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PROTON MAGNETIC RESONANCE STUDIES OF CYCLIC COMPOUNDS—III*

CIS- AND *TRANS*-2, 6-DIMETHYLMORPHOLINES

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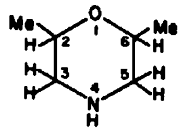
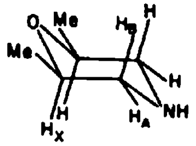
Abstract—Commercial 2,6-dimethylmorpholine has been separated into *cis*- and *trans*-isomers by vapour phase chromatography. The PMR spectra of the bases, analysed as $ABXK_3$ systems ($J_{AK} = J_{BK} = 0$), show that the most abundant isomer has the *cis*-configuration, consisting probably of a single conformation in which both methyl groups are equatorial. The *trans*-isomer is probably a mixture of rapidly inverting and energetically equivalent conformations, since the vicinal coupling constants deduced from the PMR spectrum are averages of those expected for the two conformations.

Interest in conformationally flexible cyclic systems[1] led to an examination of 2,6-dimethylmorpholine (I), which can exist as *cis*- and *trans*-isomers. The *cis*-isomer (II) is expected to be almost conformationally homogeneous, with both methyl groups disposed equatorially, whilst the *trans*-isomer is expected to be a mobile system in which the energetically equivalent conformations (III and IV), each with one methyl group equatorial and one methyl group axial, are undergoing rapid interconversion.



I



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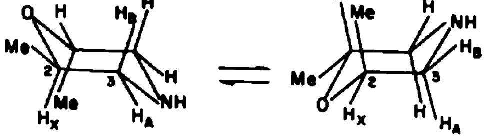

III IV

A commercial sample of 2,6-dimethylmorpholine gave a PMR spectrum (Fig. 1) which suggested that the sample consisted largely, if not entirely, of one isomer, isomer "A". However, the presence of 9% of the second isomer, isomer "B", was shown by VPC and a complete separation of the isomers was achieved by preparative

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* Part II, H. Booth, N. C. Franklin and G. C. Gidley, *Tetrahedron* 21, 1077 (1965).

[1] H. Booth, *Tetrahedron* 20, 2211 (1964).

VPC (Experimental). The stereoisomers were characterized by the preparation of their salts with picric acid and 3,5-dinitrobenzoic acid. The literature contains a number of references[2] to 2,6-dimethylmorpholine, and the recorded properties probably refer to isomer "A" or to a mixture of "A" and "B". The PMR spectrum (Fig. 2) of isomer "A" in benzene showed the expected methyl doublet (J ~ 6 c/s), centred on $\tau = 8{\cdot}97$, and a sharp signal at $\tau \simeq 8{\cdot}5$ due to the NH resonance. The

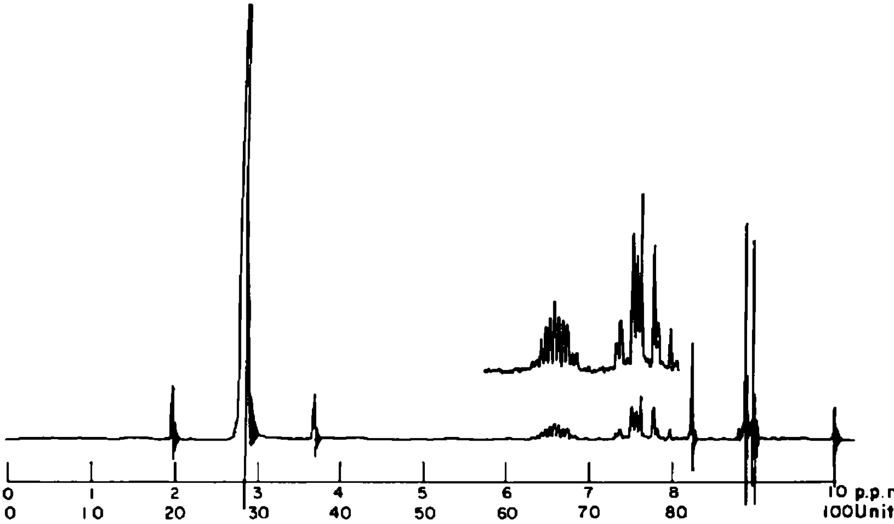

Fig. 1. Spectrum of commercial 2,6-dimethylmorpholine in benzene.

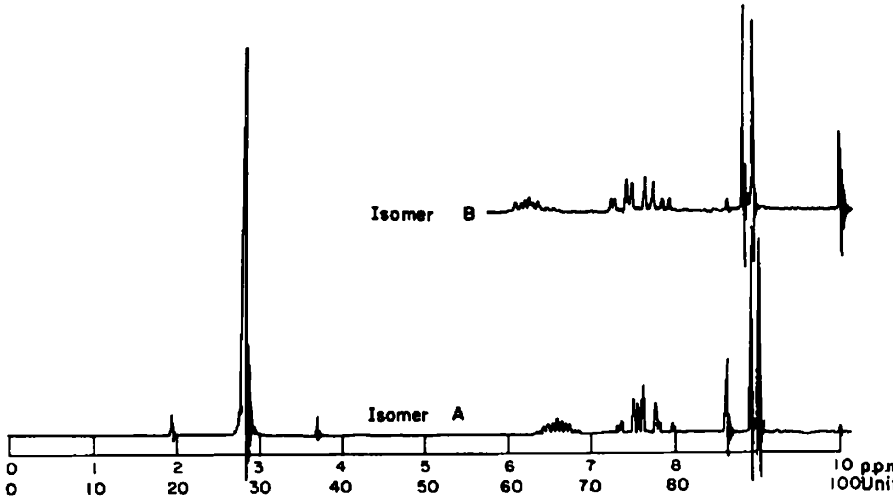

Fig. 2. Lower trace: spectrum of 2,6-dimethylmorpholine, isomer "A", (solvent: benzene). Upper trace: spectrum of 2,6-dimethylmorpholine, isomer "B" (solvent: benzene).

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[2] K. Krasuskii, *J. Gen. Chem.* **6**, 460 (1936); A. N. Nesmeyanov and I. F. Lutsenko, *Chem. Abstr.* **38**, 5498 (1944); D. L. Heywood and B. Phillips, *J. Amer. Chem. Soc.* **80**, 1257 (1958); Jefferson Chemical Co. Inc. *Chem. Abstr.* **53**, 20101 (1959); C. G. Summers, *Ibid.* **59**, 5175 (1963).

NH signal disappeared when the solution was shaken with D_2O, (the rest of the spectrum being unaffected), and its position varied with the concentration of the base. The two protons at position 3 (each of which is equivalent to the corresponding proton at position 5) form the AB part of an $ABXK_3$ system (in which $J_{AK} = J_{BK} = 0$), and the typical 8 line pattern of such a system is clearly seen between $\tau = 7{\cdot}3$ and $\tau = 8{\cdot}0$ (Figs 2 and 3). The position of the lines is indicated below, in c/s from TMS, and the labelling shown was the only one to give a satisfactory solution.

line number:	8	7	6	5	4	3	2	1
position:	162·3	159·6	150·1	147·4	144·3	134·7	132·1	122·7

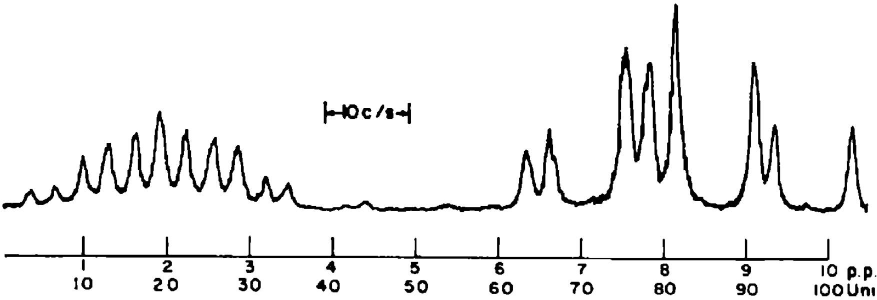

FIG. 3. Spectrum (ABX portion) of 2,6-dimethylmorpholine, isomer "A" (solvent: benzene).

The proton at position 2 is equivalent to that at position 6 and appears at $\tau = 6{\cdot}58$ as a symmetrical multiplet of 11 lines. As the X part of an $ABXK_3$ system, the resonance of the 2-proton should consist of 4 lines (X part of an ABX system), each of which is split into a 1,3,3,1-quartet because of the first-order coupling with the three protons of the methyl group. A maximum of 16 lines is thus possible for the X proton, but the coincidence or near-coincidence of some lines allows only 11 lines to be observed. The position of the four 1,3,3,1-quartets was easily fixed, since the separation between each line of the quartets equals the separation of the methyl doublet. The centres of each of the quartets were then marked, and this gave the positions of the four X lines of an ABX system. To confirm that this method of analysis was valid, the spectrum of the X proton was recorded again, but now with simultaneous irradiation at the centre of the methyl doublet. The 11-line spectrum collapsed to a 4-line spectrum (Fig. 4), and the positions of the lines corresponded exactly with the positions obtained in the first treatment. The analysis of the ABX spectrum was then straightforward, and the results are summarized in Table 1, which also includes details of the chemical shifts and coupling constants deduced from the spectrum recorded with carbon tetrachloride as solvent. A spectrum calculated from the figures of Table 1 gave an excellent fit with the observed spectrum.

The values 2·0 c/s and 10·3 c/s for the vicinal coupling constants J_{AX} and J_{BX} respectively, demonstrate that isomer "A" is the *cis*-isomer (II), in which J_{AX} is an equatorial-axial coupling (dihedral angle $\sim$60°) and J_{BX} is an axial:axial coupling (dihedral angle $\sim$180°).

The PMR spectrum (Fig. 2) of isomer "B" was interpreted in a similar way to that of isomer "A", and the results are given in Table 2.

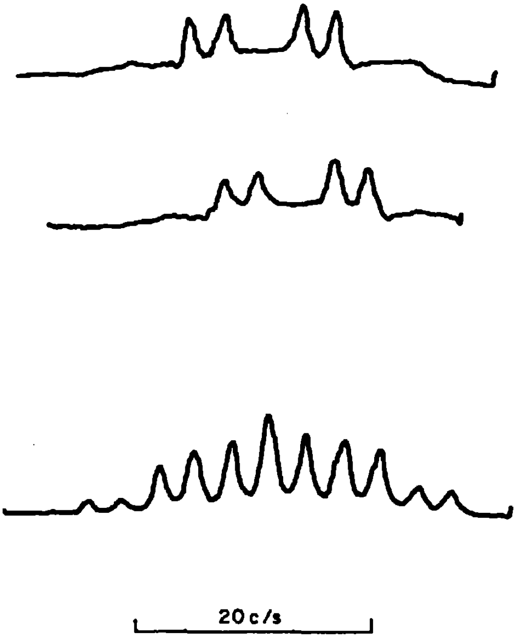

FIG. 4. Lower trace: frequency swept spectrum (X portion) of 2,6-dimethylmorpholine, isomer "A". Upper traces: frequency swept spectra (X portion) of 2,6-dimethylmorpholine, isomer "A", with simultaneous irradiation at a point 144 c/s to high field (centre of methyl doublet)

TABLE 1. SPECTRAL DATA FOR *cis*-2,6-DIMETHYLMORPHOLINE (ISOMER "A") (CHEMICAL SHIFTS IN τ VALUES, J IN C/S)

	Benzene	Carbon tetrachloride
Methyl protons (doublet)	8·97	8·97
H_A (equatorial)	7·45	7·32
H_B (axial)	7·74	7·73
H_X (axial)	6·58	6·56
J_{AB} (= Ja_3e_3)	12·10	11·80
J_{AX} (= Je_3a_2)	1·97	2·06
J_{BX} (= Ja_3a_2)	10·31	10·28

TABLE 2. SPECTRAL DATA FOR *trans*-2,6-DIMETHYLMORPHOLINE (ISOMER "B") (CHEMICAL SHIFTS IN τ VALUES, J IN C/S)

	Benzene
Methyl protons (doublet)	8·92
H_A (equatorial ⇌ axial)	7·39
H_B (equatorial ⇌ axial)	7·72
H_X (equatorial ⇌ axial)	6·26
J_{AB} (= Ja_3e_3)	11·64
J_{AX} [= $\frac{1}{2}(Je_3a_2 + Ja_3e_2)$]	3·36
J_{BX} [= $\frac{1}{2}(Ja_3a_2 + Je_3e_2)$]	5·80

The vicinal coupling constants J_{AX} and J_{BX} are 3·36 and 5·80 c/s respectively. These values are clearly averages of those in the conformations III and IV. Thus we can write

$$J_{AX} = 3{\cdot}36 = \tfrac{1}{2}(Je_3a_2 + Ja_3e_2)$$
$$J_{BX} = 5{\cdot}80 = \tfrac{1}{2}(Ja_3a_2 + Je_3e_2)$$

It appears that the four vicinal coupling constants in III and IV cannot be separately evaluated. However, if it is assumed that

$$Je_3a_2 \text{ in III} = Je_3a_2 \text{ in II}$$

and that

$$Ja_3a_2 \text{ in III} = Ja_3a_2 \text{ in II},$$

then Ja_3e_2 and Je_3e_2 are calculated to be 4·75 c/s and 1·29 c/s respectively. The values of coupling constants reported here are considered more accurate than those mentioned in a preliminary communication,[3] where the relative magnitudes were discussed in terms of stereospecific electronegativity effects. It is estimated that coupling constants are accurate to about ±0·1 c/s, except for Ja_3e_2 and Je_3e_2 which, by nature of their derivation, are accurate only to about ±0·3 c/s. It must also be stressed that the accuracy of Ja_3e_2 and Je_3e_2 is dependent on the correctness of the assumptions that Je_3a_2 in III = Je_3a_2 in II, and that Ja_3a_2 in III = Ja_3a_2 in II; it is not inconceivable that a change in orientation, from equatorial to axial, of the methyl group at position 6 will alter appreciably the values of the vicinal coupling constants on the opposite side of the ring.

EXPERIMENTAL

PMR spectra were obtained on a Perkin–Elmer R10 Spectrometer operating at 60 Mc/s. with tetramethylsilane as internal reference. IR spectra were recorded as liquid films on a Perkin–Elmer 237 Spectrometer. Commercial 2,6-dimethylmorpholine was obtained from Koch-Light Laboratories Ltd.

Fractional distillation of 2,6-*dimethylmorpholine*. The sample was distilled slowly up a spinning-band fractionating column, seven fractions, b.p. 120–145°/760 mm, being collected. Vapour phase chromatography showed that none of the fractions was pure. However, fraction 4, b.p. 142°, contained > 90% of *cis*-2,6-dimethylmorpholine (isomer "A"). The fraction richest in *trans*-2,6-dimethylmorpholine was the highest boiling fraction, b.p. 144–145°, which contained ~60% *cis*-base and ~40% *trans*-base.

Analytical vapour phase chromatography. Commercial 2,6-dimethylmorpholine (0·2 μl) was examined on a Perkin–Elmer 800 Gas Chromatograph. The 12′ × ⅛″ column was packed with Carbowax 20 M on a support of alkali-treated Chromosorb W (cf.[4]); the carrier gas was N_2. Complete separation was achieved into *cis*-2,6-dimethylmorpholine (90%) (shortest retention time), *trans*-2,6-dimethylmorpholine (9%) and an unidentified component (1%).

Preparative vapour phase chromatography. Commercial 2,6-dimethylmorpholine was separated into *cis*- and *trans*-isomers using a Wilkens Autoprep A 700 Gas Chromatograph, with He as carrier gas. The 25′ × ⅜″ Al-column was packed with Carbowax 20 M (25%) on alkali-treated Chromosorb W, and automatic injections of 0·5 ml of mixture were used. *cis*-2,6-Dimethylmorpholine (98% pure, estimated by analytical VPC) was eluted first, followed by *trans*-2,6-dimethylmorpholine (95% pure).

cis-2,6-*Dimethylmorpholine* had $n_D^{22\cdot8}$ 1·4438 and showed the following IR maxima: 765, 832, 855, 887, 918, 966, 995, 1062, 1080, 1095, 1115, 1135, 1155, 1178, 1212, 1268, 1276, 1320, 1350, 1375, 1390, 1405, 1450, 1455, 2600, 2760, 2820, 2850, 2890, 2930, 2965, 3430, 3580 cm^{-1}. The *picrate* formed yellow needles (EtOH) m.p. 199–200° (Found: C, 41·9; H, 4·8; N, 16·2. $C_{12}H_{16}N_4O_8$

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[3] H. Booth, *Tetrahedron Letters* 411 7, (1965).

[4] H. Feltkamp and K. D. Thomas, *J. Chromat*. 10, 9 (1963).

requires: C, 41·8; H, 4·7; N, 16·3%.) The 3,5-*dinitrobenzoic acid salt* formed white rhombohedra (ethyl acetate–EtOH) m.p. 179–180°. (Found: C, 47·8; H, 5·1; N, 12·7. $C_{13}H_{17}N_3O_7$ requires: C, 47·7; H, 5·2; N, 12·8%.)

trans-2,6-*Dimethylmorpholine* had $n_D^{22\cdot3}$ 1·4480 and showed the following IR maxima: 660, 765, 825, 880, 915, 940, 970, 990, 1035, 1070, 1095, 1108, 1135, 1155, 1160, 1220, 1280, 1315, 1335, 1360, 1375, 1445, 1460, 2760, 2820, 2930, 2970, 3360, 3380 cm^{-1}. The *picrate* formed yellow needles (EtOH) m.p. 161–162°. (Found: C, 41·9; H, 5·1; N, 16·0%.) The 3,5-*dinitrobenzoic acid salt* formed white rhombohedra (ethyl acetate—EtOH) m.p. 176–178°. (Found: C, 47·4; H, 5·1; N, 12·9%.)

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