2,3,5,6-Tetramethylmorpholine. V. Mechanism Study of Cyclization of 3,3'-Iminobis-2-butanols

Sven Hernestam and Gillis Stenvall

Department of Organic Chemistry, Research Division, AB Ferrosan, S-201 10 Malmö, Sweden

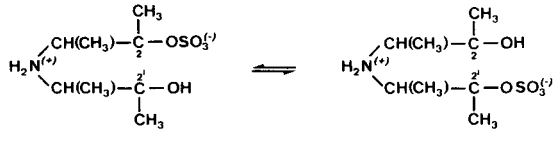
Received September 27, 1979

The mechanism of cyclization of 3,3'-iminobis-2-butanols to 2,3,5,6-tetramethylmorpholines in sulfuric acid is studied. Contrary to our prior suggestions, the ring closure seems to be exclusively a normal S_N2-type substitution. The partial inversion before the cyclization is discussed.

J. Heterocyclic Chem., **17**, 369 (1980).

In our previous paper (1) we suggested that 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° involved 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 inversion of configuration at the carbon bearing the leaving group and at the same time inversion at the carbon bearing the attacking nucleophilic group.

To elucidate if an S_N1-type carbonium ion mechanism is involved in the reaction we treated (2*R*:3*S*:2'*R*:3'*R*)-3,3'-iminobis-2-butanol with 70% (w/w) sulfuric acid at 140-150° for 15 hours. The resulting tetramethylmorpholines were separated by preparative glc into three fractions (I:83%; II:16%, III:1%). Fraction I is the (2*R*:3*R*:5*S*:6*S*)-α-isomer. Fraction III is the (2*R*:3*S*:5*R*:6*S*)-ε-isomer. Their formation can be explained by a normal S_N2-type reaction (See Figure 1). This indicates that a protonated hydroxyl group probably is the leaving group. An assumed sulfation might give an acid sulfate with complete retention of configuration (*c.f.*, 2-butanol (2,3)) but if -O-SO_3H was presumed to be the leaving group more ε-isomer might have been formed as the 2- and 2'-hydroxyl groups seem to be equivalent in a normal sulfation reaction. However, an equilibrium between



without breaking of any C-O bond and with retention of configuration cannot be excluded. Steric interaction in the S_N2-transition state might be a possible explanation for the small yield of the ε-isomer if either -OH_2^+ or -OSO_3H is the leaving group. Fraction II is the racemic (2*R*:3*R*:5*S*:6*R* and 2*S*:3*S*:5*R*:6*S*)-γ-isomer (See Figure 1) and consequently it cannot have been formed through an S_N1-type carbonium ion mechanism. A consideration of this result led us to speculate that the (2*R*:3*S*:2'*R*:3'*R*)-3,3'-iminobis-2-butanol should isomerize fairly readily under acidic conditions at the 2- and/or 2'-carbon atoms giving (2*S*:3*S*:2'*R*:3'*R*)-, (2*R*:3*S*:2'*S*:3'*R*)- and (2*S*:3*S*:2'*S*:3'*R*)-3,3'-iminobis-2-butanols as intermediates. A normal S_N2-type ring closure of these diols formed would give the racemic γ-isomer and the α-isomer. This type of reaction mechanism, first inversion and then an S_N2-type ring closure also would explain the third mechanism proposed in our previous paper (1), a reaction that seemed to imply a simultaneous inversion of configuration at both the 2-and 2'-carbon atoms at the ring closure.

It cannot be excluded that this inversion starts by a sulfation with complete retention of configuration (2) of the 3,3'-iminobis-2-butanol to give an alkyl hydrogen sulfate, which then undergoes racemization. It has been found (3) that in a reaction between *d*-2-butanol and 96% sulfuric acid at 25°, the unesterified alcohol isolated from the reaction has completely retained configuration even after extensive racemization of the *sec*-butyl hydrogen sulfate. This indicates that the alcohol does not racemize prior to sulfation and that *sec*-butyl hydrogen sulfate present in the reaction mixture is racemized easier than the alcohol present as such. However it has been shown (4) that the most probable mechanism for this racemization involves ionization to carbonium and hydrogen-sulfate ions in an S_N1-type reaction followed by reassociation to alkyl hydrogen sulfate. Thus, sulfation followed by

$$d\text{-ROSO}_3\text{H} \rightarrow \text{R}^+ + \text{HSO}_4^- \rightleftharpoons dl\text{-ROSO}_3\text{H}$$

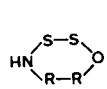
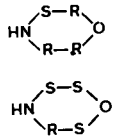
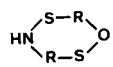
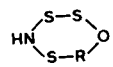
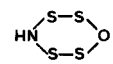
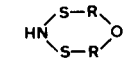
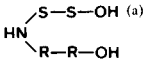
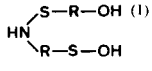
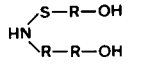
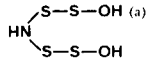
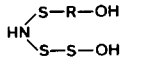
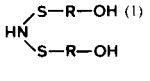
racemization does not seem to be a likely mechanism for this inversion as the appearance of carbonium ions in the reaction might have given a detectable amount of optically active γ-isomer.

In the reaction described the proposed three intermediates might be found at any time in small amounts. In order to study the reaction and to find out the best chances to identify an intermediate, all six diastereoisomeric 3,3'-iminobis-2-butanols were treated with sulfuric acid under different conditions for 15 hours according to Table 1. From these results it is likely that

0022-152X/80/020369-04$02.25

Table 1

The Ratio Between the Different 2,3,5,6-Tetramethylmorpholine Isomers

3,3'-Iminobis-2-butanol	% Sulfuric Acid (w/w)	Temperature °C						
	50	145	23	77				
	70	145	52	47	1			
	96	120	75	25				
	40	145	7	93				
	50	145	17	83				
	60	145	41	59				
	70	145	52	48				
	80	145	58	42				
	96	120	73	27				
	50	145	99	1				
	70	105	97	3				
	70	120	93	7				
	70	145	83	16	1			
	70	170	85	15				
	96	120	82	18				
	50	145				99	1	
	70	145				87	11	2
	96	120				82	15	3
	50	145				24	63	13
	70	120				32	56	12
	70	145				35	53	12
	70	170				38	50	12
	80	145				44	46	10
	96	120				66	28	6
	50	145				90	8	2
	60	145				73	22	5
	70	145				68	26	6
	96	120				68	26	6

(a) Run as a mixture of (2*S*:3*S*:2'*S*:3'*S*)- and (2*S*:3*S*:2'*R*:3'*R*)-3,3'-iminobis-2-butanols (7).

(2*R*:3*S*:2'*S*:3'*R*)-3,3'-iminobis-2-butanol might give the largest degree of inversion as 52% of the α-isomer is obtained in a normal synthetical approach. From the reaction mixture of such a run (70% (w/w) sulfuric acid, 145°) a sample was taken after 1.5 hours. As it has been found (5,6) that hydrolysis of *sec*-butyl hydrogen sulfate in basic solutions gives 2-butanol of inverted configuration the sample was alkalized at -5° to prevent hydrolysis of any alkyl hydrogen sulfate, exhaustively extracted with diethyl ether, which was dried with sodium sulfate and evaporated. The residue was used for tlc, that showed that the reaction mixture contained a small amount of (2*R*:3*S*:2'*R*:3'*R* and 2*S*:3*S*:2'*S*:3'*R*)-3,3'-iminobis-2-butanol (R_f = 0.66) and unchanged starting substance (R_f = 0.61). The alkaline

Table 2

Ratio Between the α- and γ-Isomers.

Time hours	α/γ
1/4	14:86
1/2	26:74
1	39:61
1 1/2	45:55
2 1/2	48:52
3	52:48
4	50:50
15	52:48

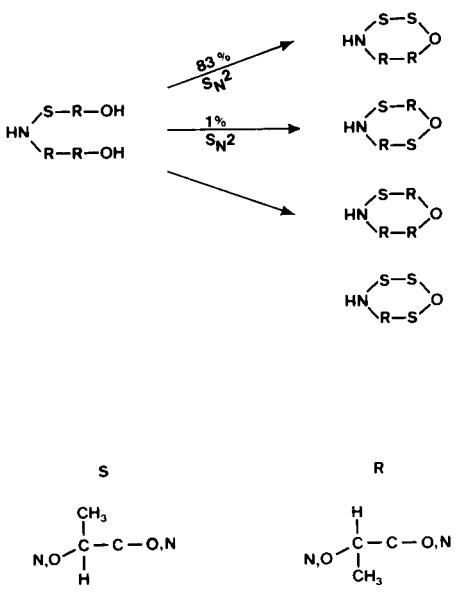
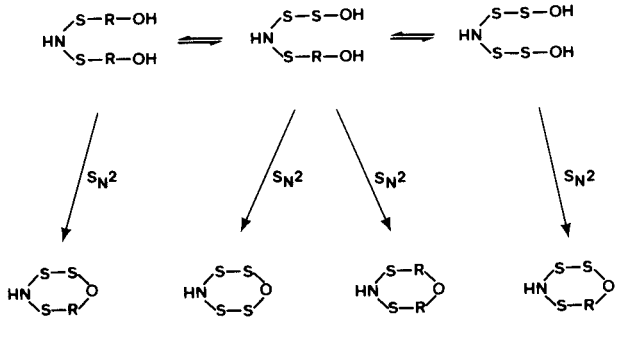


Figure 1

water solution was heated on the water bath for 12 hours and extracted with diethyl ether. No diols could be detected by tlc which implies that no detectable amount of alkyl hydrogen sulfates seems to be present in the reaction mixture. The time course was also studied by determining the ratio between the α- and γ-isomers in the reaction mixture (See Table 2). These results give a picture of the amount of the different 3,3'-iminobis-2-butanols in the reaction mixture. They also show that the ring closure is complete after about 3 hours. However, from synthetical point of view a reaction time of 15 hours is justified. Shorter reaction time gives unidentified by-products that interfere with the preparative glc separation (7). Only an insignificant decomposition and no isomerization or racemization has been observed when the 2,3,5,6-tetramethylmorpholines are treated with 70% (w/w) sulfuric



Scheme 1

acid at 140-150° for 15 hours. In the same way it was possible to prove that the reaction mixture from (2*R*:3*S*:2'*R*:3'*S*)-3,3'-iminobis-2-butanol (1) contained the (2*S*:3*S*:2'*R*:3'*S*)-isomer. These results verify that the mechanism of the reaction might be as outlined in the example in Scheme 1. This means that the cyclization of the 3,3'-iminobis-2-butanols proceeds exclusively by an intramolecular S_N2-type substitution process. The same result has been found (8) for cyclodehydrations of 1,4-diols with strong acids giving tetrahydrofurans. The yields of the different isomers of 2,3,5,6-tetramethylmorpholine might depend on i) the 3,3'-iminobis-2-butanol used, and ii) the rate of the different reactions outlined in Scheme 1. That the rates of the ring closures can differ considerably was observed when a mixture of (2*R*:3*R*:2'*R*:3'*R*)- and (2*R*:3*R*:2'*S*:3'*S*)-3,3'-iminobis-2-butanols was treated with 40% (w/w) sulfuric acid at 145° for 15 hours. The total yield of the 2,3,5,6-tetramethylmorpholines was low (< 50%) and the ratio $\alpha + \gamma + \epsilon/\beta_1 + \beta_2 + \delta$ was found to be 8:92. Furthermore, the ratio between the two isomers β_2 (2*S*:3*S*:5*S*:6*S*) and δ (2*R*:3*S*:5*S*:6*R*) in all reactions where they are obtained is about constant. That might be a further evidence that they are formed from the same intermediate, (2*S*:3*S*:2'*R*:3'*S*)-3,3'-iminobis-2-butanol, and it implies that on account of steric interaction in the transition state the 2'-hydroxyl is about four times as reactive as the 2-hydroxyl as a leaving group in this S_N2-type reaction.

From Table 1 it is obvious that both the concentration of the sulfuric acid and the temperature have an effect on the reaction rates. Higher concentrations of sulfuric acid and higher reaction temperatures both increase the yields of compounds obtained from 3,3'-iminobis-2-butanols formed in the reaction. Treating, *e.g.*, (2*R*:3*S*:2'*S*:3'*R*)-3,3'-iminobis-2-butanol with 96% (w/w) sulfuric acid at 120° for 15 hours gave an α/γ-ratio of 73:27. These more severe conditions have not been studied as a certain amount of isomerization of the 2,3,5,6-tetramethylmorpholines formed has been observed and another reaction mechanism than in diluted sulfuric acid cannot be excluded. The results also show that all six 3,3'-iminobis-2-butanols are reacting with a substantial amount of inversion before ring closure.

However, in a recent paper (9) we reported the cyclization of (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 a normal S_N2-type reaction. Only (2*R*:3*R*:2'*S*:3'*S*)-*N*-benzyl-3,3'-iminobis-2-butanol had undergone rearrangement up to a few percent before ring closure. These results mean that benzyl substitution at the N-atom seems to interfere with the inversion at the 2- and 2'-carbon atoms in the *N*-benzyl-3,3'-iminobis-2-butanols. This implies that the inversion is possible not a normal

racemization of an alcohol but might be a reaction taking part in the trigonal pentacoordinate structure of the S_N2 transition state. Further evidence that *N*-benzylsubstituents interfere with the S_N2 transition state was obtained when (2*R*:3*S*:2′*R*:3′*R* and 2*S*:3*R*:2′*S*:3′*S*)-*N*-benzyl-3,3′-iminobis-2-butanol was treated with 70% (w/w) sulfuric acid at 140-150°. This synthetic approach (7) gave a surprisingly good yield of the all *cis* (2*R*:3*S*:5*R*:6*S*)-ϵ-isomer (62%) compared to the (2*S*:3*S*:5*R*:6*R*)-α-isomer (29%). Without a *N*-benzyl substituent 1% of ϵ-isomer and 83% of α-isomer were obtained. Further work to elucidate the influence of different N-substituents on this type of cyclizations is 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 (7).

Tlc.

Pre-coated plates Kieselgel 60 F_{254}, 0.25 mm, Merck were used. The developing solvent was 2-butanol, methanol, water, ammonia: 40:40:40:5.

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

(2*R*:3*R*)-3-Amino-2-butanol (2.67 g., 0.03 mole), (9,10), 2.38 g. (0.033 mole) of (*R*:*R*)-*trans*-2,3-epoxybutane (11) and 50 ml. of 96% ethanol were heated together in a stainless steel autoclave at 120° for 5 hours. The reaction product was distilled to give 4.50 g. (93%) of an oil, (2*R*:3*S*:2′*R*:3′*R*)-3,3′-iminobis-2-butanol, b.p. 125-128° (8 mm), pure according to glc. (2*R*:3*S*:2′*R*:3′*R*)-*N*-Benzyl-3,3′-iminobis-2-butanol was prepared according to a method described earlier (7), m.p. 90-92° 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, 71.9; H, 10.3; N, 5.65; O, 12.7.

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

This compound was prepared as above from (2*S*:3*S*)-3-amino-2-butanol (10) and (*R*:*R*)-*trans*-2,3-epoxybutane (11) giving crystals of (2*R*:3*S*:2′*S*:3′*S*)-3,3′-iminobis-2-butanol, m.p. 73-76° from ligroin (b.p. 80-110°).

Anal. Calcd. for $C_8H_{19}NO_2$: C, 59.59; H, 11.88; N, 8.69; O, 19.84. Found: C, 59.6; H, 12.3; N, 8.74; O, 20.1.

Acknowledgements.

We wish to express our thanks to Dr. Hans-Dieter Becker for comments on the manuscript and for linguistic criticism. We are also grateful to Mr. H.-B. Johansson for reproducing the figures.

REFERENCES AND NOTES

(1) S. Hernestam, *J. Heterocyclic Chem.*, **16**, 1253 (1979).
(2) R. L. Burwell, Jr, *J. Am. Chem. Soc.*, **67**, 220 (1945).
(3) N. C. Deno and M. S. Newman, *ibid.*, **72**, 3852 (1950).
(4) N. C. Deno and M. S. Newman, *ibid.*, **73**, 1920 (1951).
(5) R. L. Burwell Jr, and H. E. Holmquist, *ibid.*, **70**, 878 (1948).
(6) R. L. Burwell Jr, *ibid.*, **74**, 1462 (1952).
(7) S. Hernestam and G. Stenvall, *J. Heterocyclic Chem.*, **13**, 733 (1976).
(8) M. Lj. Mihailović, S. Gojković, and Z. Cekovic, *J. Chem. Soc., Perkin Trans. I*, 2460 (1972).
(9) S. Hernestam, *J. Heterocyclic Chem.*, **16**, 595 (1979).
(10) F. H. Dickey, W. Fickett and H. J. Lucas, *J. Am. Chem. Soc.*, **74**, 944 (1952).
(11) K. Mori, S. Tamada and M. Matsui, *Tetrahedron Letters*, 901 (1978).