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**Note**

# The isolation and structure determination of two diastereoisomers of N-tridecyl-2,6-dimethylmorpholine (Tridemorph)

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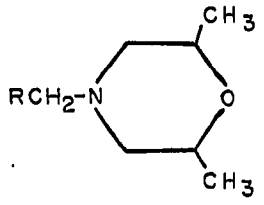
During an investigation of the morpholine series, we encountered N-tridecyl-2,6-dimethylmorpholine (I), a commercial morpholine exhibiting fungicidal activity[1]. A recent publication[2] describes a method for the identification of fungicides using thin-layer chromatography (TLC), and the authors claim to have observed substantial decomposition of I on chromatographic plates. This prompted us to report our own experience with this compound, namely its TLC separation into two stable diastereoisomers and their identification by nuclear magnetic resonance (NMR) spectroscopy.

## EXPERIMENTAL

PMR spectra were obtained on a Varian XL-100 spectrometer at 100 MHz, using 10–20% solutions in deuterochloroform. Chemical shifts are reported as parts per million downfield from the internal standard tetramethylsilane. Mass spectra were recorded on an Atlas CH 4 mass spectrometer.

Tridemorph was purchased as a 750 g/l formulation. It was separated into its isomers on TLC plates, 1-mm thick, prepared from Merck (Darmstadt, G.F.R.) silica gel $GF_{254}$ and activated for 1 h at 105°. The elution was carried out with acetone–hexane (2:1), and was repeated twice in order to improve the separation. Isomer Ia had an $R_F$ value of 0.60, while Ib had an $R_F$ value of 0.69. The gel zones were removed from the plates and washed with methylene chloride, which, after evaporation, yielded the two isomers Ia and Ib.

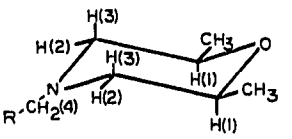
N-*n*-Tridecyl-2,6-dimethylmorpholine (II) was prepared in two steps, essentially by the method described in the literature[3–7]. A solution of 10 g (0.05 mole) of *n*-tridecylamine in 100 ml of methanol was added dropwise over a 2-h period into a refluxing solution of 11.6 g (0.2 mole) of propylene oxide in 100 ml of methanol. Refluxing was continued for a further 2 h. The solvents were removed and the residue was distilled under reduced pressure to yield 13.1 g (88%) of N,N-bis(2-hydroxypropyl)tridecylamine, b.p. 170–175°/1 mm. A 10-g amount of the latter was dissolved in 100 ml of xylene and 10 g of conc. sulphuric acid were added. The mixture was refluxed and water vapour was collected by means of a Dean and Stark trap. After



I, R = $C_{12}H_{25}$

II, R = n-$CH_3(CH_2)_{11}$

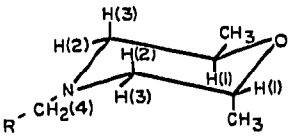
III, R = $C_6H_5$



Ia, R = $C_{12}H_{25}$

IIa, R = n-$CH_3(CH_2)_{11}$

IIIa, R = $C_6H_5$



Ib, R = $C_{12}H_{25}$

IIb, R = n-$CH_3(CH_2)_{11}$

IIIb, R = $C_6H_5$

2 h, no further water condensed in the trap and the mixture was cooled and added to a 10% sodium hydroxide solution. The organic layer was separated, and the aqueous layer washed twice with diethyl ether. The organic layer and the washings were combined, dried over anhydrous sodium carbonate and distilled under reduced pressure. The product had b.p. 130–133°/0.7 mm (ref. 7: 130–131°/0.17 mm). The yield was 7.3 g. II was separated into its isomers, IIa and IIb in the manner described for I.

N-Benzyl-2,6-dimethylmorpholine (III)[8] was prepared in a similar manner from benzylamine and propylene oxide. The crude diol was used directly for the dehydration step, and the crude product was purified and separated by column chromatography over silica by elution with acetone–hexane (1:9) to yield the diastereoisomers IIIa and IIIb. Calculated for $C_{13}H_{19}NO$: C, 76.10; H, 9.27; N, 6.83%. Found for IIIa: C, 76.49; H, 9.39; N, 7.01%. Found for IIIb: C, 76.09; H, 9.57; N, 7.20%.

## RESULTS AND DISCUSSION

When I is applied on a silica gel TLC plate and eluted with acetone–hexane, it separates into two distinct spots (*cf.*, ref. 2). The isolation of larger amounts of these fractions was achieved by carrying out the chromatography on thick-layer plates, collecting the eluted gel zones and extracting the adsorbed materials with methylene chloride. The two fractions exhibit molecular ions in their mass spectra (*m/e* 297) and are therefore isomers of I. Examination of the proton magnetic resonance (PMR) spectra of the isomers Ia and Ib (Figs. 1 and 2) shows that the area under the signals due to protons in the α-position to the oxygen atom (3.5–4.0 ppm) for both isomers is one-third of the area under the signals obtained from protons in the α-position to the nitrogen atom (1.5–2.6 ppm). Hence there are only two protons in positions 2 and 6 in the morpholine, compared with six protons in positions 3 and 5 on the ring, as well as on the α-carbon atom of the N-alkyl group. This result corresponds to substitution of two methyl groups at positons 2 and 6, as expected, thus eliminating the possibility that one of the isomers was actually an impurity with the methyl groups substituted at positions other than 2 and 6.

As the portions of the ring protons in the PMR spectra of the two isomers differ considerably, the isomerism can be attributed to ring geometry, *i.e.*, *cis–trans* relationships between the methyl groups, rather than to structural differences in the N-alkyl chain. In order to determine, however, whether there was also different branch-

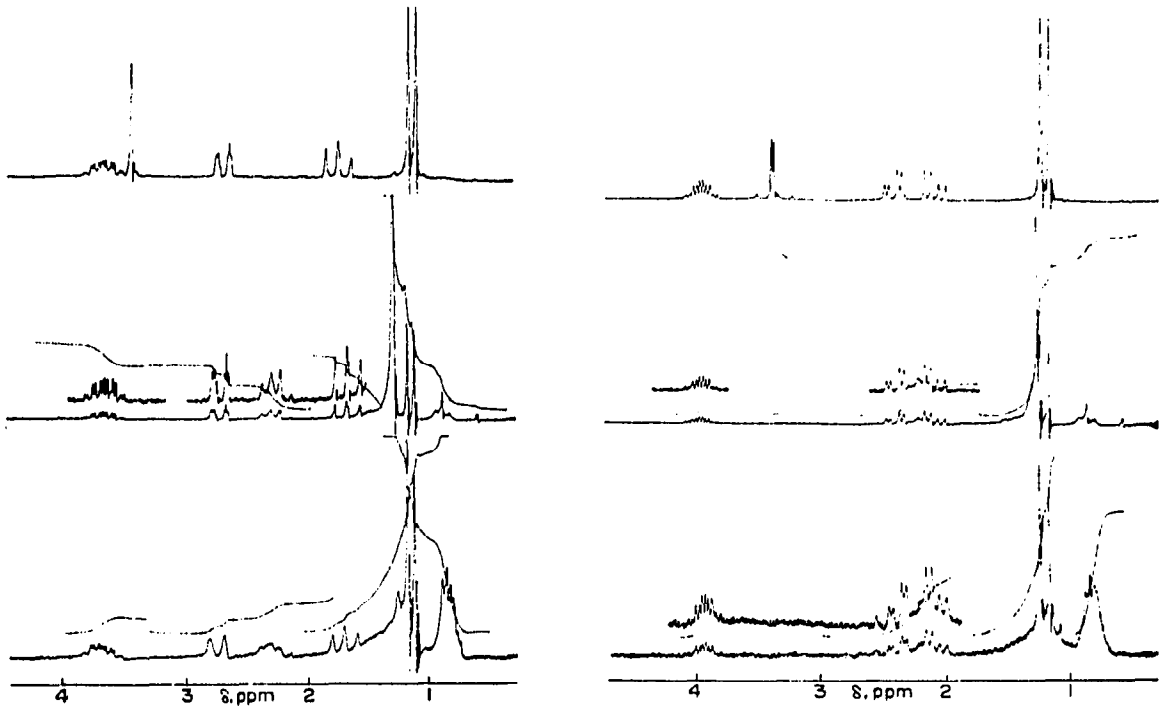



Fig. 1. PMR spectra of N-alkyl-*cis*-2,6-dimethylmorpholines. Lower trace, Ia; middle trace, IIa; upper trace, IIIa (excluding the aromatic proton region).

Fig. 2. PMR spectra of N-alkyl-*trans*-2,6-dimethylmorpholines. Lower trace, Ib; middle trace, IIb; upper trace, IIIb (excluding the aromatic proton region).

ing of the side-chain in the two fractions, we prepared the analogous N-*n*-tridecyl-2,6-dimethylmorpholine (II). Like compound I, II could be separated into two isomers, IIa and IIb, having the same $R_F$ values as Ia and Ib, respectively. However, in spite of their identical $R_F$ values, the structures of Ia and IIa, as well as those of Ib and IIb, are not identical, as shown by a comparison of their PMR spectra. Whereas IIa and IIb each exhibit a triplet at 0.86 ppm due to their terminal methyl groups, as well as a broad singlet at 1.25 ppm corresponding to the polymethylene chain, Ia and Ib show broad multiplets at the resonance frequencies of the methyl and methylene groups, with a much larger methyl to methylene ratio than in II. This shows that the N-alkyl groups in Tridemorph are highly branched. Moreover, the identical $R_F$ values of molecules with differently branched N-tridecyl groups could, in fact, mean that Ia and Ib were mixtures of isomers of the title compound, having different N-alkyl configurations. Indeed, treatment of Ia and Ib with the lanthanide shift reagent $Eu(dpm)_3$ resulted in gradual broadening of all of the resonance signals, until at a higher concentration of the reagent the spectra faded out completely. This can be explained as the result of the increased resolution, causing the ring protons of molecules with different side-chains, which would not otherwise be resolved, to resonate at slightly different frequencies. A similar phenomenon was not observed upon treatment of IIa and IIb with the lanthanide shift reagent.

TABLE I

CHEMICAL SHIFTS AND COUPLING CONSTANTS OF PROTONS IN Ia AND Ib

| *Compound* | *Chemical shift, δ (ppm)* | | | | | *Coupling constant (Hz)* | | | |
|---|---|---|---|---|---|---|---|---|---|
| | *H(1)* | *H(2)* | *H(3)* | *H(4)* | $CH_3$ | $J_{1-2}$ | $J_{1-3}$ | $J_{1-Me}$ | $J_{2-3}$ |
| Ia | 3.61 | 2.68 | 1.64 | 2.26 | 1.11 | 2–3* | 11.0 | 6.2 | 10.0 |
| Ib | 3.93 | 2.37 | 2.08 | 2.21 | 1.19 | 3.2 | 6.0 | 6.2 | 10.5 |

* Could not be measured accurately owing to second-order effects.

Analysis of the chemical shifts and coupling constants of the ring protons permitted the assignment of configuration Ia to the isomer with the lower $R_F$ value, and configuration Ib to the other isomer. Inspection of the spectra of Ib, IIb and IIIb (Fig. 2) shows that the region corresponding to protons 2 and 3 (2.0–2.5 ppm) in each spectrum can be treated as the AB portion of an ABX system, and can be analyzed as a first-order spectrum. The X part of this system is the proton in the α-position to the oxygen atom, which is further split by the adjacent methyl protons to give a ten-line pattern. Similarly, protons 2 and 3 in the spectra of Ia, IIa and IIIa (Fig. 1) give rise to a pattern that can be analyzed in first-order terms as the AM part of an AMX system. Table I lists the chemical shifts and spin–spin coupling constants that arise from the analysis of these systems[9]. The large coupling between *vicinal* protons (labelled 1 and 3) in Ia indicates that they are in a *trans*-diaxial relationship[10]. Indeed, in structure Ia these protons are *trans*-diaxial, and the molecule is practically confined to the conformation shown, in which both methyl groups are in equatorial positions. The situation is different in Ib, where the methyl groups are *trans* to each other, one being axial and the other equatorial. Here the molecule is free to interconvert between two degenerate conformations (Fig. 3), which, of course, are equally populated. This interconversion is very rapid on the NMR time scale at room temperature, and hence we observe chemical shifts and coupling constants that are average values over the two conformations. In one of the conformations protons 1 and 3 are diaxial, whereas in the other conformation they are diequatorial. In the former conformation, we would expect $J_{1-3}$ to be *ca.* 10 Hz, and in the latter *ca.* 2–3 Hz (ref. 10). The observed value is clearly a time average of these two values.

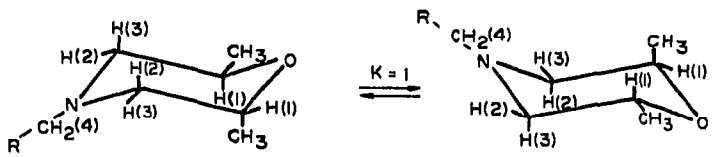



Fig. 3. Conformational equilibrium of two degenerate chair conformations in N-alkyl-*trans*-2,6-dimethylmorpholines: Ib, IIb and IIIb.

Further support for the structural assignment lies in the large difference in the H(2) and H(3) chemical shifts in Ia compared with the relatively small difference in chemical shifts in Ib. In Ia the H(3) protons are predominantly axial, and are closer to the oxygen atom than are the H(2) protons. This results in the observed wide separation between the signals for these protons. In Ib, however, protons H(2) and H(3)

constantly interconvert between axial and equatorial positions, their chemical environments being almost averaged.

Unequivocal proof of the structure was obtained through the preparation of N-benzyl-2,6-dimethylmorpholine (III), and its separation into diastereoisomers IIIa and IIIb. The close resemblance among the ring proton portions of the PMR spectra of Ia, IIa and IIIa, as well as among those of Ib, IIb and IIIb, leaves little doubt that their structures are analogous, within each group. The presence of the prochiral N-benzyl group in III introduces a probe that can sense a chiral environment in its vicinity. Hill and Chan[11] have utilized this characteristic of the benzyl group to develop a method for the assignment of configuration to secondary amines. In the *meso*-morpholine IIIa, the benzyl methylene protons are enantiotopic[12], as the molecule has a plane of symmetry, and hence give rise to a singlet at 3.4 ppm. In contrast, isomer IIIb (as well as Ib and IIb) is chiral, and hence the benzyl methylene protons are diastereotopic[12] and experience different chemical environments, resulting in an AB quartet centred at 3.34 ppm ($\Delta\nu$ 7.5 Hz, $J_{AB}$ 13 Hz) in its PMR spectrum.

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