2,3,5,6-Tetramethylmorpholine. IV. The Observation of a New Cyclization Mechanism

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A new type of cyclization, implying the simultaneous inversion of configuration at the reacting carbon atom and at the carbon atom bearing the nucleophilic group, is observed when two 3,3′-iminobis-2-butanols are dehydrated by 70% sulfuric acid at 140-150°.

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Cyclodehydrations of diols to ethers are important and common processes in heterocyclic chemistry. The mechanisms and stereochemistry of such procedures have been studied extensively, especially for 1,4-diols (1). It has been found that such cyclodehydrations with strong acids are stereoselective; meso- or erythro-1,4-diols yield only trans-2,5-dialkyltetrahydrofurans and racemic- or threo-1,4-diols are converted exclusively into *cis*-2,5-dialkyltetrahydrofurans. The results obtained indicate that these cyclizations proceed by an intramolecular S_N2-type substitution process with inversion of configuration at one chiral centre, *i.e.*, at the asymmetric carbon containing the leaving group. No free carbonium ions seem to be involved in these cyclizations.

During the 1930's, Ingold, *et al.* (2), recognized that various nucleophilic substitution reactions were related by common mechanistic patterns. The S_N1 and S_N2 types were regarded as being extremes of a graded range of mechanisms (3). The possible existence of borderline cases was recognized and hese were thought of as having intermediate mechanisms (3,4,5). These mechanisms have never been described in detail, and in the latest discussion it is emphasized that S_N1 and S_N2 are both fundamentally distinct mechanisms (6). The S_N2 reactions invariably proceed by inversion of configuration at the reacting carbon atom *via* backside displacement. The stereochemistry of the S_N1 mechanism is more variable and any result from complete inversion to complete retention of configuration at the reacting carbon atom is possible.

Independently, Ugi, *et al.* (7), and Seebach, *et al.* (8), have recently found S_N2 reactions with retention of configuration at the reacting carbon atom. Stohrer, *et al.* (9), have utilized qualitative MO arguments, extended Hückel calculations and *ab initio* calculations to develop an MO model for the S_N2 reaction with retention.

In another approach, Hammett (10) used the term ion pair in connection with organic reactions. Winstein, *et al.* (11), provided the first definitive experimental evidence for the existence of such ion pair species as organic intermediates and established that ion pairs of two distinct types, intimate and solvent separated, are in fact discrete intermediates in selected organic reactions. However, it has been emphasized that an ion pair is not simply a pair of ions, a pair of point charges, but rather an extended bond with considerable ionic character (12). This concept makes all known varieties of substitution stereochemistry at the reacting carbon potentially available, *i.e.* inversion from the intimate ion pair, retention from the solvent-separated ion pair, and racemisation from the dissociated ion pair. Furthermore, it provides the unifying links among the classically defined mechanisms of S_N1, S_N2 and borderline behaviour (12).

As far as we are aware, no example of or even theoretical considerations about simultaneous inversion of configuration at both the reacting carbon atom and at the carbon atom bearing the nucleophilic group has previously appeared in the literature.

In a recent paper (13), we reported that the cyclization of the diastereoisomeric (2*R*:3*R*:2′*R*:3′*R*)-, (2*S*:3*S*:2′*S*:3′*S*)- and (2*R*:3*R*:2′*S*:3′*S*)-*N*-benzyl 3,3′-iminobis-2-butanols with 70% (w/w) sulfuric acid at 140-150° proceeded almost exclusively by an S_N2-type substitution with inversion of configuration at the carbon containing the leaving group. Only a very small amount of produce due to a carbonium ion mechanism could be detected.

If (2*R*:3*S*:2′*S*:3′*R*)-3,3′-iminobis-2-butanol is treated with 70% (w/w) sulfuric acid at 140-150° for 15 hours, the resulting tetramethylmorpholines can be separated by preparative glc into two fractions (I′: 51%; II′: 49%). Fraction I′ is the (2*R*:3*R*:5*S*:6*S*)-α-isomer (14,15). As no significant change of configuration at the chiral centres next to the nitrogen atom has been observed (13) or is plausible, this isomer must consequently have been formed through inversion of configuration at both the reacting carbon atom and at the carbon atom bearing the nucleophilic hydroxyl group (see Figure 1). Fraction II′ is the racemic γ-isomer (14,15) (2*R*:3*R*:5*S*:6*R* and 2*S*:3*S*:5*R*:6*S*), and its formation can be explained by a normal intramolecular S_N2-type substitution process with inversion of configuration at one chiral centre (see Figure 1).

The absence of the (2*R*:3*S*:5*R*:6*S*)-ε-isomer (14,15) indicates that this cyclization does not involve detectable amounts of free carbonium ions.

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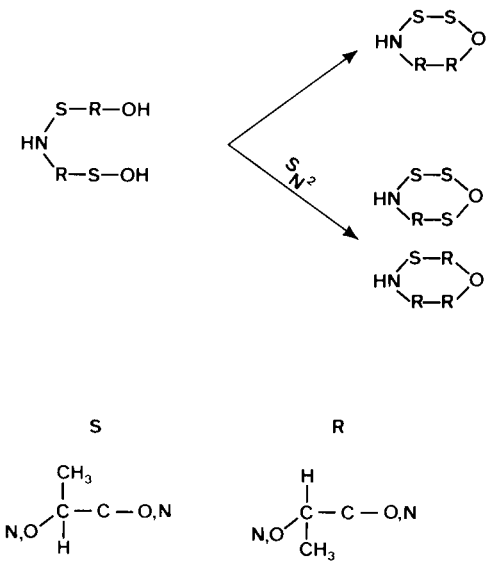

Figure 1

If we instead treat (2*R*:3*S*:2′*R*:3′*S*)-3,3′-iminobis-2-butanol in the same manner, the resulting tetramethylmorpholines can be separated by preparative glc into three fractions (I′′: 65%; II′′: 29%; III′′: 6%). Fraction I′′ is the optically active β_1-isomer (2*S*:3*S*:5*S*:6*R*) with an enantiomeric purity >99 %, as shown by the nmr technique described in our previous paper (13). Its formation can by explained by a normal S_N2-type reaction (see Figure 2). Fraction II′′ is the optically active β_2-isomer (14,15) with an enantiomeric purity >99 %. Its formation must be explained through the proposed type of mechanism for this ring closure described above, implying inversion of configuration at both the carbon atom with the leaving group and the carbon atom bearing the attacking nucleophilic hydroxyl group. Accordingly, its structure is (2*S*:3*S*:5*S*:6*S*) (see Figure 2). Fraction III′′ is the optically active δ-isomer (2*R*:3*S*:5*S*:6*R*), m.p. 58-61°, with an enantiomeric purity >99 %, and its formation might be explained by an S_N1-type reaction involving free carbonium ions. This means that the β_1-isomer might have been partly formed through this carbonium ion mechanism (see Figure 2).

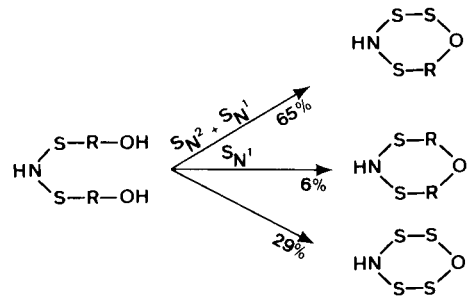

Figure 2
(S and R see Figure 1)

The yields of the different isomers are in excellent agreement with those obtained from the mixture of diastereoisomeric 3,3′-iminobis-2-butanols, resulting from the reaction between racemic *trans*-2,3-epoxybutane and ammonia (15).

In contrast to the cyclization of aliphatic 1,4-diols with strong acids, the cyclization of (2*R*:3*S*:2′*S*:3′*R*)- and (2*R*:3*S*:2′*R*:3′*S*)-3,3′-iminobis-2-butanols in 70% (w/w) sulfuric acid at 140-150° seems to involve three competing reaction mechanisms: i) an S_N2-type substitution with inversion of configuration at the carbon containing the leaving group; ii) an S_N1-type carbonium ion mechanism that gives detectable amounts of retention; and iii) a new type of reaction mechanism which implies a simultaneous inversion of configuration at the carbon atom bearing the leaving group and at the carbon atom bearing the attacking nucleophilic group. Studies directed towards further understanding of the suggested new mechanism of ring closure are in progress.

EXPERIMENTAL

Glc.

The analyses were performed on a Varian 940 instrument. The separation of the various isomers was carried out as described earlier (15).

Preparation of (2*R*:3*S*:2′*R*:3′*S*)-3,3′-Iminobis-2-butanol.

(*R*:*R*)-*trans*-2,3-Epoxybutane (16) (7.2 g., 0.1 mole), 2.0 g. (0.12 mole) of ammonia and 100 ml. of 98% methanol were heated together in a stainless steel autoclave at 120° for 5 hours. The reaction mixture was distilled, which gave 3.0 g. of (2*R*:3*S*)-3-amino-2-butanol, b.p. 62-64° (8 mm), m.p. 49-50° from isopropyl ether (17) and 4.1 g. of an oil, (2*R*:3*S*:2′*R*:3′*S*)-3,3′-iminobis-2-butanol, b.p. 125-128° (8 mm), pure according to glc. (2*R*:3*S*; 2′*R*:3′*S*)-*N*-Benzyl-3,3′-iminobis-2-butanol was prepared according to a method described earlier (15), m.p. 117-119° from ligroin (b.p. 80-110°).

Anal. Calcd. for $C_{15}H_{25}NO_2$: C, 71.67; H, 10.02; N, 5.57; O, 12.73. Found: C, 71.8; H, 10.3; N, 5.61; O, 12.9.

Preparation of (2*R*:3*S*:2′*S*:3′*R*)-3,3′-Iminobis-2-butanol.

(2*R*:3*S*)-3-Amino-2-butanol (2.67 g., 0.03 mole), 2.38 g. (0.033 mole) of (*S*:*S*)-*trans*-2,3-epoxybutane (16) and 50 ml. of 96% ethanol were heated together in a stainless steel autoclave at 120° for 5 hours. The reaction mixture was distilled to give 4.69 g. (97 %) of (2*R*:3*S*:2′*S*:3′*R*)-3,3′-iminobis-2-butanol, b.p. 127-129° (8 mm). It solidified on standing. Recrystallization from ligroin (b.p. 80-110°) gave 4.40 g. of colourless crystals, m.p. 66-69°.

Anal. Calcd. for $C_8H_{19}NO_2$: C, 59.59; H, 11.88; N, 8.69; O, 19.84. Found: C, 59.4; H, 12.2; N, 8.63; O, 20.0.

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

This compound was prepared according to a method described earlier (13), giving crystals from ligroin (b.p. 80-110°), m.p. 154-156°.

Anal. Calcd. for $C_{17}H_{26}N_2O_2$: C, 70.31; H, 9.02; N, 9.65; O, 11.02. Found: C, 70.6; H, 9.09; N, 9.60; O, 11.1.

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

This compound was prepared according to a method described earlier (13), giving crystals from ligroin (b.p. 80-110°), m.p. 185-187°.

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, 9.12; N, 9.62; O, 11.0.

Nmr Spectra.

The crude urea-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.

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