2,3,5,6-Tetramethylmorpholine. I.

Sven Hernestam and Gillis Stenvall

Department of Organic Chemistry, Research Division, AB Ferrosan, Malmö, Sweden

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The separation and characterization of the six possible isomers of 2,3,5,6-tetramethylmorpholine are described. Synthetic routes for the preparation of any isomer in fair yield from easily accessible intermediates are reported.

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As a part of our program on the synthesis of selective monoamine oxidase (MAO) inhibitors (1), we had to prepare a series of *C*-alkylmorpholines as intermediates. Rather few preparations of such compounds have been reported, although the literature on *N*-alkyl and arylmorpholines is extensive. For example, as far as we are aware, 2,3,5,6-tetramethylmorpholine cannot be found in Chemical Abstracts.

However, the substance is described in a British patent (2) as a liquid boiling at 160-168° and with the refractive index n_D^{20} 1.446. The fact that it might exist in six isomeric forms (Figure 1) is not mentioned. The main

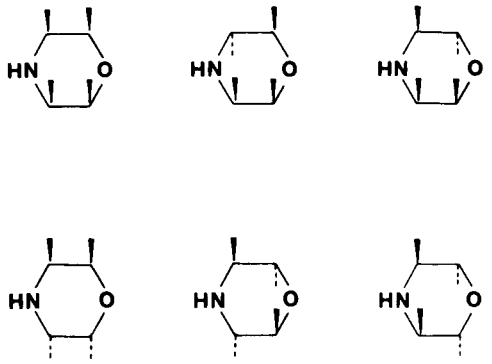


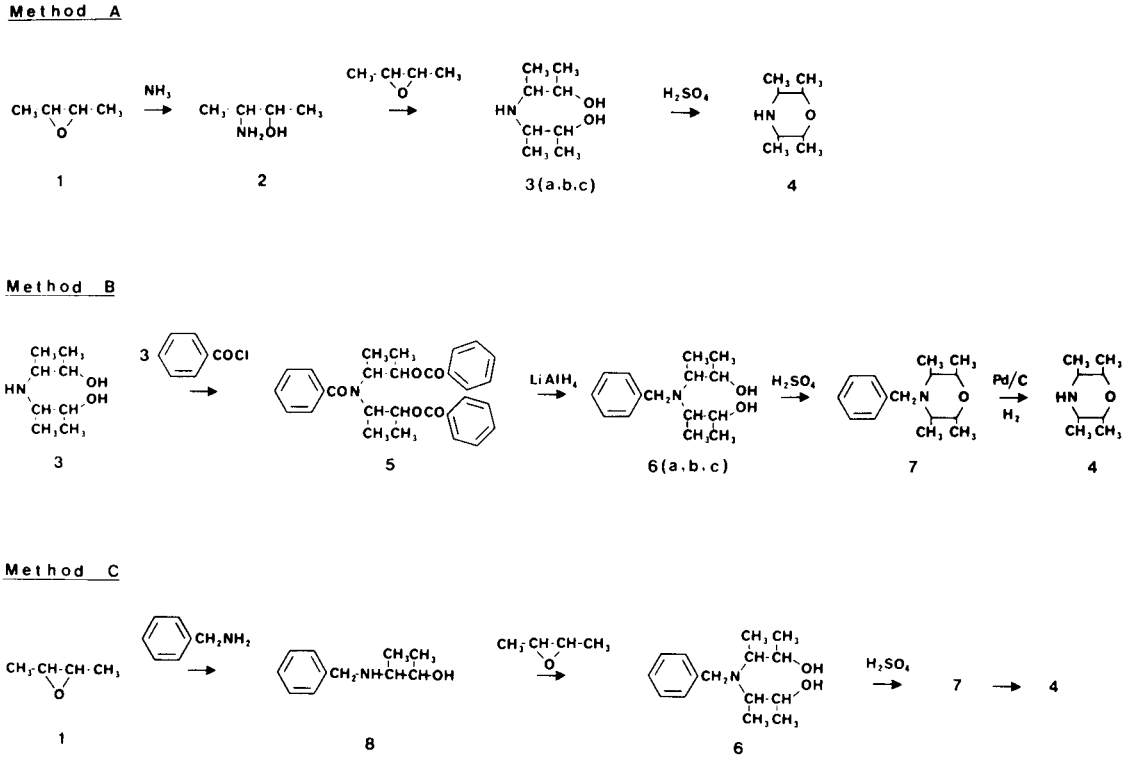
Figure 1

objectives of the work to be described in this paper were i) the development of methods of synthesis for any given isomer in yields permitting a scale of at least 100 g. and ii) the isolation of the various isomers in pure form.

Of several possible approaches, the two most logical and simple routes to the synthesis of these compounds would be either by ring closure through dehydration of the corresponding alkanolamine, 3,3′-iminobis-2-butanol, or its more sterically hindered *N*-benzyl derivative, *N*-benzyl-3,3′-iminobis-2-butanol, followed by catalytic debenzylation of the *N*-benzyl-2,3,5,6-tetramethylmorpholine obtained. The dehydration used throughout this investigation has been performed with a large excess of 70% sulfuric acid at 140-150° for at least 15 hours. Under these conditions, optimum yields were obtained (80-90%). Decreasing the temperature to 125° gave not only lower yields of 2,3,5,6-tetramethylmorpholine, but also new and unidentified compounds. Increasing the temperature to 175° gave much lower yields (3). If more concentrated sulfuric acid was used, more carbonization took place and more tar was formed, giving a lower yield of the desired 2,3,5,6-tetramethylmorpholine. Furthermore under these more severe conditions, the benzyl group underwent extensive sulfonation and the reaction product could not be isolated from the reaction mixture in a simple way. The reaction time used had to be at least 15 hours to obtain reproducible yields. The synthetic routes discussed in this paper are illustrated in Scheme 1.

Method A.

Commercial 2-butene was converted into a mixture of 2,3-epoxybutanes according to Wilson, *et al.*, (4). The 2,3-epoxybutane mixture consisted of 67% *trans*-2,3-epoxybutane and 33% *cis*-2,3-epoxybutane. This mixture was directly reacted with aqueous ammonia (see Experimental) and the resulting 3,3′-iminobis-2-butanol (**3**) was dehydrated. The 2.3,5,6-tetramethylmorpholine obtained in this way consisted of a mixture of isomers with the following composition: α, 32%; β, 46%; γ, 17%; δ, 4%; and ε, 0.5%. The isomers could be directly separated by preparative glc into five fractions. Nmr studies revealed that the β-fraction was a mixture that could not be directly separated by the use of any of our preparative glc columns. However, after benzoylation it was possible to separate the β-fraction into two forms: 63, (29)% β_1 and 37, (17)%



Scheme 1

Table I

3,3′-Iminobis-2-butanol prepared from	Isomers % α	β_1	β_2	γ	δ	ε
2 moles of *cis*-2,3-epoxybutane (**3a**)	28	45	5	21	1	<1
2 moles of *trans*-2,3-epoxybutane (**3b**)	25	35	13	24	3	<1
1 mole of DL-*threo*-3-amino-2-butanol + 1 mole of *trans*-2,3-epoxybutane (**3c**)	42	16	27	8	7	<1

Table II

N-benzyl-3,3′-iminobis-2-butanol prepared from	Isomers % α	β_1	β_2	γ	δ	ε
2 moles of *cis*-2,3-epoxybutane (**6a**)	2	56	0.5	40	1	0.5
2 moles of *trans*-2,3-epoxybutane (**6b**)	0.5	48	0.5	50	0.5	--
1 mole of DL-*threo*-3-amino-2-butanol + 1 mole of *trans*-2,3-epoxybutane (**6c**)						
crystalline	29	4		3	2	62
non-crystalline	6	16	37	1	28	12
non-crystalline (corrected)	--	19	45	1	34	--

β_2. The two separated *N*-benzoyl-2,3,5,6-tetramethylmorpholines were reduced with lithium aluminum hydride and catalytically debenzylated (**7** → **4**). The low yield (0.5%) of the ϵ-isomer makes this direct method useless for the production of all six isomers on a practical scale for our purposes. On the whole, no isomer is obtained in exceptionally good yield.

Method B.

Using method B, starting with benzoylation of 3,3′-iminobis-2-butanol (**3**) reduction of the curde reaction product **5** with lithium aluminum hydride, dehydration of *N*-benzyl-3,3′-iminobis-2-butanol (**6**) and catalytic debenzylation of *N*-benzyl-2,3,5,6-tetramethylmorpholine (**7**) gave a 2,3,5,6-tetramethylmorpholine with the following composition: α, 6%; β_1, 34%; β_2, 11%; γ, 29%; δ, 8%; and ϵ, 12%. The benzoylation must be performed under mild conditions (maximum temperature 50°), otherwise a varying degree of direct ring closure is obtained. If less than 3 moles of benzoylchloride are used a certain percentage of the amino groups is not benzoylated due to competing benzoylation of the hydroxyl groups, and the starting compound is recovered after the lithium aluminum hydride reduction.

Method C.

By reacting benzylamine with the 2,3-epoxybutane isomer mixture (67:33), dehydration of the resulting *N*-benzyl-3,3′-iminobis-2-butanol (**6**) and catalytic debenzylation of *N*-benzyl-2,3,5,6-tetramethylmorpholine (**7**) a 2,3,5,6-tetramethylmorpholine with the following composition is obtained: α, 6%; β_1, 34%; β_2, 12%; γ, 25%; δ, 10%; and ϵ, 13%. The last two methods (B and C) seem to be identical, and can be used to prepare the different isomers in about a 10 g. scale in a practical manner. In this investigation method B was preferred to method C, since the yields of the different isomers were more reproducible. This depends on the fact that in method B the preparation of *N*-benzyl-3,3′-iminobis-2-butanols is performed under milder conditions, giving no side reactions. As with method A, no isomer is obtained in exceptionally good yield. The pattern of yields seems to change substantially when the amino group is benzylated. With methods B and C, the yields of the δ- and ϵ-isomers have increased considerably while the yield of the α-isomer has decreased by a factor of five.

Dickey, *et al.*, (5) have shown that *cis*-2,3-epoxybutane and ammonia give exclusively DL-*threo*-3-amino-2-butanol (2R:3R and 2S:3S) and that *trans*-2,3-epoxybutane and ammonia give exclusively DL-*erythro*-3-amino-2-butanol (2R:3S and 2S:3R). If DL-*threo*-3-amino-2-butanol is further reacted with another mole of *cis*-2,3-epoxybutane, a 3,3′-iminobis-2-butanol (**3a**) is obtained which solidifies on standing. Glc analysis showed that the reaction product consists of two compounds in the proportions 56 ± 4% to 44 ± 4%. The two compounds are isomers, one of which is a *meso*-compound (2R:3R, 2′S:3′S) according to the proven reaction mechanism of the 2,3-epoxybutanes by Dickey, *et al.*, (5), and the other a racemate, (2R:3R, 2′R:3′R and 2S:3S, 2′S:3′S).

In the same way, the 3,3′-iminobis-2-butanols from two moles of *trans*-2,3-epoxybutane (**3b**) and from 1 mole of DL-*threo*-3-amino-2-butanol and one mole of *trans*-2,3-epoxybutane (**3c**) were prepared. By glc analysis each of these two reaction products was found, as expected, to consist of two compounds in a 50:50 ratio. The two isomers from 2 moles of *trans*-2,3-epoxybutane (**3b**) are, according to Dickey, *et al.*, (5), one *meso*-compound (2R:3S, 2′S:3′R) and one racemate (2R:3S, 2′R:3′S and 2S:3R, 2′S:3′R), and the two isomers from one mole of DL-*threo*-3-amino-2-butanol and one mole of *trans*-2,3-epoxybutane (**3c**) are two racemates (I: 2R:3R, 2′R:3′S and 2S:3S, 2′S:3′R; II: 2S:3S, 2′R:3′S and 2R:3R, 2′S:3′R). We have not yet succeeded in separating these

Table III

Isomer	Starting Material	Method	Yield %
α	DL-*threo*-3-amino-2-butanol + *trans*-2,3-epoxybutane	A	42
β_1	2 moles of *cis*-2,3-epoxybutane	B	56
β_2	DL-*threo*-3-amino-2-butanol + *trans*-2,3-epoxybutane Benzyl compound, liquid phase	B	37 (45)
γ	2 moles of *trans*-2,3-epoxybutane	B	50
δ	DL-*threo*-3-amino-2-butanol + *trans*-2,3-epoxybutane Benzyl compound, liquid phase	B	28 (34)
ϵ	DL-*threo*-3-amino-2-butanol + *trans*-2,3-epoxybutane Benzyl compound, crystalline phase	B	62

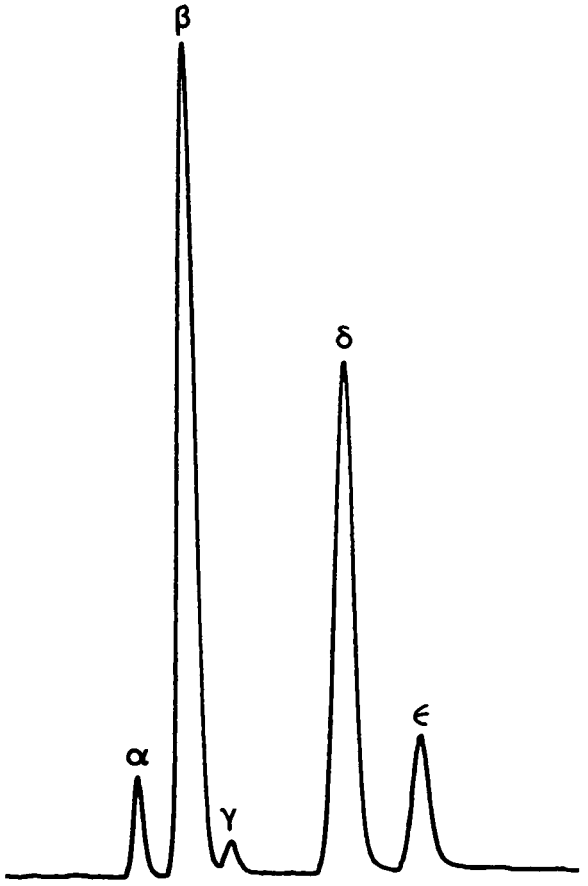


Figure 2

A typical chromatogram from a preparative glc separation of 2,3,5,6-tetramethylmorpholine prepared from **6c**, liquid phase.

mixtures into pure compounds in a practical way by preparative glc or by any other simple method. The results of dehydration (method A) of the three different reaction products are summarized in Table I.

Using method B, we found that the *N*-benzyl-3,3-iminobis-2-butanol (**6c**) from DL-*threo*-3-amino-2-butanol and *trans*-2,3-epoxybutane can be separated into one crystalline and one non-crystalline part (see Experimental). The non-crystalline part could not be totally freed from the crystalline part. Separations of the two other reaction products (**6a** and **6b**) into pure isomers have not yet been successful. The isomer composition of the four 2,3,5,6-tetramethylmorpholine mixtures obtained from this synthetic approach can be found in Table II, where we have corrected for the fact that the non-crystalline benzyl derivative contains 17% of the crystalline isomer.

Results.

As shown above all six isomers of 2,3,5,6-tetramethylmorpholine can be conveniently prepared in simple ways and with good yields. They can all be obtained in a highly pure state by preparative glc. In Table III the yields from easily prepared intermediates and the best methods to produce them are compiled.

Simple aroyl- and benzyl derivatives have been prepared from all six isomers. Their melting points are collected in Table IV, as well as some physical data on the basic isomers themselves.

Nmr studies to elucidate the structures of the 2,3,5,6-tetramethylmorpholine isomers are in progress, and will be published elsewhere.

EXPERIMENTAL

All melting points are uncorrected. Glc analyses were performed on a Varian 940 instrument.

Preparative Gas-Liquid Chromatography.

All preparative work was done on a Perkin Elmer F21 instrument equipped with a Trigger Level Programmer and with nitrogen (purity 99.99%) as the carrier gas. Chromosorb A 60/80 was used as solid support in all columns. The 2,3-epoxybutane isomers were separated on a 4.5m x 8mm column with 20% Carbowax 20M. For 2,3,5,6-tetramethylmorpholine, a 12m x 6.7mm column with 20% Carbowax 20M + 3% potassium hydroxide was used. Suitable parameters for the separation of 2,3,5,6-tetramethylmorpholine isomers were a gas flow of 75 ml. of nitrogen/minute, and a column temperature of 180-190°. This gave a retention time of about 31 minutes for the α-isomer and 53 minutes for the ϵ-isomer (see Figure 2). With automatic injections of approximately 0.4 g., the throughput was 10 g./24 hours. With some juggling of the above mentioned parameters it was often possible to process two injections simultaneously, which almost doubled the output.

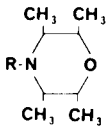
Separation of the two forms of β-*N*-benzoyl-2,3,5,6-tetramethylmorpholine turned out to be difficult. A column of 1.6 m x 24 mm with 5% PDEAS gave a rather good separation (isomer purity better than 95% in one run), but the compound left the manifold oven as a mist. Absorbents (silica gel and charcoal) in the collecting traps did not help at all. The problem was solved by electrostatic precipitation. Cylindrical traps with electrodes (stainless steel wire mesh) inside and outside and with about 10 KV DC across them gave an electric field causing the mist to agglomerate. Suitable parameters for this separation were a gas flow of 200-250 ml. of nitrogen/minute and a column temperature of 170-180°. This gave a retention time of about 50 minutes for the β_1-isomer and 65 minutes for the β_2-isomer (both peaks tailed rather badly). Automatic injections of approximately 0.1 g. gave a throughput of 2 g./24 hours. Except for the benzoyl compounds, all isomers were obtained directly with better than 99% purity.

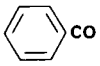
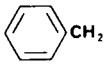
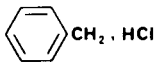
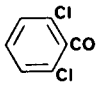
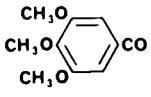
Preparation of 3,3′-Iminobis-2-butanol (**3b**).

One hundred g. (1.39 moles) of *trans*-2,3-epoxybutane and 50 ml. of aqueous 25% ammonia (0.67 mole) were heated together in a stainless steel autoclave at 120° for 5 hours. The reaction mixture was distilled, which gave 91 g. of 3,3′-iminobis-2-butanol (**3b**) (two isomers 50:50), b.p. 128-132° (8 mm). It solidified on standing.

Table IV

2,3,5,6-Tetramethylmorpholines and Derivatives
M.p. °C



R	Isomers α	β1	β2	γ	δ	ε
H	18-21 n_D^{25} = 1.4416	liquid n_D^{25} = 1.4450	liquid n_D^{25} = 1.4430	liquid n_D^{25} = 1.4438	37-40	-1 - +2 n_D^{25} = 1.4548
H,HCl	162-164	178-180	191-194	142-144	152-155	221-223
	159-162	viscous oil	viscous oil	82-84	73-77	111-114
	31-33	18-21	viscous oil	9-10	21-23	51-54
	166-168	182-185	216-218	209-211	201-204	217-220
	133-135	128-130	105-107	150-152	168-171	166-169
	89-92	91-93	77-80	108-112	viscous oil	120-124

Preparation of DL-*threo*-3-Amino-2-butanol.

One hundred g. (1.39 moles) of *cis*-2,3-epoxybutane and 400 ml. of aqueous 25% ammonia (5.4 moles) were heated together in a stainless steel autoclave at 120° for 5 hours with efficient stirring. Excess ammonia and most of the water were removed by distillation at atmospheric pressure through a 30 cm packed column until the flask temperature reached 105°. The remaining water was then removed at reduced pressure (100 mm Hg), using a 100 cm column packed with small glass rings. The DL-*threo*-3-amino-2-butanol (**2**) was purified by distillation through this column, yield 72.5 g. (59%), b.p. 60-65° (8 mm). 3,3′-Iminobis-2-butanol (**3a**) (19.5 g.) b.p. 128-132° (8 mm), was obtained from the distillation residue. The DL-*threo*-3-amino-2-butanol was glc pure.

Preparation of 3,3′-Iminobis-2-butanol (**3c**).

One hundred g. (1.12 moles) of DL-*threo*-3-amino-2-butanol (**2**), 100 ml. of water and 72 g. (1 mole) of *trans*-2,3-epoxybutane were heated together in a stainless steel autoclave at 120° for 5 hours with efficient stirring. The reaction mixture was disitlled to give 142 g. (88%) of 3,3′-iminobis-2-butanol (**3c**) (two isomers 50:50), b.p. 128-132° (8 mm). It solidified on standing.

Preparation of 2,3,5,6-Tetramethylmorpholine (**4**).

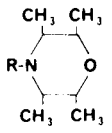
3,3′-Iminobis-2-butanol (**3**) (161 g., 1 mole) was added with stirring and cooling to 750 ml. of 70% sulfuric acid. The mixture was kept in a glass autoclave at 140-150° for 15 hours. An excess of 20% sodium hydroxide solution was added with stirring and efficient cooling. The product was extracted with diethyl ether, and the ether extract dried over sodium sulfate. Evaporation of the ether gave a crude product which was directly analyzed and then distilled. 2,3,5,6-Tetramethylmorpholine, (119 g., 83%) b.p. 160-174° was obtained.

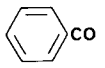
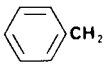
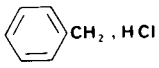
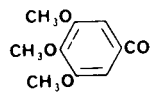
Preparation of *N*-Benzyl-3,3′-iminobis-2-butanol (**6b**).

Benzylamine (107 g., 1 mole), 100 ml. of 96% ethanol and 155 g. (2.15 moles) of *trans*-2,3-epoxybutanel were heated together in a stainless steel autoclave at 170° for 24 hours with efficient

Table V

2,3,5,6-Tetramethylmorpholine Derivatives
Analyses % Found



R		Calcd.	Isomers α	β_1	β_2	γ	δ	ε
H,HCl	Cl	19.73	19.8	19.8	19.9	19.9	20.0	19.9
	C	72.84	72.6	73.1	73.0	72.6	72.7	72.8
	H	8.56	8.65	8.48	8.52	8.70	8.60	8.62
	N	5.66	5.69	5.60	5.70	5.70	5.62	5.60
	O	12.94	13.0	12.8	13.1	12.9	12.8	13.0
	C	77.20	77.0	76.7	76.6	77.1	76.8	76.7
	H	9.94	9.81	9.83	9.87	9.72	9.96	9.97
	N	6.00	6.01	5.91	5.96	6.00	6.04	5.90
	O	6.86	6.93	6.83	6.78	6.89	7.00	6.80
	Cl	13.14	13.2	13.1	13.2	13.3	13.0	13.0
	C	56.97	56.8	56.7	56.8	56.7	56.9	56.8
	H	6.06	6.14	6.15	5.99	6.07	6.15	6.16
	N	4.43	4.44	4.42	4.65	4.42	4.35	4.56
	O	10.12	10.2	10.7	10.2	10.3	10.1	9.99
	Cl	22.42	22.7	22.3	22.5	22.7	22.6	22.6
	C	64.07	63.7	63.9	64.4	63.9	64.2	63.8
	H	8.07	8.04	8.07	8.12	8.07	8.12	8.09
	N	4.15	4.20	4.64	4.21	4.62	4.05	4.06
	O	23.71	23.9	23.6	22.9	23.7	23.8	23.7

stirring. The reaction mixture was distilled, which gave 226 g. (90%) of *N*-benzyl-3,3′-iminobis-2-butanol (**6b**) (mainly two isomers 50:50), b.p. 128-135° (0.01 mm). It crystallized spontaneously.

Preparation of *N*-Benzyl-3,3′-iminobis-2-butanol (**6c**).

To a mixture of 81 g. (0.5 mole) of 3,3′-iminobis-2-butanol (**3c**) 170 g. of triethylamine and 1000 ml. of dry benzene, 225 g. (1.6 moles) of benzoyl chloride was slowly added with stirring and efficient cooling. The reaction mixture was maintained at 45-50° with stirring for 24 hours. The triethylamine hydrochloride formed was filtered off, and the benzene solution was slowly added to a slurry of 75 g. of lithium aluminum hydride in 3 l. of diethyl ether. The reaction mixture was refluxed for 6 hours and then decomposed according to Amundsen, *et al.*, (6). After filtration, the solvents were evaporated and the residue distilled. *N*-Benzyl-3,3′-iminobis-2-butanol (**6c**) (89 g., 71%) (two isomers 50:50), b.p. 120-132° (0.01 mm), was obtained. The product (**6c**) was dissolved in 200 ml. of hot ligroin (b.p. 80-110°). In the refrigerator 35 g. of a precipitate of white crystals, m.p. 73-75° (isomerically pure), was obtained. The residue was distilled, b.p. 120-132° (0.01 mm), and gave 51 g. of a colourless, viscous oil which by glc analysis was shown to contain two isomers (83:17).

Preparation of *N*-Benzyl-2,3,5,6-tetramethylmorpholine (**7**).

N-Benzyl-3,3′-iminobis-2-butanol (**6**) (226 g., 0.9 mole) was added with stirring and cooling to 650 ml. of 70% sulfuric acid. The mixture was kept in a glass autoclave at 140-150° for 15 hours. An excess of 20% sodium hydroxide solution was added with stirring and efficient cooling. The organic layer was separated and the residue extracted with diethyl ether. The combined organic phases were dried with sodium sulfate, filtered and evaporated. Distillation gave a fraction of 176 g. (84%) of *N*-benzyl-2,3,5,6-tetramethylmorpholine (**7**), b.p. 145-158° (8 mm).

Debenzylation of *N*-Benzyl-2,3,5,6-tetramethylmorpholine.

Catalytic hydrogenation of 233 g. (1 mole) of *N*-benzyl-2,3,5,6-tetramethylmorpholine (**7**) in 300 ml. of acetic acid over 7.5 g. of 10% Pd/C was performed at 100° and at 2000 psi in a stainless steel autoclave with efficient stirring. After about 12 hours, the theoretical amount of hydrogen had been absorbed. To the filtrate obtained from the hydrogenation, 150 ml. of concentrated hydrochloric acid was added, whereupon the acetic acid and the water were evaporated under a good vacuum. An excess of 20% sodium hydroxide solution was added to the residue with efficient cooling. The product was extracted with diethyl ether and the ether extract

dried over sodium sulfate. Evaporation of the ether gave a crude product which was directly analyzed and then distilled. 2,3,5,6-Tetramethylmorpholine (133 g., 93%) b.p. 160-174°, was obtained.

Preparation of β-*N*-Benzoyl-2,3,5,6-tetramethylmorpholine.

To a mixture of 14.3 g. (0.1 mole) of β-2,3,5,6-tetramethylmorpholine, 15 g. of triethylamine and 100 ml. of dry benzene, 14.1 g. (0.1 mole) of benzoyl chloride was slowly added with stirring. The reaction mixture was refluxed for 1 hour. The benzene solution was washed with water and evaporated. The residue was distilled to give 24.0 g. (97%) of a viscous oil, b.p. 92-94° (0.01 mm).

Preparation of *N*-(3,4,5-Trimethoxybenzoyl)-2,3,5,6-tetramethylmorpholine (γ isomer).

To a mixture of 14.3 g. (0.1 mole) of γ-2,3,5,6-tetramethylmorpholine, 15 g. of triethylamine and 100 ml. of dry benzene, 23.0 g. (0.1 mole) of 3,4,5-trimethoxybenzoyl chloride was added. The reaction mixture was refluxed for 1 hour. The benzene solution was washed with water and evaporated, and the crystalline residue was recrystallized from ligroin (b.p. 80-110°), giving 30.3 g. (90%) of colourless crystals, m.p. 108-112°.

Preparation of *N*-Benzyl-2,3,5,6-tetramethylmorpholine (δ isomer).

To a slurry of 5 g. of lithium aluminum hydride in 200 ml. of diethyl ether, a diethyl ether solution of 24.7 g. (0.1 mole) of δ-*N*-benzoyl-2,3,5,6-tetramethylmorpholine was slowly added. The reaction mixture was refluxed for 4 hours and then decomposed according to Amundsen, *et al.* (6). After filtration the ether was evaporated and the residue distilled. 22.0 g. (94%) of product, b.p. 80-84° (0.01 mm), was obtained, which crystallized in the refrigerator, m.p. 21-23°. The hydrochloride, recrystallized from ethanol diethyl ether, had m.p. 201-204°.

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