2,3,5,6-Tetramethylmorpholine. III. Synthesis of the Enantiomeric Pair of the β_1-Isomer

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Received September 18, 1978

The cyclodehydration of optically active *N*-benzyl-3,3′-iminobis-2-butanols with sulfuric acid is described. Morpholines with high optical purity are obtained.

J. Heterocyclic Chem., **16**, 595 (1979).

The successful resolution of even simple organic compounds is occassionally difficult to achieve. In any event, resolution is often tedious. In this note we outline a feasible approach to directly synthesize the enantiomers of the isomers of a series of substituted morpholines starting from easily accessible appropriately substituted optically active ethanolamines.

We have recently (1) presented the strategy for the synthesis of any isomer of 2,3,5,6-tetramethylmorpholine in fair yield by using two approaches (Methods A and B in Scheme 1) and by choosing the proper starting compounds. In connection with our studies (2) to elucidate the reaction mechanisms of the cyclodehydrations in Method A and B (Scheme 1), we have found a very simple and useful way to obtain the enantiomers (2*R*:3*R*:5*R*:6*S*)- and (2*S*:3*S*:5*S*:6*R*)-2,3,5,6-tetramethylmorpholine, in fair yield and with very high optical purity. These enantiomers correspond to the β_1-isomer, which was synthesized (1) and its structure elucidated (3) earlier in this series.

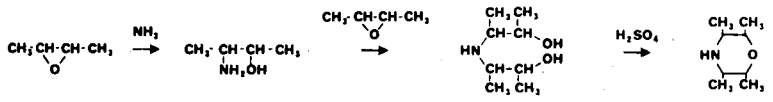
If (2*R*:3*R*)-threo-3-amino-2-butanol (4) is reacted with *cis*-2,3-epoxybutane, two 3,3′-iminobis-2-butanols are formed in the proportion of 56% to 44%. The two compounds are isomers; one is an optically active isomer (2*R*:3*R*; 2′*R*:3′*R*) which is formed according to the reaction mechanism for 2,3-epoxybutanes demonstrated by Dickey, *et al.*, (4), and the other is a meso-compound (2*R*:3*R*; 2′*S*:3′*S*).

If this mixture of 3,3′-iminobis-2-butanols is treated according to Method B (1) in Scheme 1, the resulting tetramethylmorpholines can be separated by preparative glc into three fractions (I′ 1%; II′ 56%; III′ 43%). Fraction II′ is isomerically pure within the limits of detection, and has the same retention time as the β_1-isomer in glc. The enantiomeric purity was confirmed as > 99% by reacting this morpholine with (-)-(*S*)-1-phenylethyl isocyanate and inspecting the relative intensities of the nmr signals for the methyl protons in the crude reaction product (see Figure 1, Spectrum I). This enantiomer has undoubtedly been formed from (2*R*:3*R*; 2′*R*:3′*R*)-*N*-benzyl-3,3′-iminobis-2-butanol and must consequently have the structure (2*R*:3*R*:5*R*:6*S*). This indicates that this cyclization, performed with a large excess of 70% (w/w) sulfuric acid at 140-150° for 15 hours, proceeds by an intramolecular S_N2-type substitution process with inversion of configuration at one chiral center, *i.e.*, at the asymmetric carbon containing the leaving group. Mihailović, *et al.* (5), have recently proposed the same reaction mechanism for the cyclodehydration of alkane-1,4-diols with strong acids. Furthermore, the lack of any (2*R*:3*R*:5*R*:6*R*)-isomer (β_2) indicates that this cyclization does not involve detectable amounts of free carbonium ions.

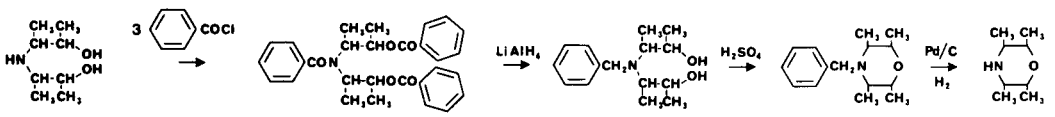
If instead, we started with (2*S*:3*S*)-threo-3-amino-2-butanol and carried out the same operations as described

SCHEME 1

Method A



Method B



0022-152X/79/030595-02$02.25

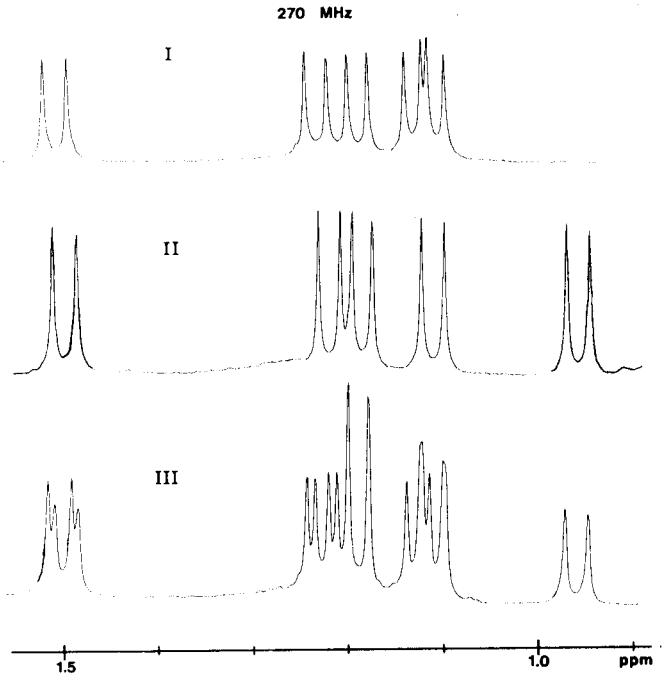


Figure 1. Methyl part of the ^{1}H-nmr Spectra.

above, we obtained, as expected, exactly the same gas-liquid chromatogram (I'' 2%; II'' 55%; III'' 43%) for the morpholine mixture. However, fraction II'' gave a derivative with (-)-(*S*)-1-phenylethyl isocyanate with Spectrum II (see Figure 1), which also showed very high enantiomeric purity. This enantiomer has been formed from (2*S*:3*S*; 2'*S*:3'*S*)-*N*-benzyl-3,3'-iminobis-2-butanol and must accordingly have the structure (2*S*:3*S*:5*S*:6*R*). The β_1-racemate was reacted with (-)-(*S*)-1-phenylethyl isocyanate in the same manner and the nmr spectrum of the crude reaction product (see Figure 1, Spectrum III) was used for comparison.

Fractions III' and III'', corresponding to the γ isomer (1,3), were racemic, as shown by the nmr technique used throughout this paper, and must have been formed from (2*R*:3*R*; 2'*S*:3'*S*)-*N*-benzyl-3,3'-iminobis-2-butanol by the same type of intramolecular S_N2-type substitution process proposed above. A small amount (1-2%) of the (2*S*:3*S*:5*R*:6*R*)-isomer (fractions I' and I''), corresponding to the α-isomer (1,3) was obtained. This indicates that we cannot exclude that the cyclization of (2*S*:3*S*; 2'*R*:3'*R*)-*N*-benzyl-3,3'-iminobis-2-butanol also involves carbonium ions as intermediates. These results also indicate that no detectable change of configuration occurs at the chiral centers next to the nitrogen atom.

Studies directed toward the syntheses of the enantiomers of the additional three isomers of 2,3,5,6-tetramethylmorpholine are in progress and will be published elsewhere (2).

EXPERIMENTAL

Glc.

The analyses were performed on a Varian 940 instrument. The preparative work was carried out as described earlier (1).

(*S*)-*N*-(1-Phenylethyl)-(2*R*:3*R*:5*R*:6*S*)-2,3,5,6-tetramethylmorpholine-4-carboxamide.

A solution of 1.00 g. of (-)-(*S*)-1-phenylethyl isocyanate and 1.00 g. of (2*R*:3*R*:5*R*:6*S*)-2,3,5,6-tetramethylmorpholine in 50 ml. of benzene was boiled for 1 hour. The benzene was evaporated under reduced pressure and the crystalline residue was kept under high vacuum for 1 hour before being directly used for nmr studies. Recrystallization from ligroin (b.p. 80-110°) gave 1.85 g. of colourless crystals, m.p. 127-130°.

Anal. Calcd. for $C_{17}H_{26}N_2O_2$: C, 70.31; H, 9.02; N, 9.65; O, 11.02. Found: C, 70.5; H, 9.15; N, 9.55; O, 11.2.

(*S*)-*N*-(1-Phenylethyl)-(2*S*:3*S*:5*S*:6*R*)-2,3-5,6-tetramethylmorpholine-4-carboxamide.

This compound was prepared as above giving crystals from ligroin (b.p. 80-110°), m.p. 139-141°.

Anal. Calcd. for $C_{17}H_{26}N_2O_2$: C, 70.31; H, 9.02; N, 9.65; O, 11.02. Found: C, 70.4; H, 9.19; N, 9.59; O, 11.1.

Nmr Spectra.

The crude compounds were dissolved in deuteriochloroform in concentrations of about 6 mole %. Spectra were run on a Bruker 270 MHz Ft-nmr instrument at ambient temperature.

Acknowledgement.

The author is grateful to Dr. R. E. Carter for linguistic criticism, to Mr. G. Stenvall for experimental assistance and to Mr. H.-B. Johansson for reproducing the figures.

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