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The cyclization of *N*-substituted 3,3'-iminobis-2-butanols to *N*-substituted 2,3,5,6-tetramethylmorpholines in sulfuric acid is studied. The ring closure seems to be exclusively a normal  $S_N2$ -type substitution with partial inversion of configuration before the cyclization. The steric influence of the *N*-substituents on the  $S_N2$ -reaction and on the inversion is discussed.

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As part of our study of the ring closure of 3,3'-iminobis-2-butanols with sulfuric acid, we investigated the reaction of *N*-substituted derivatives. As we have shown in our previous papers (1,2,3) the ring closure seems to follow exclusively a normal  $S_N2$ -type pattern but gives different yields of the different isomers depending on whether the nitrogen atom is benzylated or not. This could mean that the *N*-substituent may interfere with the  $S_N2$  transition state. The results also show that all six possible 3,3'-iminobis-2-butanols (3) are reacting with a substantial amount of inversion before ring closure. On the other hand ring closure of *N*-benzyl-[(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*)]-3,3'-iminobis-2-butanols (4) gives only a negligible amount (1-2%) of inversion (1).

If *N*- $R_1$ -(2*R*:3*R*;2'*R*:3'*S* and 2*S*:3*S*;2'*S*:3'*R*)-3,3'-iminobis-2-butanol is treated with sulfuric acid at elevated temperature for 15 hours, the resulting *N*- $R_1$ -tetramethylmorpholines can either be separated directly by glc ( $R_1$  = alkyl) or first transformed by hydrogenation ( $R_1$  = aryl- $CH_2$ -) to the corresponding tetramethylmorpholines and then separated. The hydrogenation was performed in 96% ethanol with 10% palladium on charcoal as catalyst at 50° and at 1500 psi. At higher temperatures in certain preparations a good yield of *N*-ethyl- $\epsilon$ -2,3,5,6-tetramethylmorpholine was obtained. A similar kind of *N*-alkylation has been observed upon hydrogenation of pyridines in alcoholic solution using nickel catalysts (5). Any extensive alkylation of the five other tetramethyl morpholine-isomers was not observed even if the temperature was raised to 125°. The results (see Table I) show that if  $R_1$  is ethyl or a bulkier group, a surprisingly good yield is obtained of

the all *cis*(2*R*:3*S*;5*R*:6*S*)- $\epsilon$ -isomer compared to the other less sterically hindered possibility, the (2*S*:3*S*;5*R*:6*R*)- $\alpha$ -isomer in the  $S_N2$  ringclosure reaction. This means that the 4- and 4'-methyl groups most likely force the *N*-substituents towards the  $S_N2$  transition area. After all the sterical influence of the  $R_1$ -substituent must be such that the total steric repulsion is greater in state 1 than in state 2 (Figure 1).

If this is correct the methyl groups above the plane in state 2 may interfere less with each other than the *N*-ethyl group with the 1- and 1'-methyl groups in state 1. Although it is known that the geometry of transition states is not the same as in the normal molecule: a carbon atom at a reaction site does not necessarily conform to a tetrahedral shape (6), this sterical interaction can be visualized using a Drieding molecular model. On the other hand when the nitrogen atom is unsubstituted, the methyl groups in state 2 give such a high steric repulsion that only a trace amount of the  $\epsilon$ -isomer is obtained. Since the *N*-methyl substitution gives an intermediate result, the steric influence of the *N*-methyl group on the 1- and 1'-methyl groups must be rather small compared with the steric influence of the methyl groups above the plane in state 2. Any further dramatic increase of the yield of the  $\epsilon$ -isomer by increasing the bulkiness of  $R_1$  has not been found but it can be stated that it appears as if benzyl groups give a somewhat lower  $\alpha/\epsilon$  ratio than straight alkyl groups, nor has any influence of the ratio  $\alpha/\epsilon$  by changing the *N*-substituent from benzyl to substituted benzyl groups been seen, which means that any electronic influence of the  $R_1$ -substituent on the  $S_N2$  transition state is most unlikely.

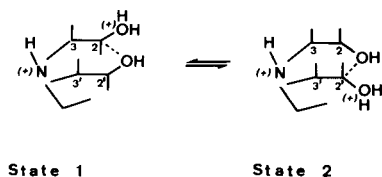
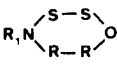
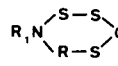
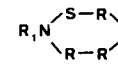
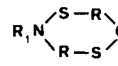
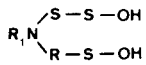
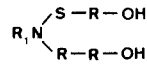
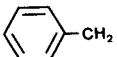
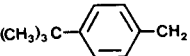
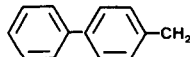
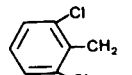
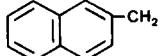
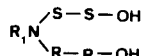
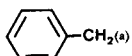
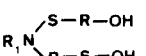
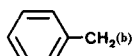


Figure 1

A similar steric influence has been observed (Table II) at the ring closure of *N*- $R_1$ -(2*S*:3*S*;2'*R*:3'*S* and 2*R*:3*R*;2'*S*:3'*R*)-3,3'-iminobis-2-butanol. When  $R_1$  = H, a  $\beta_2/\delta$  ratio of 53/12 is obtained. With full steric interaction,  $R_1$  = Et or bulkier groups, a  $\beta_2/\delta$  ratio of 47/37 is obtained. Also in this case, the methyl substituent gives an intermediate result  $\beta_2/\delta$  = 63/22. It is not immediately obvious why the two pairs of diagonal *cis*-methyl groups (giving  $\beta_2$ )

Table I

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

$N-R_1-3,3'$ -Iminobis-2-butanol $R_1$	% Sulfuric Acid (w/w)	Temperature		 	
 			$\alpha$	$\gamma$	$\epsilon$
H (3)	50	145	99	1	—
	70	145	83	16	1
CH <sub>3</sub>	50	145	85	—	15
	70	145	83	4	13
C <sub>2</sub> H <sub>5</sub>	50	145	43	1	56
	70	145	41	4	55
n-C <sub>7</sub> H <sub>15</sub>	70	145	43	4	53
	50	145	30	1	69
	70	100	26	1	73
	70	145	27	2	71
	60	145	31	2	67
	60	145	28	2	70
	70	145	27	3	70
	60	145	30	3	67
 H (3)	50	145	23	77	—
	70	145	52	45	1
CH <sub>3</sub> (a)	50	145	14	86	—
	70	145	24	72	4
	70	145	3	97	—
 H (3)	50	145	17	83	—
	70	145	52	48	—
CH <sub>3</sub> (b)	50	145	7	92	1
	70	145	15	80	5
	70	145	1	99	—

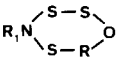
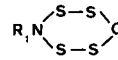
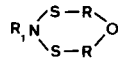
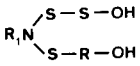
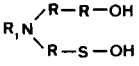
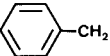
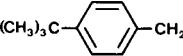
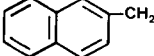
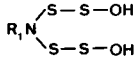
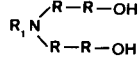
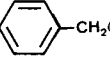
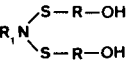
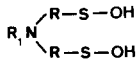
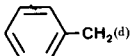
(a) Run as a mixture of  $N-R_1$ -[(2*S*:3*S*; 2'*S*:3'*S*), (2*R*:3*R*; 2'*R*:3'*R*)- and (2*S*:3*S*; 2'*R*:3'*R*)]-3,3'-iminobis-2-butanol (10). (b) Run as a mixture of  $N-R_1$ -[(2*S*:3*R*; 2'*R*:3'*S*), (2*R*:3*S*; 2'*R*:3'*S*)- and (2*S*:3*R*; 2'*S*:3'*R*)]-3,3'-iminobis-2-butanol (10).

in the transition state seem to exert a greater steric influence on the  $N$ -substituent than the two pairs of vicinal *cis*-methyl groups, giving the  $\delta$ -isomer. However, it might depend on some kind of steric distortion which changes

the spatial arrangement of the transition state and/or some kind of solvent interaction, which cannot be anticipated but which makes different degrees of conformational freedom available to these two systems.

Table II

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

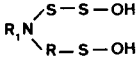
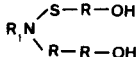
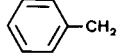
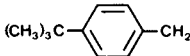
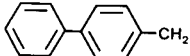
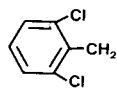
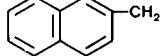
<i>N</i> -R <sub>1</sub> -3,3'-Iminobis-2-butanol R <sub>1</sub>	% Sulfuric Acid (w/w)	Temperature			
			$\beta_1$	$\beta_2$	$\delta$
H (3)	50	145	24	63	13
	70	145	35	53	12
CH <sub>3</sub>	50	145	8	70	22
	70	145	15	63	22
C <sub>2</sub> H <sub>5</sub>	50	145	8	52	40
	70	145	16	47	37
	50	145	10	49	41
	70	100	17	47	36
	70	145	20	42	38
	60	145	16	48	36
	60	145	14	45	41
					
H (3)	50	145	99	1	—
	70	145	87	11	2
CH <sub>3</sub> (a)	50	145	98	2	—
	70	145	95	4	1
	70	145	98	1	1
					
H (3)	50	145	90	8	2
	70	145	68	26	6
CH <sub>3</sub> (c)	50	145	98	2	—
	70	145	94	5	1
	70	145	98	1	1

(a) Run as a mixture of *N*-R<sub>1</sub>-[(2*S*:3*S*; 2'*S*:3'*S*)], (2*R*:3*R*; 2'*R*:3'*R*) and (2*S*:3*S*; 2'*R*:3'*R*)]-3,3'-iminobis-2-butanol (10). (b) Run as a mixture of *N*-R<sub>1</sub>-[(2*S*:3*S*; 2'*S*:3'*S*) and (2*S*:3*S*; 2'*R*:3'*R*)]-3,3'-iminobis-2-butanol (1) so the tetramethylmorpholines are optically active. (c) Run as a mixture of *N*-R<sub>1</sub>-[(2*S*:3*R*; 2'*R*:3'*S*)], (2*R*:3*S*; 2'*R*:3'*S*) and (2*S*:3*R*; 2'*S*:3'*R*)]-3,3'-iminobis-2-butanol (10). (d) Run from *N*-R<sub>1</sub>-(2*R*:3*S*; 2'*R*:3'*S*)-3,3'-iminobis-2-butanol (2) so the tetramethylmorpholines are optically active.

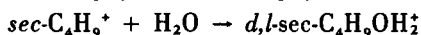
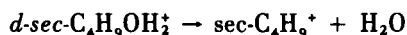
From Tables I and II it is evident that a significant amount of inversion is taking place for most diols before ring closure. When alcohols are dissolved in strong protonic acids they generally accept a proton from the acid to form a positively charged intermediate. As stated

previously, the oxonium compounds of the 3,3'-iminobis-2-butanol normally undergo a ring closure forming an ether bond in a normal S<sub>N</sub>2 reaction by a nonprotonated hydroxyl group approaching from the back to expel a water molecule from the oxonium salt of the alcohol. From

Table III

R <sub>1</sub>	M.p., °C	Molecular Formula					Analyses %	
			Calcd.	Found	Calcd.	Found		
H; HCl	129-131	C <sub>8</sub> H <sub>20</sub> NO <sub>2</sub> Cl	48.59	10.20	7.09	17.93		
			48.8	10.5	7.01	18.0		
CH <sub>3</sub> , <i>p</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> SO <sub>3</sub> H	107-110	C <sub>16</sub> H <sub>29</sub> NO <sub>3</sub> S	55.31	8.41	4.03			
			55.8	8.52	3.91			
C <sub>2</sub> H <sub>5</sub> , HCl	154-157	C <sub>10</sub> H <sub>24</sub> NO <sub>2</sub> Cl	53.20	10.71	6.21	15.71		
			53.0	10.7	6.18	15.6		
<i>n</i> -C <sub>7</sub> H <sub>15</sub> , HCl	98-101	C <sub>15</sub> H <sub>34</sub> NO <sub>2</sub> Cl	60.89	11.58	4.73	11.98		
			61.0	11.5	4.59	12.0		
	73-75	C <sub>15</sub> H <sub>25</sub> NO <sub>2</sub>	71.67	10.02	5.57			
			71.5	10.10	5.49			
	141-144	C <sub>19</sub> H <sub>33</sub> NO <sub>2</sub>	74.22	10.82	4.57			
			74.0	10.6	4.61			
	118-121	C <sub>21</sub> H <sub>29</sub> NO <sub>2</sub>	77.02	8.93	4.28			
			77.3	8.96	4.09			
	134-137	C <sub>13</sub> H <sub>23</sub> NO <sub>2</sub> Cl <sub>2</sub>	56.26	7.24	4.37	22.14		
			55.9	7.20	4.29	22.1		
	134-137	C <sub>19</sub> H <sub>27</sub> NO <sub>2</sub>	75.71	9.03	4.65			
			76.0	8.95	4.60			

racemisation studies of 2-butanol it is known that the oxonium compound undergoes a unimolecular reaction resulting in racemization (7).



As stated earlier, a carbonium ion intermediate in this type of reaction would give in the ring closure of (2*R*:3*S*; 2'*R*:3'*R*)-3,3'-iminobis-2-butanol, a certain amount of the optically active  $\gamma$ -isomer through an S<sub>N</sub>1-reaction. However, we have not found any optically active  $\gamma$ -isomer (3), which most probably means that a free carbonium ion is not an intermediate. Tentatively, we believe that an aziridine ring structure (Figure 2) might exist as an intermediate.

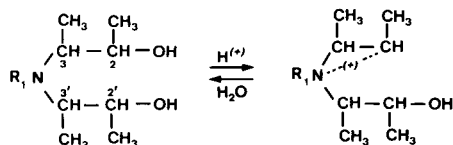


Figure 2

A real covalent bond between the nitrogen atom and the 2-carbon atom cannot be formed. Otherwise an extensive isomerisation at the carbon atoms next to the nitrogen atom would have occurred. No such reaction has been observed. The charge distribution in the ammonium-carbonium ion intermediate is such that no S<sub>N</sub>1-type ring closure is obtained. On the other hand, we believe that the postulated three-ring intermediate can react with a water and/or sulfuric acid molecule in the sulfuric acid medium giving both *S* and *R* configuration at the 2- and 2'-carbon atoms. The *S/R* ratio might depend on steric factors. A three-ring intermediate has been proposed for the racemization of L(+)-2 $\alpha$ -tropanol (8). Furthermore, alkylations with aliphatic nitrogen mustards resemble an S<sub>N</sub>2 process because the rate-controlling step is the reaction of the readily formed, yet relatively stable, aziridinium ion with an available nucleophile (9). The assumed three-ring intermediate can also explain why *N*-substitution gives a smaller degree of inversion. The bulkiness of the *N*-substituents would make the intermediate three-ring structure formation more difficult by interference with the methyl-groups. Furthermore it must be emphasized that we believe that the formation of this three-ring inter-

Table IV



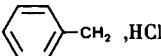
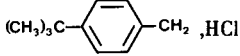
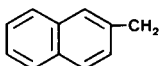
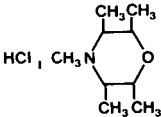
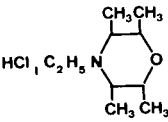
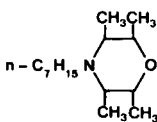
R <sub>1</sub>	M.p., °C	Molecular Formula	Analyses %			
			C	H	N	Cl
H	69-71	C <sub>8</sub> H <sub>19</sub> NO <sub>2</sub>	59.59 59.1	11.88 11.7	8.69 8.62	
CH <sub>3</sub> , HCl	122-124	C <sub>9</sub> H <sub>22</sub> NO <sub>2</sub> Cl	51.05 51.4	10.48 10.4	6.62 6.49	16.74 16.8
C <sub>2</sub> H <sub>5</sub> , HCl	164-167	C <sub>10</sub> H <sub>24</sub> NO <sub>2</sub> Cl	53.20 53.5	10.71 10.9	6.21 6.11	15.71 15.6
 , HCl	177-179	C <sub>15</sub> H <sub>26</sub> NO <sub>2</sub> Cl	62.59 62.8	9.11 9.01	4.87 4.72	12.32 12.3
 , HCl	152-156	C <sub>11</sub> H <sub>34</sub> NO <sub>2</sub> Cl	66.35 66.4	9.96 10.1	4.07 3.92	10.31 10.2
	106-109	C <sub>19</sub> H <sub>27</sub> NO <sub>2</sub>	75.71 75.4	9.03 8.99	4.65 4.59	

Table V

R <sub>1</sub>	M.p., °C	Analyses	
		Calcd./	Found
		Cl	
α	160-163	18.30	18.1
β <sub>1</sub>	169-172		18.2
β <sub>2</sub>	202-205		18.1
γ	139-142		18.0
δ	186-188		18.2
ε	277-280		18.3
			
α	187-190	17.07	17.1
β <sub>1</sub>	163-166		17.2
β <sub>2</sub>	129-132 (a)		16.7
γ	149-152		17.0
δ	190-193		17.2
ε	299-302		17.1
			
α: p-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> SO <sub>3</sub> H	69-72	(b)	
γ: p-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> SO <sub>3</sub> H	95-98	(c)	
ε, HCl	190-193	11.90	11.9

(a) Very hygroscopic (b) Equivalent weight: 413.5 (Calcd. for C<sub>22</sub>H<sub>39</sub>NO<sub>2</sub>S: 413.63). (c) Equivalent weight: 414.0.

mediate is very likely a reaction competing with a normal S<sub>N</sub>2 ring closure, and in some way involved in the trigonal pentacoordinate structure of the S<sub>N</sub>2 transition state.

As stated previously, the concentration of sulfuric acid has an obvious effect on the inversion (3). However, the intimate mechanism that would explain why the concentration of the sulfuric acid should facilitate the formation of an intermediate three-ring transition state cannot be directly understood. It seems that this reaction fundamentally differs from the racemization of *d*-2-butanol but further insight is needed to reveal the true reaction mechanism.

## EXPERIMENTAL

### Glc.

The analyses were performed on a Varian 3700 instrument. Preparation of (2*R*:3*S*;2'*R*:3'*R* and 2*S*:3*R*;2'*S*:3'*S*)-3,3'-Iminobis-2-butanol.

Crystalline *N*-benzyl-3,3'-iminobis-2-butanol (10) (25.1 g.) m.p. 73-75°, the diol prepared from *D,L*-threo-3-amino-2-butanol and *trans*-2,3-epoxybutane, was hydrogenated in 200 ml. of 96% ethanol over 1 g. of 10% palladium on charcoal at 50° and at 1500 psi in a stainless steel autoclave with efficient stirring. After about 3 hours, the theoretical amount of hydrogen had been absorbed. The filtrate obtained from the hydrogenation was evaporated under good vacuum. The residue was distilled giving 15.0 g. (93%) of diol, b.p. 125-128° (8 mm). The hydrochloride, recrystallized from ethanol-diethyl ether, had m.p. 129-131° (for analysis see Table III).

Preparation of (2*S*:3*S*;2'*R*:3'*R* and 2*R*:3*R*;2'*S*:3'*R*)-3,3'-Iminobis-2-butanol.

The mother liquor from the preparation of *N*-benzyl-(2*R*:3*S*;2'*R*:3'*R* and 2*S*:3*R*;2'*S*:3'*S*)-3,3'-iminobis-2-butanol, see example 6c (10), prepared

from **D,L**-threo-3-amino-2-butanol and *trans*-2,3-epoxybutane, was evaporated under a good vacuum. The residue (53 g.) was hydrogenated as described in the example above giving 35 g. of 3,3'-iminobis-2-butanol, which by glc analysis was shown to contain two isomers (83:17). Recrystallization twice from 400 ml. of ligroin (b.p. 80-110°), gave 24.0 g. of glc pure colourless crystals, m.p. 69-71° (for analysis see Table III).

#### Preparation of *N*-Alkyl- and *N*-Aralkyl-3,3'-iminobis-2-butanol.

These compounds were synthesized according to a procedure for benzyl compounds reported previously from this laboratory (10). Methyl chloroformate was used as an acylating agent to make the methyl derivatives (for physical and analytical data see Tables III and IV).

#### Preparation of *N*-Alkyl-2,3,5,6-tetramethylmorpholines.

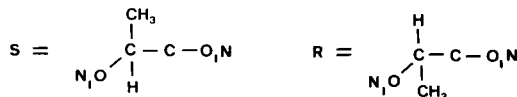
The methyl derivatives were synthesized according to Eschweiler-Clarke (11). The ethyl and heptyl derivatives were prepared according to the procedures described for benzyl compounds (10) (for physical and analytical data see Table V).

#### Acknowledgement.

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