \alpha\beta\alpha\alpha'$	ABX	$\nu_X + \frac{1}{2}J_{CX} + D_+ + D_-$	$\sin^2(\phi_+ - \phi_-)$
10	$\alpha\beta\alpha\beta' \rightarrow \beta\alpha\alpha\alpha'$	ABX	$\nu_X + \frac{1}{2}J_{CX} - D_+ - D_-$	$\sin^2(\phi_+ - \phi_-)$
11	$\beta\alpha\beta\beta' \rightarrow \alpha\beta\beta\alpha'$	ABX	$\nu_X - \frac{1}{2}J_{CX} + D_+ + D_-$	$\sin^2(\phi_+ - \phi_-)$
12	$\alpha\beta\beta\beta' \rightarrow \beta\alpha\beta\alpha'$	ABX	$\nu_X - \frac{1}{2}J_{CX} - D_+ - D_-$	$\sin^2(\phi_+ - \phi_-)$

$$D_\pm = \tfrac{1}{2}[[\nu_0\delta_{AB} \pm \tfrac{1}{2}(J_{AX} - J_{BX})]^2 + J^2_{AB}]^{\frac{1}{2}}$$

$$\tan 2\phi_\pm = \frac{J_{AB}}{(\nu_0\delta_{AB} \pm \frac{1}{2}[J_{AX} - J_{BX}])}$$

* The wave functions of the stationary states, between which transitions take place, are designated as in Ref. 9, the order being A, B, C, X. Those wave functions which are perturbed due to mixing with other wave functions with the same total spin are indicated by a prime (′).

So under these conditions the 56 lines of the general ABCX spectrum simplify to ten lines in the ABC region and twelve lines in the X region, of which the four combination transitions will have practically zero intensity in most cases. The general appearance of this simplified ABCX spectrum is sensitive to the relative signs of J_{AX} and J_{BX} only.

C. *Discussion of the observed spectra*

(i) Threo-2,3-*diphenyl*-3-*amino*-1-*propanol*, cis- *and* trans-4,5-*diphenyl-tetrahydro*-1, 3-*oxazinone*-2 *and* cis- *and* trans-2-(p-*nitrophenyl*)-4,5-*diphenyl-tetrahydro*-1,3-*oxazine* (Fig. 2). All the above compounds can be analysed satisfactorily as simplified ABCX systems and the results are given in Table 2. All ABCX spectra are virtually concentration independent over the same range of concentrations in deuterochloroform. *Threo*-2,3-diphenyl-3-amino-1-propanol is more soluble than the other compounds and a saturated solution gives quite a different ABCX spectrum. The parameters given in Table 2 were obtained from ca. 10% w/v solutions with the exception of the additional parameters obtained from the *threo*-aminopropanol as a saturated solution. However, it is not too profitable to draw any conclusions from this concentration dependence of the one compound.

(ii) Erythro-2,3-*diphenyl*-3-*amino*-1-*propanol.* The observed spectrum of this compound is much simpler than those of the above compounds, there being only a doublet for the A and B protons, a doublet for the C proton and two triplets for the X proton.

It has been shown[11] that for the AB part of an ABX spectrum to appear as a simple doublet:

$$\frac{(\nu_0\delta_{AB} + L)^2}{2|J_{AB}|} < \Delta\nu_{\frac{1}{2}}$$

where $L = \frac{1}{2}|J_{AX} - J_{BX}|$ and $\Delta\nu_{\frac{1}{2}}$ is the half height width of the observed spectral line, ca. 0·5 c/s for this spectrum. If this is so the doublet separation is $\frac{1}{2}|J_{AX} + J_{BX}|$. It can be shown that this also applies to the AB part of the simplified ABCX spectrum, the X part of the spectrum being a doublet of triplets as observed. The triplet separation is $\frac{1}{2}|J_{AX} + J_{BX}|$ and the doublet separation $|J_{CX}|$.

Another condition for the AB parts of ABX and simplified ABCX spectra to appear as a doublet is:

$$|J_{AX}|, |J_{BX}| \text{ and } \left|\frac{\nu_0\delta_{AB}}{J_{AB}}\right| \to 0.$$

However this would make the X parts of ABX and simplified ABCX spectra appear as a singlet and doublet, respectively. Also, for these molecules it is most unlikely that $|J_{AX}|$ and $|J_{BX}| \to 0$.

(iii) Threo- *and* erythro-2,3-*diphenyl*-3-N,N-*dimethyl*-2-*amino*-1-*propanol.* The chemical shifts of all four saturated C-protons are much closer together for these molecules, the ABCX system becoming ABCD. Due to there being insufficient resolvable lines in the spectra and the fact that even if $J_{AD} = J_{BD} = 0$ the ABCD Hamiltonian still contains two 4×4 and one 6×6 submatrix,[9] analyses were not attempted.

D. *Discussion of the NMR parameters obtained* (Table 2)

(i) Threo-2,3-*diphenyl*-3-*amino*-1-*propanol and its cyclized products—the* trans-*tetrahydro-oxazines.* As $J_{CX} = \pm 9{\cdot}0$ c/s for the *threo* form, this suggests that it consists predominantly of form III as J_{CX} for I would be expected to be 2–4 c/s.[12] The values of ±9·3 and ±2·7 c/s for J_{AX} and J_{BX} suggest that there is restricted rotation about the C_1–C_2 bond. On the basis of molecular models this is at first unexpected until one realises that rotation can easily be prevented by internal hydrogen bonding between the NH_2 and OH-groups to form a six-membered cyclohexane-type ring with both phenyl groups in equatorial positions. This conformation is in agreement with the values of J_{AX} and J_{BX}, corresponding to dihedral angles of about 180° and 60°.

This is further supported by the very similar coupling constants of the *trans*-tetrahydro-oxazine and *trans*-tetrahydro-oxazin-2-one which have rigidly bonded cyclohexane-type rings. It is unlikely that these rings would "flip" since the form with two equatorial phenyl-groups would be preferred to the alternative on steric grounds. The *p*-nitrophenyl group is presumably also in an equatorial position.

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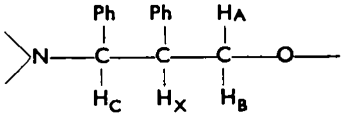
[11] R. J. Abraham and H. J. Bernstein, *Canad. J. Chem.* 39, 216 (1961)

[12] M. Karplus, *J. Chem. Phys.* 30, 11 (1959).

Table 2. NMR parameters of the aminoalcohols, tetrahydro-oxazines and tetrahydro-oxazinones



$$>N-\overset{Ph}{\underset{H_C}{C}}-\overset{Ph}{\underset{H_X}{C}}-\overset{H_A}{\underset{H_B}{C}}-O-$$

Compound[a]	J_{AX}[b]	J_{BX}[b]	J_{CX}[b]	J_{AB}[b]	$\nu_0\delta_{AB}$[b]	$(\tau_A + \tau_B)/2$[c]	τ_C[c]	τ_X[c]	τ_{NH}[c] and/or τ_{OH}	τ_{C_2-H}[c]
Erythro-aminopropanol	6·0[d]	6·0[d]	8·0	*d*	*d*	6·40	5·82	7·03	7·90	—
Threo-aminopropanol	9·3	2·7	9·0	11·3	12·0	6·03	5·75	6·93	6·93	—
Threo-aminopropanol (saturated)	8·6	4·7	9·4	11·6	10·1	6·04	5·78	6·96	6·96	—
cis-Tetrahydro-oxazinone	11·5	2·5	5·0	12·0	13·5	5·52	5·12	6·27	5·23	—
cis-Tetrahydro-oxazine	4·8	3·2	4·5	12·5	9·2	5·43	5·30	6·57	7·03	4·42
trans-Tetrahydro-oxazinone	10·8	4·2	9·8	11·6	10·1	5·63	5·35	6·92	[e]	—
trans-Tetrahydro-oxazine	11·4	4·6	10·2	11·7	19·4	5·82	5·68	6·88	8·15	4·55

[a] All solutions were ca. 10% w/v in $CDCl_3$, except where indicated, with TMS as an internal reference.

[b] J_{AX}, J_{BX}, J_{CX}, J_{AB} and $\nu_0\,\delta_{AB}$ are given in c/s. The estimated errors are ±0·2 c/s for J_{AX}, J_{BX} and $\nu_0\delta_{AB}$, and ±0·1 c/s for J_{CX} and J_{AB}. In all cases, J_{AX} and J_{BX} have the same sign, the relative signs of J_{CX} and J_{AB} being unobtainable from the analysis of simplified ABCX spectra.

[c] $(\tau_A + \tau_B)/2$, τ_C, τ_X, τ_{NH} and τ_{OH}, and τ_{C_2-H} are given in ppm (τ scale) and the estimated errors are ±0·01 ppm. From the analyses of the ABCX spectra it is not possible to distinguish between A and B transitions, even though J_{AX} and J_{BX} can be distinguished in some cases by using Karplus's relations.[18]

[d] See text.

[e] No N—H resonance was observed.

The coupling constants of the tetrahydro-oxazines would not be in agreement with conformations having two axial phenyl groups.

(ii) Erythro-2,3-*diphenyl*-3-*amino*-1-*propanol and its cyclized products—the* cis-*tetrahydro-oxazines.* As was pointed out earlier the only unambiguous parameters for the *erythro*-propanol are $|J_{CX}|$ and $|J_{AX} + J_{BX}|$, being 8·0 and 12·0 c/s, respectively. This value of J_{CX} is in agreement with the proposed conformation of *erythro* form (II) and rules out the other two conformations which would be expected to have smaller values of J_{CX} (2–4 c/s) corresponding to a dihedral angle of about 60°.[12]

Since internal hydrogen bonding cannot take place with the *erythro*-propanol, on the basis of molecular models it seems unlikely that any rotamer about the C_1–C_2 is greatly preferred over others. If this is the case, J_{AX} and J_{BX} would be expected to be about equal to:

$$J_{AX} = J_{BX} = \tfrac{1}{3}(J_{trans} + 2J_{gauche})$$

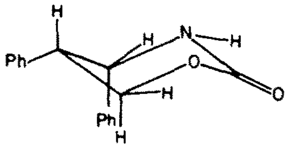
Using typical values of $J_{trans} = 10$ and $J_{gauche} = 4$ c/s, $J_{AX} = J_{BX} = 6$ c/s, in agreement with the observed values of $|J_{AX} + J_{BX}| = 12{\cdot}0$ c/s. If $J_{AX} = J_{BX}$ and $\Delta\nu_{\frac{1}{2}} = 0{\cdot}5$ c/s,

$$\begin{aligned} \nu_0\delta_{AB} &< |(2\Delta\nu_{\frac{1}{2}} \,.\, J_{AB})^{\frac{1}{2}}| \\ &< |3{\cdot}5 - 4{\cdot}2| \text{ c/s} \end{aligned}$$

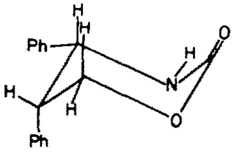
depending upon the value of $|J_{AB}|$ (taken as 12–18 c/s).

So in spite of its deceptive simplicity this spectrum could be a true ABCX spectrum with $J_{AC} = J_{BC} = 0$, $J_{AX} = J_{BX} = 6{\cdot}0$ c/s and $4{\cdot}2 > |\nu_0\delta_{AB}| > 0$, and *not* an AB_2X spectrum.

The ABCX spectrum of the *cis*-tetrahydro-oxazinone is quite different from that of the *erythro*-aminoalcohol, from which it was made, and the coupling constants show quite definitely that IV is the preferred conformation rather than the alternative V, both having one axial and one equatorial phenyl group:

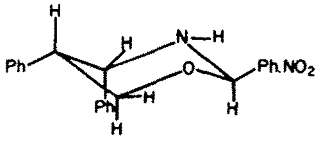


IV

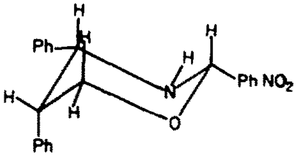


V

However the ABCX spectrum of the *cis*-tetrahydro-oxazine is different from those of both the *cis*-tetrahydro-oxazinone *and* the parent *erythro*-aminoalcohol. The coupling constants show that for this compound VII is the preferred conformation, the *p*-nitrophenyl group being assumed equatorial:



VI



VII

It is not possible to say from the NMR spectra whether the N-hydrogen atoms of the tetrahydro-oxazines and tetrahydro-oxazinones are equatorial or axial.