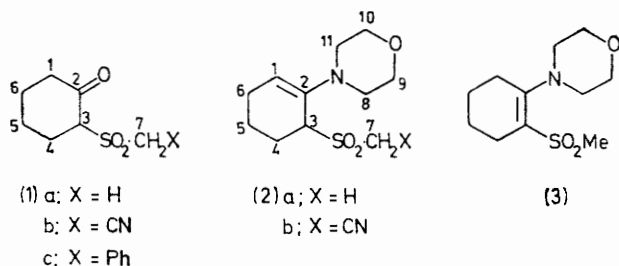


Reinvestigation of the Reaction between 2-Methylsulphonylcyclohexanone and Morpholine: Long-range Effect of a Chiral Centre on the Chemical Shift Equivalence of Morpholine Protons

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The reaction between 2-methylsulphonylcyclohexanone (1a) and morpholine leads only to 3-methylsulphonyl-2-morpholinocyclohexene (2a),† and not to a mixture with the 1-methylsulphonyl isomer (3) as reported previously. A complexity in the ¹H n.m.r. spectrum is explained by the distant chiral centre at C-3, which renders the geminal methylene protons α to nitrogen diastereotopic.

IN part of a study of the cycloaddition reactions of thione SS-dioxides, Borowitz¹ reported that 3-methylsulphonyl-2-morpholinocyclohexene (2a)† and its 1-methylsulphonyl isomer (3) are formed in the ratio *ca.* 2 : 1 in the acid-catalysed reaction between morpholine and 2-methylsulphonylcyclohexanone (1a) in refluxing toluene.



The structures and relative proportions of the two compounds were assigned from the ¹H n.m.r. spectrum (solvent CCl₄-CH₂Cl₂) of the crude product. Pyrolysis of 1-morpholino-7-thiabicyclo[4.2.0]octane 7,7-dioxide was also reported to give these two products in the same ratio.

We have noted² that whereas the assignments made in ref. 1 imply that the C-8 and C-11† geminal protons in compound (2a) have equivalent chemical shifts, non-equivalence was found in the cyano-analogue (2b). We suggested that the difference might arise from lack of free rotation about the bond between the rings in compound (2b), due to a weak intramolecular electrostatic interaction between the morpholine nitrogen atom and methylene group α to the cyano-function.

† Non-systematic numbering adopted for convenience.

‡ This method obviates the necessity for handling methanethiol and the intermediate thioether.

¹ I. J. Borowitz, *J. Amer. Chem. Soc.*, **1964**, **86**, 1146.

² M. P. Sammes, C. M. Wylie, and J. G. Hoggett, *J. Chem. Soc. (C)*, **1971**, 2151.

Other workers^{3,4} have noted chemical shift non-equivalence among the 2- and 6-protons of a morpholino-group when it is attached directly to a chiral centre. However, the results of Del Buttero and Maiorana⁴ for a series of *cis*- and *trans*-3-morpholinotietan 1,1-dioxides imply that steric interaction between the morpholine and a nearby bulky group is an additional requirement for observable non-equivalence, and thus that intrinsic anisochronism is small.

Recently⁵ we provided further evidence for restricted rotation about the inter-ring bond, and for an intramolecular electrostatic interaction in compound (2b), and suggested that the non-equivalence in the C-8 and -11 geminal protons arose from this in conjunction with the presence of the distant chiral centre at C-3. This led us to suggest that the ¹H n.m.r. spectrum, interpreted by Borowitz¹ in terms of a mixture of compounds (2a) and (3), might have arisen from a single substance, (2a), since, by analogy with (2b), the C-8 and -11 protons should be diastereotopic. The added requirement of steric interaction was also present, though the intramolecular electrostatic interaction proposed for the cyano-compound (2b) would be unlikely to be present in structure (2a).

We now report the preparation of a pure sample of compound (2b), and an analysis of its ¹H n.m.r. spectrum.

RESULTS AND DISCUSSION

The oxo-sulphone (1a) was prepared by the reaction between 2-chlorocyclohexanone and sodium methanesulphinate.‡ Its m.p., and that of its 2,4-dinitrophenylhydrazone agreed in the values reported in ref. 1, but

³ P. Ferruti, A. Segre, and A. Fere, *J. Chem. Soc. (C)*, **1968**, 2721.

⁴ P. Del Buttero and S. Maiorana, *J.C.S. Perkin I*, **1973**, 2540.

⁵ M. P. Sammes, R. L. Harlow, and S. H. Simonsen, *J.C.S. Perkin II*, in the press.

differed from those given for an earlier preparation.⁶ The acid-catalysed reaction between compound (1a) and morpholine in boiling toluene gave a high yield of the enamine (2a), with no trace of the isomer (3). The ¹H n.m.r. spectra (solvent CDCl₃) of compounds (1a) and (2a) are compared with those of (1b) and (2b) in the Table.

The spectrum of compound (2a) closely resembles that of the reported mixture of (2a) and (3),¹ and is similar to that of the cyano-analogue (2b), which also shows four triplets between δ 2.4 and 3.2. Strictly, the morpholine unit gives rise to an eight spin system in the ¹H n.m.r. as a consequence of the chiral centre at C-3. However, it may be approximated to an ABX₂ system, in which only the geminal protons at C-8 and -11 are considered to be diastereotopic, and giving rise to the AB portion. The parameters extracted by this approximation are $\Delta\delta_{AB}$ 0.48, δ_A 2.57, δ_B 3.05, δ_X 3.76; $|J_{AB}|$ 12.0, $|J_{AX}| = |J_{BX}| = 4.5$ Hz.

The triplets centred at δ 2.66 and 2.95 are twice as intense as those at 2.47 and 3.14, which accounts for the reported¹ 2:1 ratio of isomers. Likewise, solvent

¹H N.m.r. data (CDCl₃; internal standard Me₄Si) for enamine sulphones (2a and b) and oxo-sulphones (1a and b)

Protons attached at †	(2a)	(2b)	(1a)	(1b)
C-1	5.28 ^a	5.49 ^a	2.53 ^b	2.54 ^b
C-3	3.75 ^c	4.15	3.80 ^a	4.17 ^a
C-4	2.20 ^b	2.25 ^b	2.53 ^b	2.54 ^b
C-5	1.75 ^b	1.80 ^b	1.94 ^b	2.00 ^b
C-6	2.20 ^b	2.25 ^b	1.94 ^b	2.00 ^b
C-7	3.04	4.68 ^d	3.01	4.33 ^e
		4.08		4.17
C-8 and -11 ^f	3.14	3.16		
	2.95	2.96		
	2.66	2.67		
	2.47	2.47		
C-9 and -10	3.76 ^a	3.77 ^a		

† For numbering see formulae.

^a Triplet. ^b Most intense peak of multiplet. ^c Approximate value; hidden by CH₂-O signal. ^d ABq, J 16.3 Hz. ^e ABq, J 16.4 Hz. ^f Central peak of each of four triplets.

absorption (CH₂Cl₂; δ 5.30) would have masked the signal of the olefinic proton at C-1, and the peak at δ 7.15 assigned¹ to this proton may have arisen from a trace of toluene.

It appears that, by analogy with the cyano-compound (2b),⁵ steric interaction between the methylsulphonyl and morpholino groups in compound (2a) results in restricted rotation about the C-N bond linking the two rings. This is evidenced by the low-field position of the C-1 proton signal, indicating little overlap between the C=C bond and the nitrogen lone pair,* and the large value of $\Delta\delta_{AB}$, indicating a high population of a preferred conformation.

Finally, the large difference in chemical shift between the C-3 protons of compounds (1a and b) and of (2a and

b) seems to arise from the nature of the distant group X. This is borne out by the phenyl analogue (1c), which exhibits a δ value of 3.81.⁸

EXPERIMENTAL

¹H N.m.r. spectra were run on a Perkin-Elmer R 20 spectrometer for 10% solutions in CDCl₃ with Me₄Si as internal reference. I.r. spectra were recorded on a Perkin-Elmer 577 spectrophotometer for Nujol mulls. Polystyrene was used in calibration.

2-Chlorocyclohexanone⁹ and sodium methanesulphinate¹⁰ were prepared by known methods. The latter was extremely hygroscopic.

2-Methylsulphonylcyclohexanone (1a).—2-Chlorocyclohexanone (0.1 mol) and sodium methanesulphinate (0.1 mol) were heated together under reflux in ethanol (100 cm³) for 2 h. The precipitated sodium chloride was removed from the cooled solution, and the filtrate evaporated at 100°C under reduced pressure. The resulting syrup was dissolved in chloroform, and passed down a column of alumina (activity V) with the same solvent as eluant. The eluate, which showed a yellow fluorescence to u.v. light, was dried (MgSO₄) and evaporated, and the residual oil triturated with anhydrous ether to yield the sulphone (33%). Recrystallisation from ether gave white prisms, m.p. 52–53° (lit.,¹ 53.5–55.5°) (Found: C, 47.7; H, 6.65; S, 18.1. Calc. for C₇H₁₂O₃S: C, 47.7; H, 6.85; S, 18.2%), ν_{\max} 3 035, 3 013 (Me), 1 699 (C=O), 1 295, 1 144, and 1 125 cm⁻¹ (SO₂); 2,4-dinitrophenylhydrazone, m.p. 193–194° (lit.,¹ 192–194°).

3-Methylsulphonyl-2-morpholinocyclohexene (2a).—2-Methylsulphonylcyclohexanone (0.021 mol) and morpholine (0.046 mol; dried and redistilled) were heated together under reflux in dry toluene (120 cm³) in the presence of a trace of toluene-*p*-sulphonic acid for 72 h. The vapours were condensed and passed through a Soxhlet thimble containing 4A molecular sieves, before being returned to the flask. No attempt was made to exclude oxygen. The cooled product was filtered, the solvent and the excess of morpholine were removed under reduced pressure, and the residue was recrystallised from benzene–light petroleum (b.p. 80–100°) (2:3) to give the enamine (95%) as needles, m.p. 117–118° (Found: C, 53.9; H, 7.5; N, 5.7. C₁₁H₁₉NO₃S requires C, 53.85; H, 7.8; N, 5.7%), ν_{\max} 3 020, 3 000 (Me), 1 652 (C=C), 1 292, 1 127, and 1 120 cm⁻¹ (SO₂).

2-Cyanomethylsulphonylcyclohexanone (1b).—3-Cyanomethylsulphonyl-2-morpholinocyclohexene² (0.5 g) was dissolved with warming in sulphuric acid (10%; 10 cm³), and the solution was cooled and extracted with ether (2 × 15 cm³). The extract was dried (MgSO₄) and evaporated to give an oil (0.27 g, 72%), which solidified on cooling. Recrystallisation [benzene–light petroleum (b.p. 80–100°) (1:1)] gave the sulphone, m.p. 68° (Found: C, 47.5; H, 5.5; N, 6.9. C₈H₁₁NO₃S requires C, 47.75; H, 5.5; N, 6.95%), ν_{\max} 2 262 (CN), 1 708 (C=O), 1 336, and 1 125 cm⁻¹ (SO₂).

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⁸ J. J. Looker, *J. Org. Chem.*, 1966, **31**, 2973.

⁹ M. S. Newman, M. D. Farbmán, and H. Hipsher, *Org. Synth.*, Coll. Vol. III, 1955, 188.

¹⁰ N. H. Nilsson, C. Jacobsen, O. N. Sørensen, N. K. Haunsøe, and A. Senning, *Chem. Ber.*, 1972, **105**, 2854.

* In 1-morpholinocyclohexene, the olefinic proton absorbs at δ 4.55.⁷

⁶ W. E. Truce and R. H. Knopse, *J. Amer. Chem. Soc.*, 1955, **77**, 5063.

⁷ W. D. Gurowitz and M. A. Joseph, *J. Org. Chem.*, 1967, **32**, 3289.