I

THE STEREOCHEMISTRY OF THE OPENING OF THE IMINE RING WITH VARIOUS REAGENTS

II

THE ATTEMPTED REDUCTION OF NATURALLY OCCURRING THREONINE TO 3-AMINO-2-BUTANOL

Thesis by

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ABSTRACT

The 2, 3-iminobutanes react with acetic acid to give products that are easily converted without isolation into 3-acetamido-2-acetoxybutanes. Comparisons of the latter with samples of known configuration demonstrate that ring opening occurs in a trans manner.

Attempts to prepare 3-p-toluenesulfonamido-2-p-toluenesulfonoxybutane by reaction of 2, 3-iminobutane with p-toluenesulfonic acid, followed by treatment with p-toluenesulfonyl chloride, have failed. Under mild conditions the ring is not attacked, and under strenuous conditions elimination of ammonia occurs.

The ring of the N-ethyl-2, 3-iminobutanes, as well as that of the simple 2, 3-iminobutanes, is opened by aqueous ammonia and ethylamine at elevated temperatures to give products which demonstrate that an inversion occurs. Many new imines, amino alcohols, and diamines have been synthesized. They are described, along with some of their derivatives.

Both DL- and naturally occurring threonine have been reduced to derivatives of the corresponding 2-amino-1, 3-butanediols. Attempts to reduce the latter to derivatives of the 3-amino-2-butanols have not yet succeeded.

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THE STEREOCHEMISTRY OF THE OPENING OF THE IMINE RING WITH VARIOUS REAGENTS

INTRODUCTION

The ring of 2,3-iminobutane has been found to open in a trans manner with water* and ammonia (1), but the effects of many other reagents remain to be studied. This investigation was undertaken to determine the stereochemical paths of the reactions with acetic acid, aliphatic amines, and a representative strong oxygenated acid.

The choice for the last-named was p-toluenesulfonic acid, mainly because of an advantage it shared with acetic acid: the normal products of ring opening should be transformed easily into well characterized derivatives of the 3-amino-2-butanols; thus the product from reaction with p-toluenesulfonic acid could be made to yield 3-p-toluene-2-p-toluenesulfonoxybutane, and that with acetic acid to yield 3-acetamido-2-acetoxybutane. Since a complete set of the isomers of these end products is known (1), a direct comparison would be possible.

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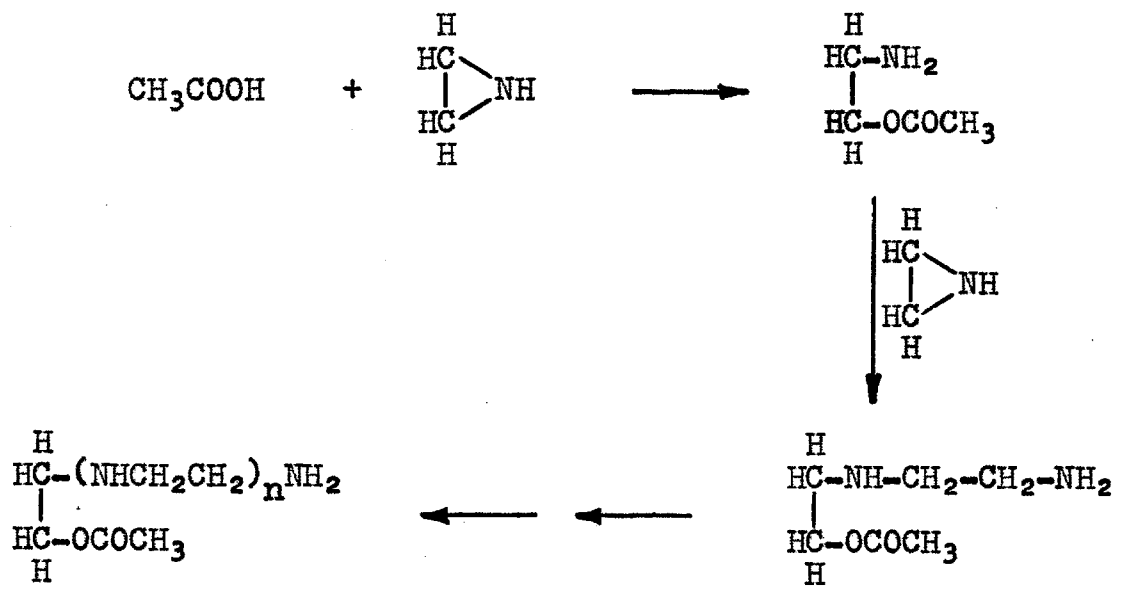
* Cyclohexene imine has been found to behave in a similar manner with water and hydrogen chloride (2).

A. ACETIC ACID AND THE IMINE RING*

DISCUSSION

Previous to the present work the reaction of cyclic imines with acetic acid had been reported only once in the literature (4): ethyleneimine was treated at dry ice temperature with twice its molar quantity of glacial acetic acid to give a product isolated as the oxalate. Isolation of the primary product itself was complicated by the fact that it underwent an oxygen-to-nitrogen acyl migration when distilled. In addition, the oxalate analyzed excessively high in nitrogen, undoubtedly due to compounds resulting from further reaction of the primary product with ethyleneimine.

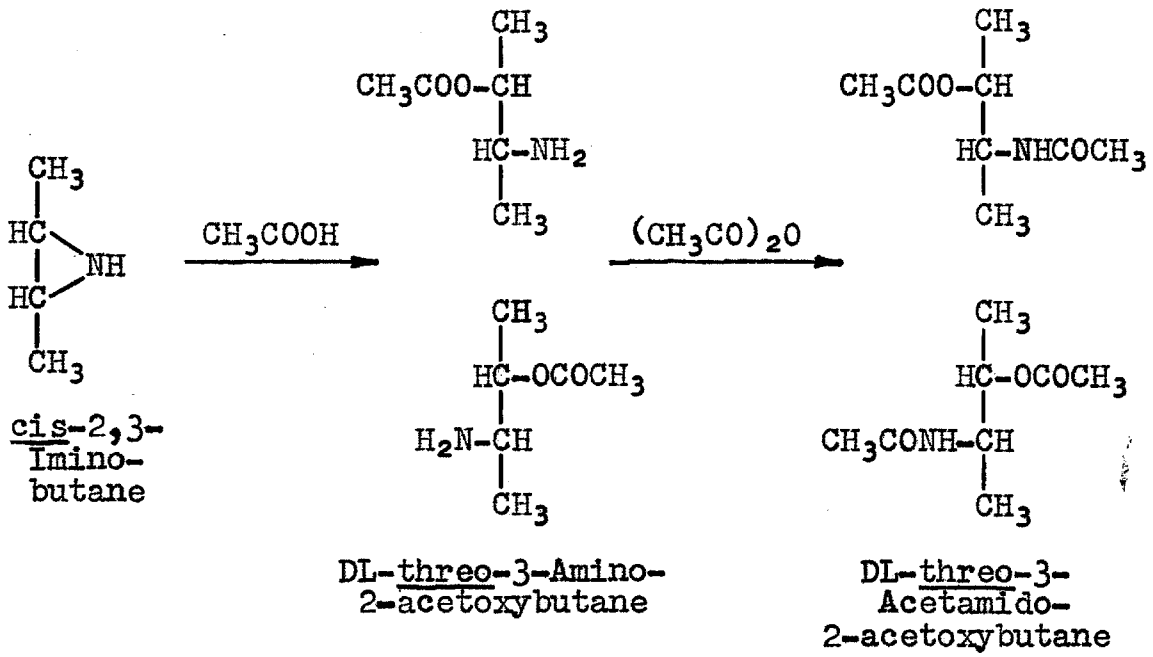


* Published as contribution no. 1927 of the Gates and Crellin Laboratories of the California Institute of Technology (3).

In the present work two steps were taken to avoid these pitfalls: first, a high excess of acetic acid was employed to minimize further reaction of product with 2, 3-iminobutane; and second, the immediate product, 3-amino-2-acetoxybutane, was converted without isolation to 3-acetamido-2-acetoxybutane by treatment with acetic anhydride at room temperature. As shown in the following table of physical constants, cis-2, 3-iminobutane gave DL-threo-3-acetamido-2-acetoxybutane in essentially quantitative yield. Likewise L(-)-trans-2, 3-iminobutane yielded L(-)-erythro-3-acetamido-2-acetoxybutane, demonstrating that in both cases an inversion took place, i.e. trans opening of the ring occurred.

ROTATIONS AND MELTING POINTS OF
3-ACETAMIDO-2-ACETOXYBUTANES

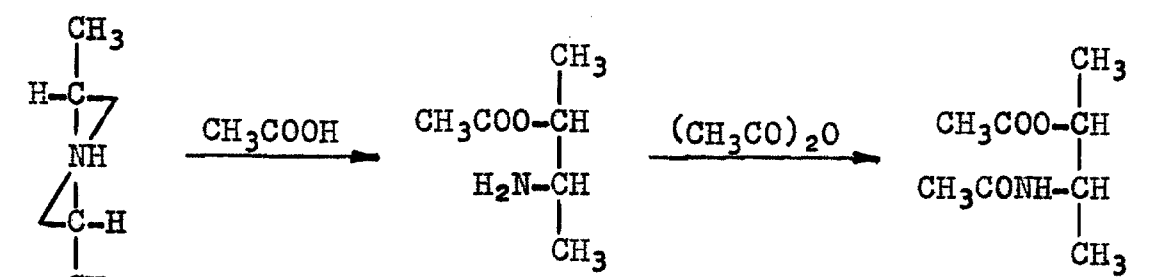
		$(\alpha)^{25}D$ (°)	Melting Point (°C.) Pure Compound	Mixture
1	DL-erythro	0	51.5-52.8	1 and 5: softens 25
2	DL-threo	0	73.3-74.4	2 and 5: 73.4-74.5
3	L(-)-erythro	-33.0	62.5-63.2	3 and 6: 62.6-64.3
4	L(-)-threo	-35.0	59.6-60.7	4 and 6: <29-37
5	Product from cis-imine	0	74.3-74.7	
6	Product from L(-)-imine	-30.6	63.3-63.9	



cis-2,3-Imino-butane

DL-threo-3-Amino-2-acetoxybutane

DL-threo-3-Acetamido-2-acetoxybutane



L(-)-trans-2,3-Imino-butane

L-erythro-3-Amino-2-acetoxybutane

L(-)-erythro-3-Acetamido-2-acetoxybutane

EXPERIMENTAL (3)

The cis-2,3-iminobutane and L(-)-trans-2,3-iminobutane were prepared from meso-2,3-butanediol and D(-)-threo-2,3-butanediol respectively, by methods previously employed (1), except that in the preparation of the chlorohydrin (5) the reaction mixture was saturated with hydrogen chloride at ca. -30°C.

Cis-2,3-Iminobutane and Acetic Acid

To 60 g. (1.0 mole) of glacial acetic acid, kept at a temperature below 30°C., was added with stirring, 7.1 g. (0.10 mole) of cis-2,3-iminobutane over 30 minutes. After standing 2 days, there was added with stirring 20.4 g. (0.20 mole) of acetic anhydride (redistilled) over a period of 40 minutes. The temperature was kept below 25°C. After standing another 2 days, the apparatus was equipped for fractionation, and the excess acetic acid and acetic anhydride distilled at 12 mm. pressure through an 8-inch column of Raschig rings, until the pot temperature reached 60°C. It was then subjected to a pressure of 1 mm. for 2 hours, with the temperature kept at 60°C.

After cooling, the viscous material was placed in a vacuum desiccator over potassium hydroxide and sulfuric acid (1 mm. pressure). After 3 days a small amount was solidified in dry ice, and used to seed the large portion. All quickly solidified to give 16.9 g. (98%) of very light-colored material; m.p. 71.5-73.5°C. (cor.).

Recrystallization from dry diisopropyl ether gave 13.1 g. (76%) of white prisms, m.p. 74.3-74.7°C. (cor.).

L(-)-trans-2, 3-Iminobutane and Acetic Acid

The reaction was carried out as for the inactive imine, but on a smaller scale (0.05 mole of imine). The diacetate solidified readily without being seeded, even before being placed in a desiccator. A yield of 8.5 g. (98%) resulted. Recrystallization from dry diisopropyl ether gave 7.4 g. (85%) of pure product, m.p. 63.3-63.9°C. (cor.).

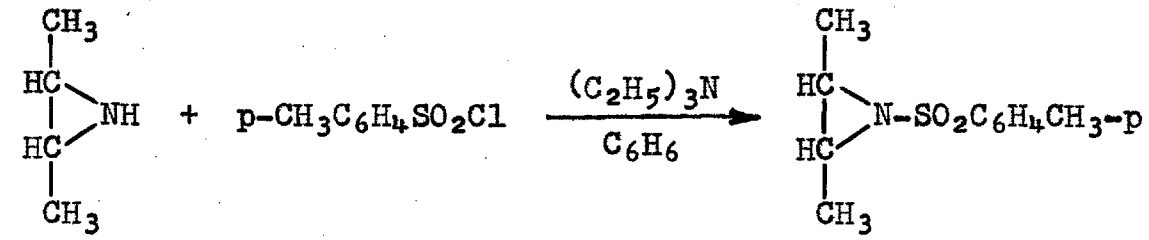
B. P-TOLUENESULFONIC ACID AND THE IMINE RING

DISCUSSION

In order for a strained heterocycle to be opened chemically, two rather obvious requirements must be satisfied: first, the substrate itself must be susceptible to attack, and second, there must be present a satisfactory assailant.

Ethyleneimine homologs in general meet the first condition stated above. Although a compound such as 2,3-iminobutane has only secondary carbons available (which are less vulnerable to nucleophilic attack than the primary), nevertheless it is reactive to a large collection of nucleophiles of varying strength. This is especially true when an acid is present, since quarternization of the ring nitrogen weakens the system considerably. An example of this is the reaction of hydrogen chloride with cyclohexeneimine (2). Even such a weak nucleophile as chloride ion opens the ring under these conditions.

It was hoped, therefore, that p-toluenesulfonic acid would open the ring, with its strength as a protonating agent outweighing the deficiencies of the anion. Trial experiments were performed with cis-2,3-iminobutane and an excess of p-toluenesulfonic acid, with water, benzene, diethyl ether, diisopropyl ether and tetrahydrofuran as solvents. In the case of the aliphatic ethers a second phase formed immediately, and afforded upon treatment with p-toluenesulfonyl chloride in pyridine a crystalline solid which turned out to be N-p-toluenesulfonyl-cis-2,3-iminobutane, identical to a sample synthesized by the method of Bestian (6):



cis-2,3-Iminobutane

N-p-Toluenesulfonyl-cis-2,3-iminobutane

Attention then turned to the use of more strenuous conditions: fused acid at elevated temperatures. But several hours at 40°C. gave the same result as when a solvent was employed, and increase of the temperature to 100°C. did not improve the situation. As it was evident from the imine's reluctance to react that a large excess of acid was not necessary, a few experiments were carried out for one week at 100°C., with an acid to imine molar ratio of two. A high-melting solid separated from the dark reaction mixture upon cooling. Treatment with p-toluenesulfonyl chloride in pyridine gave a crystalline compound which later proved to be p-toluenesulfonamide. The original crystals were undoubtedly ammonium p-toluenesulfonate, and as such represented a 42% yield, based on cis-2, 3-iminobutane.

In the forlorn hope that the concentration of p-toluenesulfonate ion in the forementioned experiments could be raised, the sodium, potassium, and lithium salts of the acid were prepared. They proved to be almost insoluble in the fused anhydrous acid.

Apparently ring opening will not occur under mild conditions, due to the low nucleophilicity of the p-toluenesulfonate ion. In this respect it resembles sulfate and perchlorate ions. The

process by which elimination of ammonia occurs is as yet unknown.

EXPERIMENTAL

p-Toluenesulfonic acid monohydrate was from Matheson, Coleman and Bell. It was recrystallized from concentrated hydrochloric acid and dried in a vacuum desiccator over soda-lime until free of chloride ion.

Pyridine was dried by refluxing over potassium hydroxide, and then fractionating, discarding the forerun.

Triethylamine was from Matheson, Coleman and Bell. It was dried over potassium hydroxide, then fractionated.

p-Toluenesulfonyl chloride was Eastman White Label material, recrystallized from hexane.

Diisopropyl ether was freed of peroxides with sodium sulfite solution, washed, dried over calcium chloride and fractionated. The fraction boiling above 67°C. (ca. 750 mm.) was collected.

All melting points are corrected. Microanalyses marked (E) are by A. Elek; those marked (S) by G. Swinehart.

Reaction of cis-2,3-Iminobutane with p-Toluenesulfonic Acid

Twenty grams (0.105 mole) of p-toluenesulfonic acid monohydrate was dried by the azeotropic distillation of 300 ml. of dry diisopropyl ether, leaving 150 ml. of reddish solution. This was treated with Norit, filtered, cooled, and to it was added slowly 1.0 g. (0.014 mole) of cis-2,3-iminobutane*, the temperature being kept near 25°C. A milky oil formed upon the addition of each drop,

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* See page 5, this thesis.

collecting to a reddish oil at the bottom of the flask. This was removed, cooled for several days, and then desiccated at 2 mm. pressure over sulfuric acid. Treatment with 7 ml. of pyridine caused solidification of most of the material, but a further 7 ml. redissolved this. It was then treated with 2.80 g. (0.015 mole) of p-toluenesulfonyl chloride and allowed to stand one day at room temperature. Acidification at 0°C. with 6N hydrochloric acid gave a clear solution, which was extracted 3 times with diethyl ether. Evaporation of the ether gave 1.95 g. of almost white crystals. Recrystallization from diisopropyl ether gave material of melting point 95.1-95.9°C.

Mixed melting point with DL-erythro-3-p-toluenesulfonamido-2-p-toluenesulfonoxybutane (m.p. 94.5-96.3°C.) (1): 69-77°C.

Mixed melting point with N-p-toluenesulfonyl-cis-2,3-iminobutane (m.p. 94.8-96.0°C.; see below): 94.4-95.5°C.

N-p-Toluenesulfonyl-cis-2,3-iminobutane (6)

A 100-ml. 3-necked flask, equipped with drying tube, sealed stirrer and a dropping funnel, contained a solution of 2.4 g. (0.034 mole) of cis-2,3-iminobutane and 3.4 g. (0.034 mole) of triethylamine in 20 ml. of dry benzene. This was cooled in an ice bath, and there was added, over 45 minutes, a solution of 6.4 g. (0.034 mole) of p-toluenesulfonyl chloride in 40 ml. of dry diethyl ether. The white precipitate of triethylamine hydrochloride was filtered off, rinsed with 100 ml. of benzene, and dried: 4.2 g. (91%). The filtrate and washings were evaporated under aspirator vacuum and the resulting white solid dried under vacuum: 7.53 g. (98%).

Four recrystallizations from diisopropyl ether gave colorless

prisms, m.p. 94.9-96.1°C. Calculated for $C_{11}H_{15}NSO_2$: C 58.63, H 6.71, N 6.22, S 14.22. Found (E): C 58.52, H 6.71, N 6.15, S 13.15.

N-p-Toluenesulfonyl-L-trans-2,3-iminobutane

This was prepared exactly as the cis- isomer, using L(-)-trans-2,3-iminobutane. Six recrystallizations from diisopropyl ether gave colorless rods, m.p. 78.4-79.4°C. $(\alpha)^{25}D$ - 19.0° (a = -0.68°, c = 3.59, butanone).

Calculated for $C_{11}H_{15}NSO_2$: C 58.63, H 6.71, N 6.22, S 14.22. Found (S): C 58.83, H 6.99, N 6.58, S 14.27.

N-p-Toluenesulfonyl-1,2-iminobutane

This was prepared in a similar manner from 1,2-iminobutane, 92% of the theoretical yield of triethylamine hydrochloride being isolated. The product failed to solidify until refrigerated at 5°C. It remelted between 10 and 15°C. when allowed to come to room temperature. Since its value as a derivative was therefore very limited no further work was done with it.

p-Toluenesulfonamide from cis-2,3-Iminobutane

A 3.80 g. (0.020 mole) sample of p-toluenesulfonic acid monohydrate in a test tube was freed of water by being subjected to a 1 mm. pressure at 120°C. for one-half hour. To it was added slowly, with cooling, 0.71 g. (0.010 mole) of cis-2,3-iminobutane. The tube was almost sealed by being drawn to a capillary tip, and was placed in an ampoule oven at 100°C. for 6 days. Upon cooling, the tube was opened and the black tarry mixture it contained was extracted with 3-10 ml. portions of acetone, leaving behind 0.80 g. of almost-white

crystals.

A 0.35 g. sample of these crystals was treated in the cold with 0.46 g. (0.0024 mole) p-toluenesulfonyl chloride in 1 ml. of pyridine. After standing 24 hours the solution was cooled to 0°C. and acidified strongly with 6 N hydrochloric acid. The resulting precipitate* was washed with hydrochloric acid and dried in a desiccator. Seven recrystallizations from benzene gave a product with melting point 136.8-137.8°C.

Mixed melting point with sample of p-toluenesulfonamide (m.p. 138.0-139.5°C.): 137.8-138.4°C.

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* In some cases no precipitate formed, a result due to the moderate water solubility of the product, about which no such suspicion had yet been entertained.

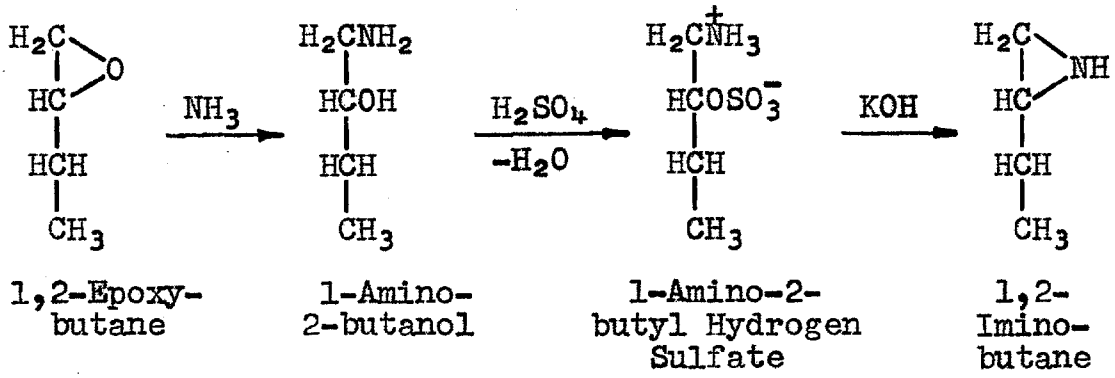
C. ETHYLAMINE AND AMMONIA AND THE IMINE RING

DISCUSSION

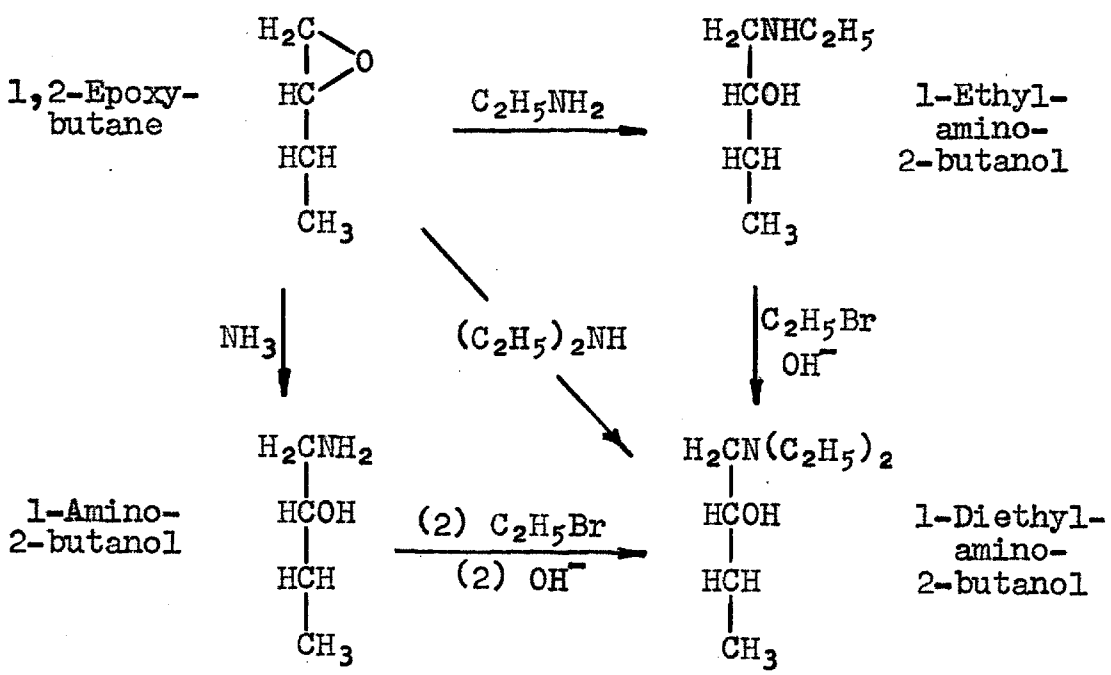
Although occasionally used as a preparative method, only once (1) has the reaction between an ethyleneimine and ammonia been studied stereochemically to determine the mechanism. That work was done in this laboratory, and involved the reaction at 100°C. of 2,3-iminobutane with liquid ammonia in the presence of large amounts of ammonium chloride. The present experiments were undertaken with a two-fold aim: first, to determine possible milder conditions under which ethylamine could be induced to open the imine ring in good yield, and second, to use the method developed to determine the stereochemical path of the reaction.

At about the time that this work was begun, there became available from the Dow Chemical Company a product termed 'Butylene Oxide, Mixed Isomers', consisting mostly of 1,2-epoxybutane. This was recognized as a valuable starting material for the preparation of 1,2-iminobutane, with which it was intended to do preliminary experiments. The commercial material was later supplanted by a 'Straight Chain Isomer' grade, from which it was found that reasonably pure 1,2-epoxybutane could be isolated by fractional distillation.

This purified material reacted with aqueous ammonia to produce 1-amino-2-butanol (7), and the latter was converted into 1,2-iminobutane by the method previously used to synthesize the 2,3- isomers (1):



In addition, the same oxide was treated with aqueous ethylamine to obtain 1-ethylamino-2-butanol, characterized by its conversion to the hydrochloride of 1-diethylamino-2-butanol*, and comparison of the latter with a reference sample prepared from 1-amino-2-butanol:



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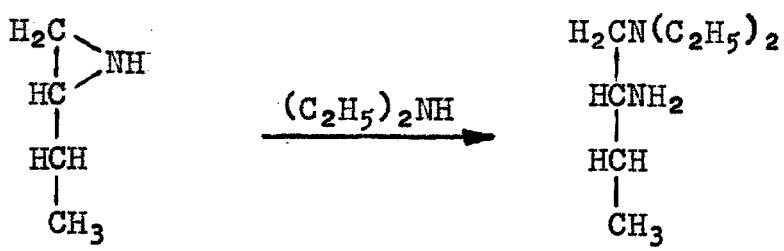
* Diethylamine and 1,2-epoxybutane also gave this compound.

Apparently attack by these amines, like that by ammonia (7), is at the primary carbon atom predominantly, if not exclusively.

Little or no product was obtained when anhydrous ethylamine was heated with 1,2-iminobutane. Previous investigators (8, 9) have used anhydrous aluminum chloride or amine hydrochloride in these reactions, but a procedure was desired which would avoid the possibility of complication by chloride ion.

In an attempt to emulate the success attained with epoxybutanes and excess aqueous amines or ammonia (1), and to obtain a system with lower vapor pressure for reasons of safety and convenience, a sample of 1,2-iminobutane was treated with a 20-molar excess of 70°/o aqueous ethylamine, a fortnight at 100°C. being allowed out of respect for the lower reactivity of the imines versus oxides. This procedure proved effective, resulting in a 45°/o yield of diamine; this was increased to 78°/o by use of a still higher temperature (120°C.). When water was present, even diethylamine reacted with 1,2-iminobutane at 100°C. to give a 34°/o yield of product, uncharacterized but probably 1-diethylamino-2-aminobutane:

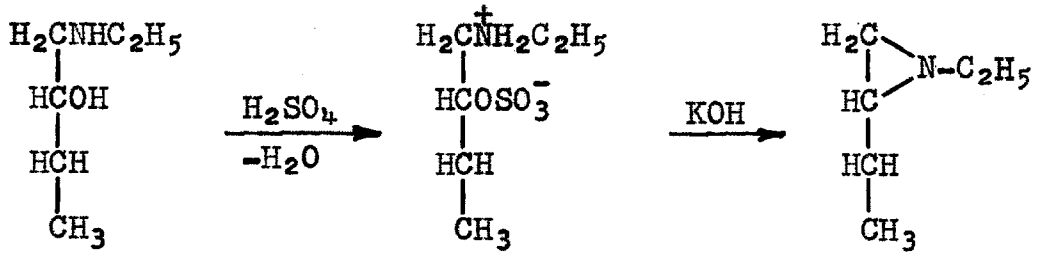


1,2-Iminobutane

1-Diethylamino-2-aminobutane

Anhydrous diethylamine, like anhydrous ethylamine, was ineffective under the same conditions.

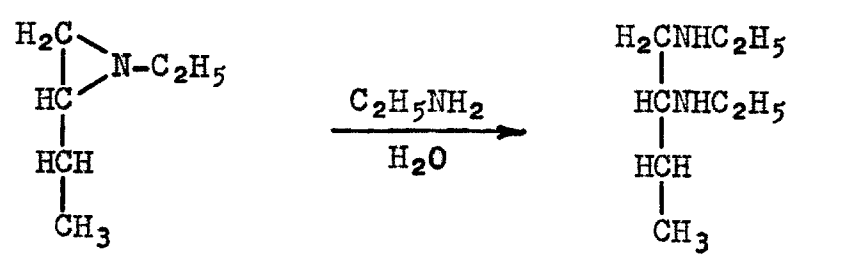
Application of this procedure to the reaction with 1,2-epoxybutane substantially increased the yield of 1-ethylamino-2-butanol. The latter was now used to prepare, via the sulfate ester, N-ethyl-1,2-iminobutane (1,2-diethylaziridine):



1-Ethylamino-2-butanol | 1-Ethylamino-2-butyl Hydrogen Sulfate | N-Ethyl-1,2-iminobutane

Good yields were obtained despite the fact that the sulfate ester could not be obtained as a crystalline solid, drying instead to a glassy material.

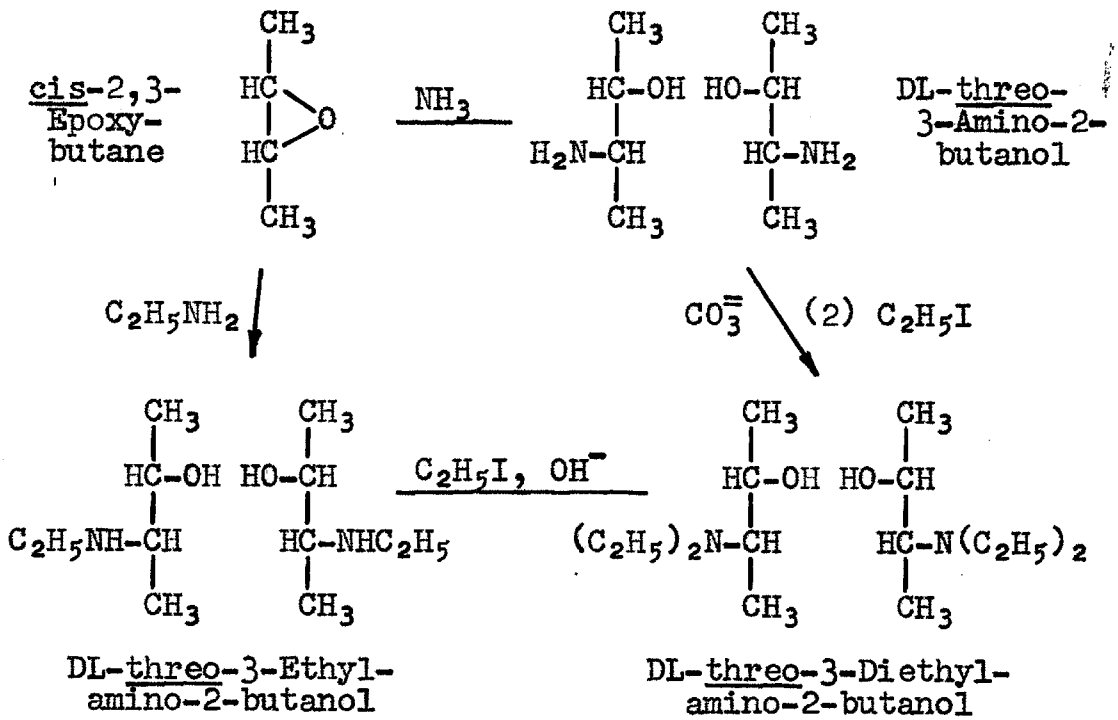
The conditions employed with the simple imine and ethylamine were applied in the case of this new imine. The result was a 55% yield of 1,2-bis-ethylaminobutane:



N-Ethyl-1,2-iminobutane | 1,2-Bis-ethylaminobutane

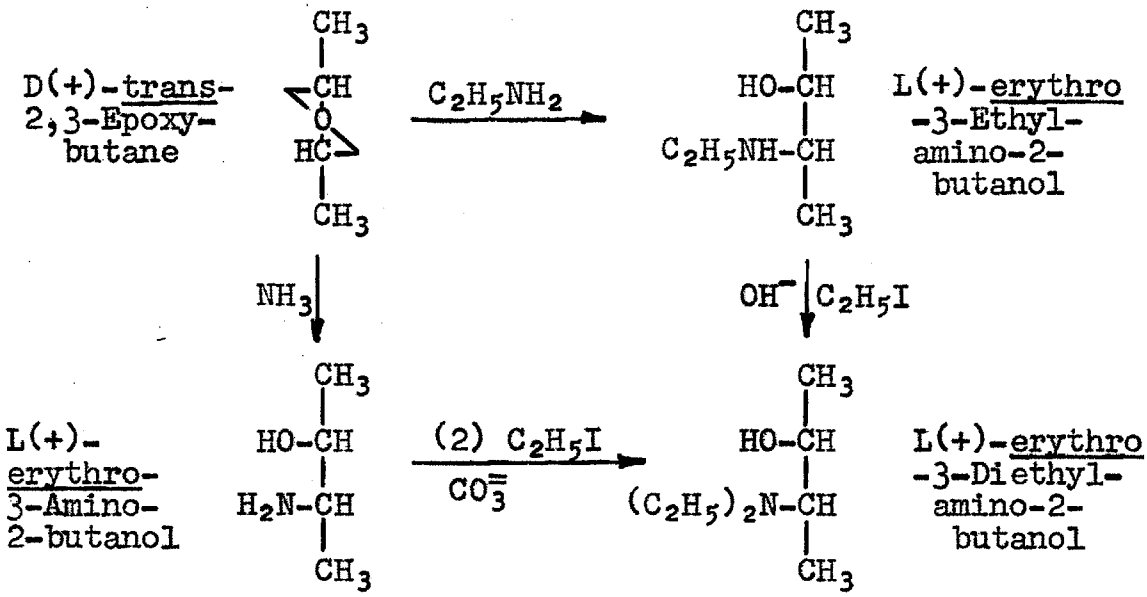
The method was now available; it remained to apply it to the problem of greater import: ethylamine and the pure 2, 3-iminobutanes.

When cis-2, 3-epoxybutane and aqueous ethylamine were heated together, yields of up to 85% of a 3-ethylamino-2-butanol resulted. This proved to be the DL-threo- isomer when the 3-diethylamino-2-butanol derived from it was compared with that derived from DL-threo-3-amino-2-butanol (1) and found to be identical:

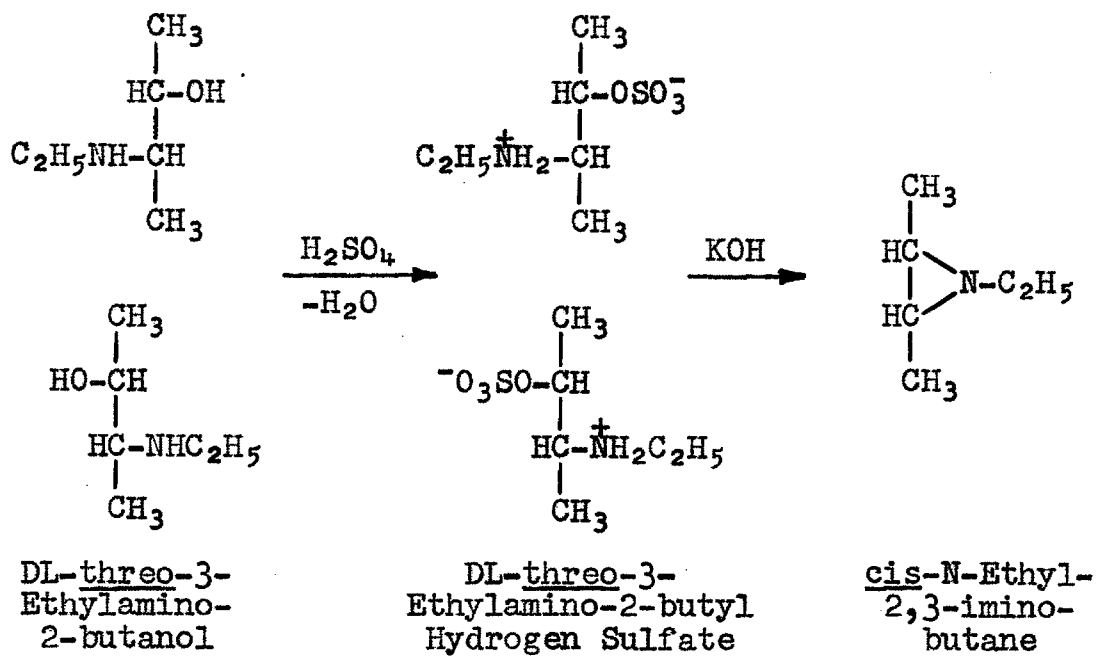


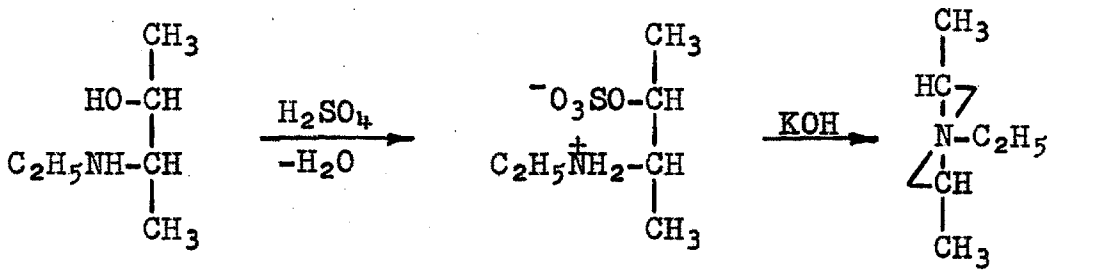
Thus a trans opening of the oxide ring occurs with ethylamine, exactly as with ammonia.

In similar manner, L(+)-erythro-3-ethylamino-2-butanol was obtained from D(+)-trans-2, 3-epoxybutane and ethylamine, and linked to the known L(+)-erythro-3-amino-2-butanol (1).



These new secondary amino alcohols were used to prepare, via the sulfate esters, two new imines: namely cis-N-ethyl-2, 3-iminobutane from DL-threo-3-ethylamino-2-butanol, and L(+)-trans-N-ethyl-2, 3-iminobutane from L(+)-erythro-3-ethylamino-2-butanol:





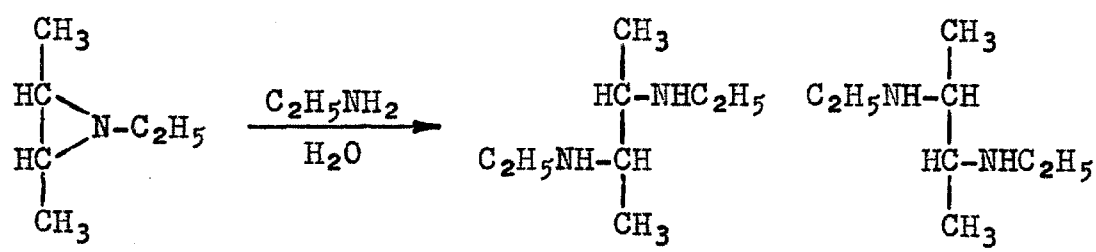
L(+)-erythro-3-Ethylamino-2-butanol

L-erythro-3-Ethylamino-2-butyl Hydrogen Sulfate

L(+)-trans-N-Ethyl-2,3-iminobutane

In each case the sulfate intermediates turned out to be crystalline solids, unlike that from 1-ethylamino-2-butanol.

A 49% yield of product resulted when the cis N-ethyl imine reacted with excess aqueous ethylamine at 120°C. for two weeks; this was identified by the analysis of derivatives as a 2,3-bis-ethylaminobutane. To determine whether it had the DL-threo or meso configuration it was resolved with L(-)-dibenzoyltartaric acid; the less soluble salt was purified and converted to a free base with a specific rotation of +106.0°. The residue from the mother liquor, after decomposition and purification as the hydrochloride, afforded the enantiomorph, with rotation -103.7°. This established the original configuration as DL-threo.

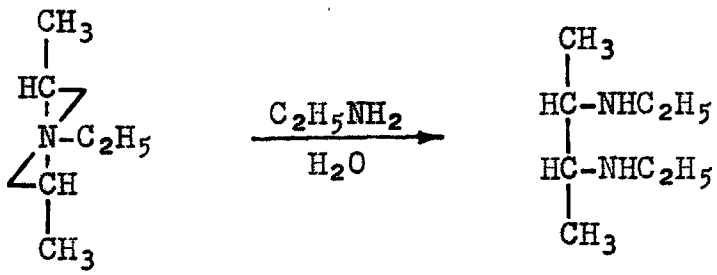


cis-N-Ethyl-2,3-iminobutane

DL-threo-2,3-Bis-ethylaminobutane

By ethylation of the p-toluenesulfonyl derivative of L(+)-threo-2, 3-butanediamine (1), the dextrorotatory form was shown to have the L-threo configuration.

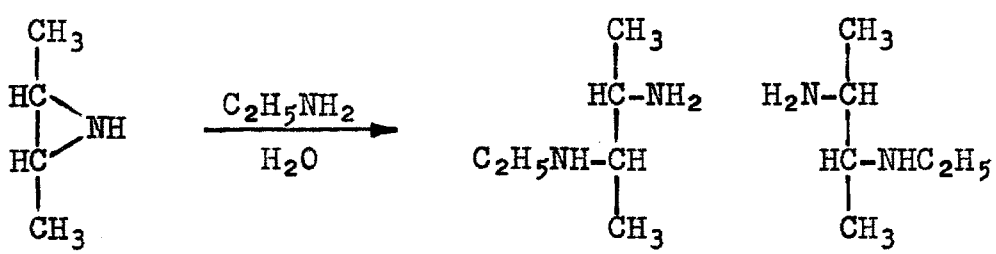
The active N-ethyl imine and ethylamine yielded a diamine whose rotation was $+0.48^{\circ}$. This was undoubtedly the meso isomer, contaminated with about 0.5% of active isomer; the p-toluenesulfonyl and acetyl derivatives were both high-melting, as expected for meso compounds, and optically inactive after purification.



L(+)-trans-N-Ethyl-2,3-iminobutane

meso-2,3-Bis-ethylaminobutane

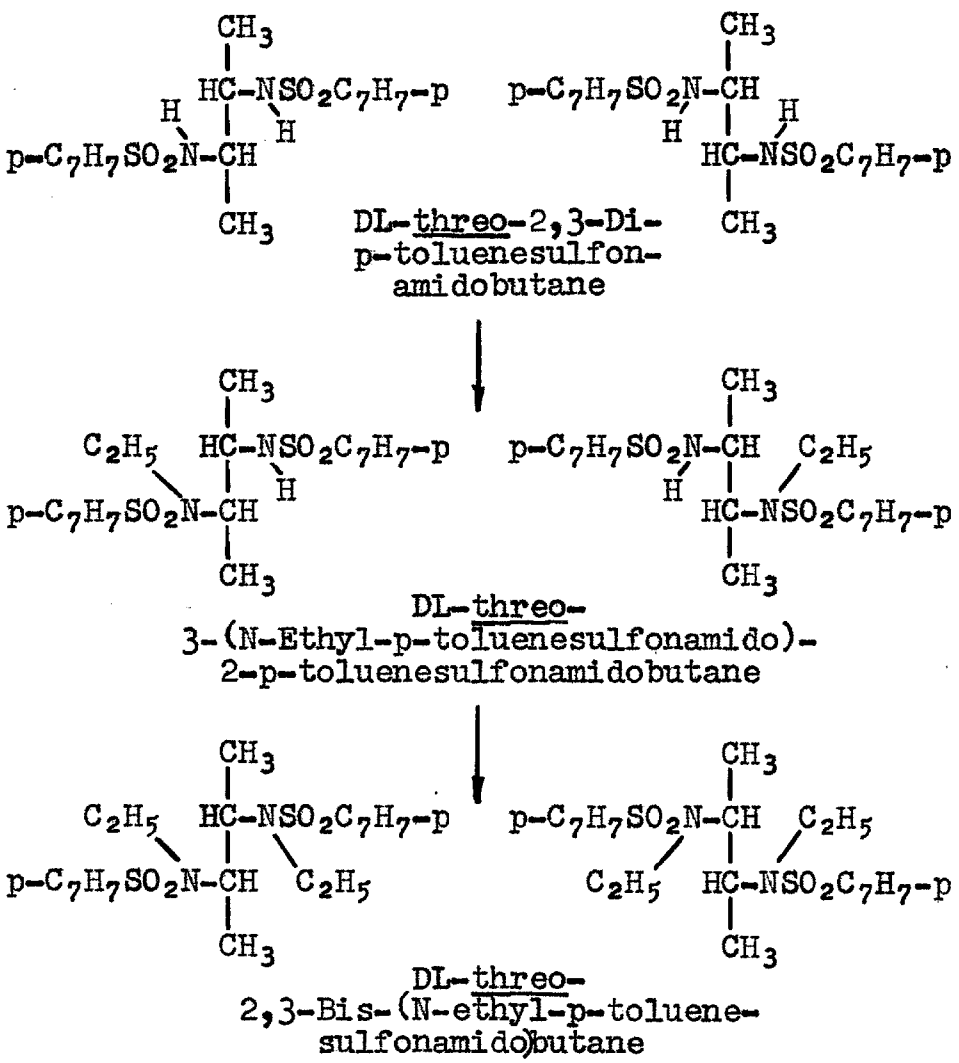
Aqueous ethylamine also opened the ring of the simple 2, 3-iminobutanes. Thus cis-2, 3-iminobutane gave DL-threo-3-ethylamino-2-aminobutane, identified by its ethylation with ethyl iodide to the resolvable DL-threo-2, 3-bis-ethylaminobutane:



cis-2,3-Imino-butane

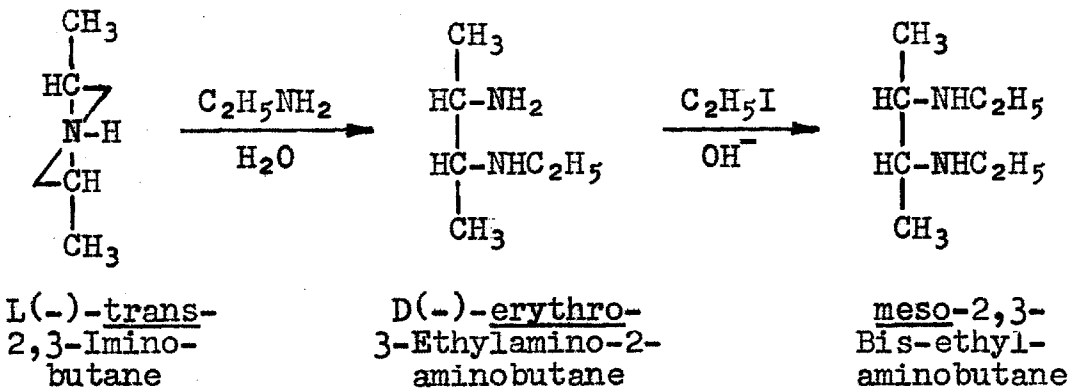
DL-threo-3-Ethylamino-2-aminobutane

In addition, it proved possible by ethylation to obtain the di-p-toluenesulfonyl derivative of DL-threo-3-ethylamino-2-aminobutane from that of DL-threo-2,3-butanediamine, and then further to ethylate the former to the corresponding derivative of DL-threo-2,3-bis-ethylaminobutane:



When L(-)-trans-2,3-iminobutane reacted with ethylamine an optically active dibasic amine, D(-)-erythro-3-ethylamino-2-aminobutane resulted; it was ethylated to the internally compensated

meso-2, 3-bis-ethylaminobutane with ethyl iodide:

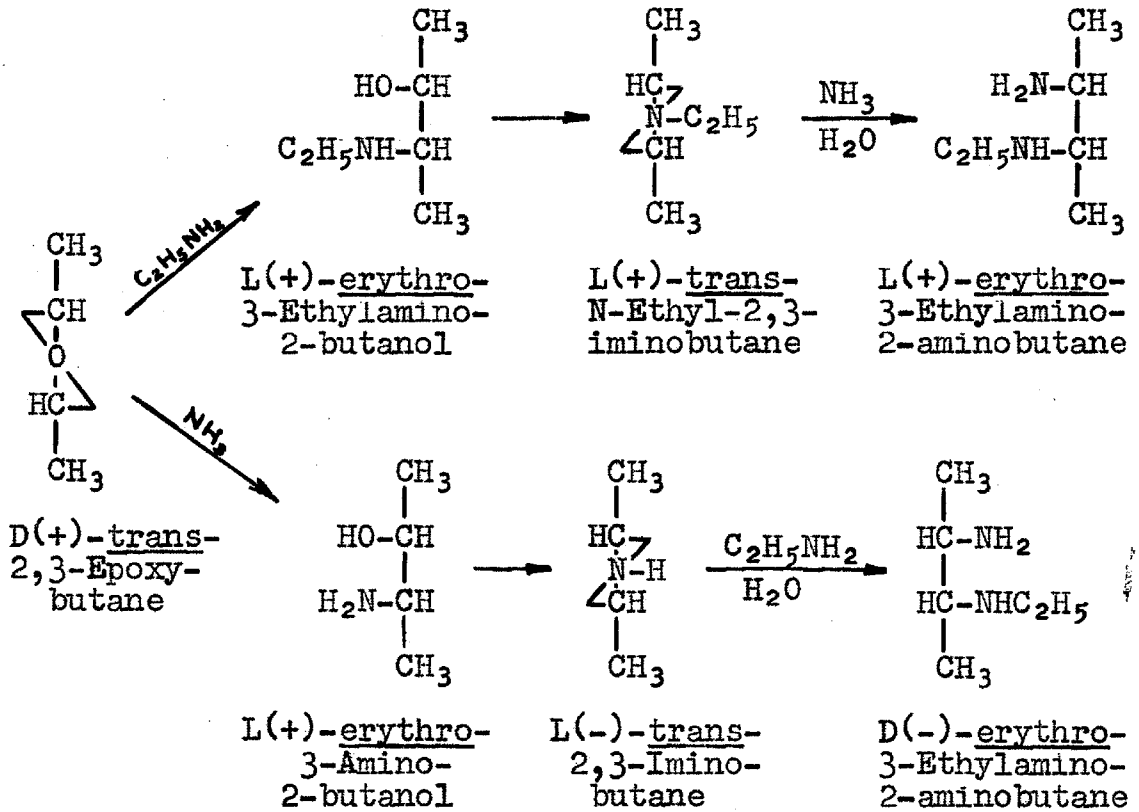


L(-)-trans-2,3-Imino-butane

D(-)-erythro-3-Ethylamino-2-aminobutane

meso-2,3-Bis-ethyl-aminobutane

It was recognized that if all the ring openings with amines and ammonia occurred with inversion at the attacked carbon atom, the scheme: active OXIDE to AMINO ALCOHOL to IMINE to DIAMINE would lead to one active diamine if the two amines used were dissimilar, and to its enantiomorph if their order in the reaction scheme were reversed. All the pertinent reactions except one (that of active N-ethyl imine with ammonia) already having been carried out, the missing experiment was performed (using aqueous ammonia as reactant) to complete the reaction scheme given on the following page.



Both the free bases and their derivatives possessed physical properties befitting enantiomorphs; the prediction was upheld.

The use of aqueous ammonia to open rings was extended to the case of the 2, 3-iminobutanes, where liquid ammonia without a catalyst had failed and ammonium chloride catalysis in a bomb tube had been resorted to (1). Yields of 67% and 71% respectively, of meso-2, 3-butanediamine from L(-)-trans-2, 3-iminobutane and DL-threo-2, 3-butanediamine from cis-2, 3-iminobutane resulted after two weeks reaction with an excess of concentrated ammonium hydroxide at 100°C. This is another case of water catalysis.

Two general conclusions can be drawn from the following tables of physical constants. They concern the optical rotatory powers of the ethylamino and N-ethyl-p-toluenesulfonamido groups.

It has been demonstrated (1) with the 2, 3-disubstituted butanes that a hydroxy or amino group with D- configuration in the 3- position causes levorotation, the effect being stronger with the latter. Evidently ethylation of the amino group intensifies this effect, since while with L-erythro-3-amino-2-butanol the hydroxyl group all but cancels the rotation due to the amino group, to give a rotation of $+0.85^{\circ}$, the L-erythro-3-ethylamino- and L-erythro-3-diethylamino-2-butanols have specific rotations of $+31.2^{\circ}$ and $+95.5^{\circ}$ respectively. This is confirmed by all the diamines studied: the active threo-2, 3-bis-ethylaminobutanes, in which the effects of each group should be complementary, rotate light in the same direction as but to a greater degree (106°) than the simple diamines of like configuration (29.5°); and when the rotations of the erythro-3-ethylamino-2-aminobutanes are measured, it is found that the effect of the ethylamino group outweighs that of the amino group: L-erythro-3-ethylamino-2-aminobutane has a specific rotation of $+37.2^{\circ}$. The only exception to this rule occurs in the 3-membered ring compounds (which are not, after all, completely analogous to the compounds with relatively free rotation between carbons 2 and 3): L-trans-N-ethyl-2, 3-iminobutane is dextrorotatory ($+24.7^{\circ}$), while the simple L-trans-imine has a specific rotation of -102° and the trans-oxide would have a rotation of -59°.

Although p-toluenesulfonylation of the simple amino or hydroxyl groups completely reverses the sign of their rotation, (the p-toluenesulfonyl derivatives of the dextrorotatory diols, simple

amino alcohols and simple diamines are levorotatory) it simply decreases the magnitude of the effect of the ethylamino group. The rotatory power of the resultant N-ethyl-p-toluenesulfonamido group is weak (-6.8° under the assumption of simple algebraic addition of the effect of two such groups in D(-)-threo-2, 3-bis-(N-ethyl-p-toluenesulfonamido)-butane) but nevertheless it is sufficient to overcome the effects of the otherwise strong p-toluenesulfonamido and p-toluenesulfonoxy groups when in the same molecule. Thus while the p-toluenesulfonamido group would be expected from its high rotation in L(-)-threo-2, 3-di-p-toluenesulfonamidobutane (-70.3°) to cause dextrorotation in L-threo-3-(N-ethyl-p-toluenesulfonamido)-2-p-toluenesulfonamidobutane, the compound is weakly dextrorotatory (+2.2°), as dictated by the ethylated group. Likewise the rotations of the erythro-3-(N-ethyl-p-toluenesulfonamido)-2-p-toluenesulfonamidobutanes and 3-(N-ethyl-p-toluenesulfonamido)-2-p-toluenesulfonoxybutanes, where the two groups would be expected to act in conjunction, rather than in opposition, are surprisingly low. (+21.3° and +9.2° respectively, for the L- isomers). All of this is probably due to the spatial restrictions placed on the molecule by the additional ethyl groups.

Little has been gained from a study of the acetyl derivatives. The behavior of the acetamido group is anomalous when ethylated.

PHYSICAL CONSTANTS

OF SOME

2, 3-DISUBSTITUTED BUTANES*

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*Those marked in this manner are taken from reference (1) and are included for comparison purposes.

Groups in Position 2	3	Isomer	B. P. (°C.)	mm.	m.p. (°C.)	$\eta^{25}D$	d^{25}	$(\alpha)^{25}D$ (o)
-OH	$-NH_2$	DL-threo	69-70*	20	18-20*	1.4445*	0.930*	
-OH	-NHEt	DL-threo	69.3-70.2	20		1.4366	0.879	
-OH	$-NEt_2$	DL-threo	71.0-71.2	20		1.4240	0.843	
-OH	$-NH_2$	L(+)-erythro	87.7-88.3	40	49.2-49.3*	1.4488*	0.938*	+0.85*
-OH	-NHEt	L(+)-erythro	69.2-69.5	20	18-19	1.4387	0.888	+31.2
-OH	$-NEt_2$	L(+)-erythro	83.7-84.9	20		1.4377	0.861	+95.5
O		cis	59.7*	742		1.3802*	0.823*	
NH		cis	82.5-82.9*	747		1.4172*	0.817*	
NEt		cis	81.0-81.8	746		1.3968	0.743	
O		D(+)-trans	53.5-53.7*	745		1.3705*	0.800*	+59.0*
NH		L(-)-trans	74.5-74.8*	746		1.4070*	0.788*	-105.7
NEt		L(+)-trans	91.0-91.8	745		1.4042	0.760	+24.7
$-NH_2$	$-NH_2$	DL-threo	57-58*	60		1.4408*	0.850*	
-NHEt	-NHEt	DL-threo	64.6-65.8	20		1.4299	0.809	
$-NH_2$	$-NH_2$	meso	59-60*	60		1.4420*	0.856*	
-NHEt	-NHEt	meso	63.8-64.5	20		1.4297	0.806	
-OH	-OH	D(-)-threo	77.5-77.6*	10	19.7*	1.4308*	0.987*	-13.2*
$-NH_2$	$-NH_2$	L(+)-threo	58-59*	60		1.4462*		+29.5*
-NHEt	-NHEt	D(-)-threo	64.9-65.2	20		1.4299	0.781	-103.7
-NHEt	-NHEt	L(+)-threo	65.0-65.8	20		1.4302	0.781	+106.0
$-NH_2$	-NHEt	DL-threo	82.1-83.3	100		1.4328	0.816	
$-NH_2$	-NHEt	D(-)-erythro	85.1-85.7	100		1.4347	0.823	-36.7
$-NH_2$	-NHEt	L(+)-erythro	84.1-85.0	100		1.4340	0.823	+37.2

MELTING POINTS AND SPECIFIC ROTATIONS OF p-TOLUENESULFONYL AND ACETYL DERIVATIVES OF SOME 2, 3-DISUBSTITUTED BUTANES*

Groups in Position 2	3	Isomer	M. P. °C. (cor.)	$(a)^{25}D$ (o)
-OTs	-NHTs	DL-threo*	125.7-126.7	
-OTs	-NEtTs	DL-threo	111.1-111.5	
-OTs	-OTs	D(+)-threo*	65.1-65.5	+37.2
-OTs	-NHTs	D(+)-threo*	140.1-141.0	+42.5
-OTs	-NHTs	L(-)-erythro*	104.2-105.2	-7.14
-OTs	-NEtTs	L(+)-erythro	-	+9.2
____NTs____		cis	94.9-96.1	
____NTs____		L(-)-trans	78.4-79.4	-19.0
-NHTs	-NHTs	DL-threo*	179.3-180.7	
-NHTs	-NEtTs	DL-threo	150.6-151.6	
-NEtTs	-NEtTs	DL-threo	135.8-136.7	
-NHTs	-NHTs	L(-)-threo*	201.1-202.8	-70.3
-NHTs	-NEtTs	L(+)-threo	111.3-112.0	+2.2
-NEtTs	-NEtTs	L(+)-threo	138.7-139.5	+13.7
-NEtTs	-NEtTs	D(-)-threo	138.5-139.5	-13.3
-NHTs	-NHTs	meso*	168.5-169.0	
-NHTs	-NEtTs	D(-)-erythro	149.9-150.7	-23.8
-NHTs	-NEtTs	L(+)-erythro	148.0-148.8	+21.3
-NEtTs	-NEtTs	meso	241.8-243.3	
-NHAc	-NHAc	DL-threo*	178.6-178.9	
-NHAc	-NEtAc	DL-threo	80.4-81.0	
-NEtAc	-NEtAc	DL-threo	68.3-69.6	
-OAc	-OAc	D(+)-threo*	25.7-25.9	+13.7
-OAc	-NHAc	D(+)-threo*	59.3-60.5	+35.0
-OAc	-NHAc	L(-)-erythro*	62.3-63.3	-33.0
-NHAc	-NHAc	L(-)-threo*	199.3-199.7	-56.8
-NEtAc	-NEtAc	D(-)-threo	72.0-72.7	-25
-NEtAc	-NEtAc	L(+)-threo	71.0-71.7	+30
-NHAc	-NHAc	meso*	277.9-280.0	
-NEtAc	-NEtAc	meso	76.5-77.3	
-NHAc	-NEtAc	D(+)-erythro	93.6-94.6	+7.1
-NHAc	-NEtAc	L(-)-erythro	93.9-94.6	-6.8

*Taken from previous work and included for comparison purposes (1, 10).

EXPERIMENTAL

Acetic anhydride was from Baker and Adamson, with assay 90-95%, and was fractionated at atmospheric pressure.

Denatured ethanol consisted of approximately 85% ethanol, 10% methanol, and 5% water.

L(-)-Dibenzoyltartaric acid was prepared by the method of Butler and Cretscher (11).

Diethylamine was Matheson, Coleman and Bell material. It was fractionated through a 15-inch column of Raschig rings, B. P. 54.0-54.8°/742 mm.

Diisopropyl ether was shaken with 10% sodium sulfite solution, then with water, dried over calcium chloride and fractionated. The fraction boiling below 67°C. was discarded.

Diethylene glycol monobutyl ether was Eastman technical grade, and was fractionated through a 15-inch column of Raschig rings, the fraction boiling at 86.6-87.7°C./3 mm. being collected. B. P. 120.9°/20 mm.

1,2-Epoxybutane was isolated from 'Butylene Oxides, Straight Chain Isomers' kindly supplied by the Dow Chemical Company. Drying over potassium carbonate and fractionation through a 40-cm. column of helices afforded a central fraction, representing about 40% of the total, B. P. 62.2-62.3°C./743 mm.

Ethylamine was a 70% aqueous solution from Matheson, Coleman and Bell. It was used as supplied. Recovered ethylamine was distilled through a 40-cm. column of helices, using ice water circulated by a centrifugal pump in the condensers, and then diluted

with distilled water to a 70% concentration by weight.

Ethyl bromide was fractionated Eastman White Label material.

Ethyl iodide was student-prepared material, dried and distilled through a 45-cm. column of Raschig rings, the fraction with boiling point 69.2-69.8°C./744 mm. being collected.

p-Nitrobenzoyl chloride was from Matheson, Coleman and Bell, and was recrystallized from carbon tetrachloride.

Oxalic acid was reagent grade 'Oxalic Acid, Anhydrous Powder' from Baker and Adamson.

Pyridine was technical material, refluxed over potassium hydroxide and then fractionated through a 15-inch column of Raschig rings; a typical lot had boiling point 112.5-113.0°C./740 mm.

p-Toluenesulfonyl chloride was Eastman White Label material and was recrystallized from hexane.

Triethylamine was from Matheson, Coleman and Bell, and was fractionated through a 60-cm. column of Raschig rings, B.P. 87.7-87.8°C./745 mm.

cis- and D(+)-trans-2,3-Epoxybutanes, DL-threo- and L(+)-erythro-3-amino-2-butanols, cis- and L(-)-trans-2,3-iminobutanes were prepared according to the directions previously worked out in these laboratories (1, 3, 5), with two exceptions: in the preparation of the 3-chloro-2-butanols the saturation with hydrogen chloride was carried out at ca -30°C., thereby increasing the yield in this step; the L(+)-erythro-3-amino-2-butanol was fractionated through a column of Raschig rings, using a slow stream of cooling water in the condenser to prevent solidification, B.P. 87.7-88.3°/40 mm.

The physical constants corresponded closely to those found previously, except that the L-trans-2, 3-iminobutane was found to have a rotation of -83.28°. (previous value -80.37°). In all cases the compounds boiled over a very short range (0.3 to 1.0°).

L(-)-threo-2, 3-Di-p-toluenesulfonamidobutane was synthesized from L(+)-threo-2, 3-butanediamine according to the directions of Dickey, Fickett and Lucas (1). The diamine was obtained from a sample of its acid tartrate salt prepared by W. Fickett. The melting point was 201.4-202.2°C. (lit.:201.1-202.8°C.) and the specific rotation -69.2° (lit.: -70.3°).

All melting points are corrected. Microanalyses marked (E) are by A. Elek, those marked (S) by G. Swinehart.

1-Amino-2-butanol

Seventy-two grams (1.0 mole) of 1, 2-epoxybutane was added in 6 portions to a 4-pound bottle (30 moles) of reagent grade ammonium hydroxide cooled to 5°C. It was then allowed to stand at room temperature for 14 days. The ammonia was distilled off through a 15-inch column of Raschig rings until a pot temperature of 105°C. was reached. Most of the water was then removed under a vacuum of about 100 mm., to a pot temperature of 110°C. A still base (25 ml. of diethylene glycol monobutyl ether) was added and the material fractionated through a 24-inch column of Raschig rings. After a 10 g. forerun there was collected 58 g. (65%) of 1-amino-2-butanol, B.P. 79.7-81.2°C./20 mm. Purification via the neutral oxalate (see following paragraph) followed by decomposition with a slight excess of barium hydroxide and fractionation as above yielded

material with boiling point 82.0-83.0°C./20 mm., $\eta^{25}D$ 1.4482.

Neutral Oxalate of 1-Amino-2-butanol

To a solution of 25.0 g. (0.28 mole) of 1-amino-2-butanol in 125 ml. of dry diethyl ether was added slowly with stirring a solution of 12.8 g. (0.142 mole) of anhydrous oxalic acid in 150 ml. of dry diethyl ether. A white precipitate formed immediately, accompanied by some heat. The product was filtered off and dried in a vacuum desiccator over sulfuric acid to yield 36 g. (100%) of white solid. Two recrystallizations from ethanol-water gave 30 g. (83%) of shimmering water-soluble colorless plates, m.p. 195-196°C.; lit. (12): 196-200°C.

1-Benzamido-2-butanol

In a 20-ml. test tube was placed 10 ml. of 3N sodium hydroxide solution and 1.78 g. (0.020 mole) of 1-amino-2-butanol; this was cooled to 0°C. and there was added with stirring 3.2 g. (0.023 mole) of benzoyl chloride. The white precipitate which formed was allowed to stand 3 hours, and then the mixture was acidified to pH 2 with 6N hydrochloric acid. The solid was filtered off, desiccated over night and recrystallized from 25 ml. of benzene to give 2.7 g. (70%) of 1-benzamido-2-butanol, m.p. 112.1-113.1°C.; lit. (12): 112-113.5°C.

1-p-Nitrobenzamido-2-p-nitrobenzoxybutane

A solution of 0.45 g. (0.0050 mole) of 1-amino-2-butanol in 8 ml. of pyridine was treated at 0°C. with 1.87 g. (0.0100 mole) of p-nitrobenzoyl chloride in 4 portions. The pale yellow precipitate which formed was allowed to stand over night. After the addition of 10 ml. of water the mixture was acidified with 6N hydrochloric acid

while cooling and stirring; 10 ml. of 1N sodium bicarbonate solution was then added, and the material filtered and washed with 100 ml. of water. Drying in a desiccator gave 1.8 g. (93%) of yellow powder. Five recrystallizations from ethanol-water gave colorless needles, m.p. 119.2-120.2°C. Calculated for $C_{18}H_{17}N_3O_7$: C 55.81, H 4.42, N 10.85. Found (E): C 56.61, H 4.62, N 11.08.

1-Amino-2-butyl Hydrogen Sulfate

A solution of 47.0 g. (0.53 mole) of 1-amino-2-butanol in 100 ml. of water was titrated to the methyl orange end point with 19.8N sulfuric acid: 27.5 ml. required, an assay of 103%. A further 27.5 ml. of acid was added, and the water removed under aspirator vacuum and steam heat to yield a pink solid, which was then dried to constant weight at 1 mm. pressure and 100°C. (13 hours were required, exclusive of interruptions to grind lumps.) The white inner salt had melting point 224-226°C. (bath preheated to 200°C.).

1,2-Iminobutane

A 1-liter 3-necked flask was equipped with 1) a Claisen head attached to a Friedrichs condenser, and having a long-stem dropping funnel running down its neck, 2) a mercury-sealed stirrer and 3) a pot thermometer. In it was placed 85.9 g. (0.508 mole) of 1-amino-2-butyl hydrogen sulfate and 350 ml. of water (incomplete solution). With cooling to 0°C. there was added over 20 minutes a solution of 125 g. (2.2 moles) of potassium hydroxide in 125 ml. of water. Heating was then begun. At 100°C. mild boiling began, with the product distilling at 60-70°C. Heating was continued until the distilling temperature reached 99°C. The distillate (100 ml.) was saturated at

0°C. with potassium hydroxide. The organic layer was separated, dried over potassium hydroxide and then distilled through an 8-inch column of helices to give 18.0 g. (50%) of 1,2-iminobutane, B.P. 87.6-88.5°C./743 mm., $\eta^{25}D$ 1.4177. The yield could probably be improved by continued distillation from the original reaction mixture, which still smelled strongly ammoniacal.

1-Ethylamino-2-butanol

In a 600-ml. Pyrex glass ampoule* was placed 21.6 g. (0.300 mole) of 1,2-epoxybutane and 450 ml. (ca. 6 moles) of 70% aqueous ethylamine. It was sealed and kept at 100°C. in an electrically heated oil bath for 5 days. The excess ethylamine was removed by distillation through an 8-inch column of Raschig rings, to a pot temperature of 96°C. Then most of the water was removed through a longer column (60-cm.) at 100 mm. pressure (aspirator). Twenty-five milliliters of diethylene glycol monobutyl ether was then added, and the product distilled at 20 mm. pressure (oil pump). A total yield of 28.4 g. (81%) resulted, with a central cut boiling at 78.0-79.2°C./20 mm. The material solidified over night in the receiver: m.p. 30-33.5°C.

1-(N-Ethyl-p-toluenesulfonamido)-2-p-toluenesulfonoxybutane

A solution of 0.58 g. (0.0050 mole) of 1-ethylamino-2-butanol in 2 ml. of pyridine was treated at 0°C. with a solution of 1.91 g. (0.100 mole) of p-toluenesulfonyl chloride in 6 ml. of pyridine. The resulting solution acquired a dark color as it stood over night at

*After use of this type of vessel for many experiments, one exploded with considerable damage to the surroundings. The final few reactions with 70% aqueous ethylamine were therefore carried out in 220-ml. stainless steel reaction tubes, with threaded caps and Teflon gaskets. Heat was applied in an ampoule oven.

room temperature. It was then acidified at 0°C. with 6N hydrochloric acid, to give an oil which solidified upon scratching. The yellow solid was filtered off, washed several times with water, and dried: 1.95 g. (92%). Five recrystallizations from 95% ethanol gave colorless needles, m.p. 98.2-99.1°C. Calculated for $C_{20}H_{27}NS_2O_5$: C 56.44, H 6.40, N 3.29, S 15.07. Found (E): C 56.00, H 6.23, N 3.28, S 14.78.

1-Diethylamino-2-butanol from 1-Amino-2-butanol (13)

In a 500-ml. round bottom flask were placed 17.8 g. (0.200 mole) of 1-amino-2-butanol, 44 g. (0.40 mole) of ethyl bromide, and a solution of 45 g. (0.41 mole) of sodium carbonate in 150 ml. of water. Refluxing was carried out for 8 hours, using a Friedrichs condenser with ice water circulated by a centrifugal pump. After cooling the aqueous (more dense) layer was full of white crystals. Both liquid layers were decanted, saturated with potassium hydroxide pellets, and filtered through coarse sintered glass. The layers were separated and the aqueous phase extracted 3 times with 60-ml. portions of diethyl ether previously used to rinse the inorganic crystals in the reaction flask. The combined extracts were dried over potassium hydroxide, filtered, and the ether distilled off at atmospheric pressure. After the addition of 10 ml. of diethylene glycol monobutyl ether vacuum fractionation through an 8-inch column of helices gave, after a small forerun, 9.0 g. (31%) of 1-diethylamino-2-butanol, B.P. 71.8-72.5°C./20 mm., $\eta^{25}D$ 1.4279.

Hydrochloride of 1-Diethylamino-2-butanol

Attempted preparation of the p-nitrobenzoate ester, hydrochloride of 1-diethylamino-2-butanol by mixing diethyl ether

solutions of equivalent amounts of the amino alcohol and p-nitrobenzoyl chloride led to the isolation of the simple hydrochloride, m.p. 150.6-151.8°C. (from ethyl acetate).

1-Diethylamino-2-butanol from 1-Ethylamino-2-butanol

There were weighed into a 200-ml. Erlenmeyer flask 23.4 g. (0.200 mole) of 1-ethylamino-2-butanol and 21.8 g. (0.200 mole) of ethyl bromide. The resulting solution was cooled in an ice bath and stirred with the exclusion of moisture. After 3 hours a pasty white mass had formed. This was treated, with cooling and stirring, with 60 ml. of 50% sodium hydroxide solution in 8 portions. The resulting layers were separated and the aqueous phase extracted with 25 ml. of diethyl ether. Cloudiness resulted when this was combined with the original organic phase, but it disappeared when potassium hydroxide pellets were added to dry the solution. Filtration (Whatman no. 50) was performed into a 100-ml. 3-necked flask, and the ether distilled through an 8-inch column of helices, to a pot temperature of 108°C. A still base (15 ml. of diethylene glycol monobutyl ether) was added, and the material vacuum distilled at 20 mm. pressure. After a 2.6 g. forerun, 18.5 g. (64%) of 1-diethylamino-2-butanol was obtained, B.P. 71.5-72.4°C./20 mm., $\eta^{25}D$ 1.4281.

The hydrochloride, when prepared in the same manner as that of 1-diethylamino-2-butanol, had melting point 150.6-151.0°C. This was not lowered when mixed with a sample of the latter.

1-Diethylamino-2-butanol from 1,2-Epoxybutane

An ampoule (see footnote, p. 34) containing 12 g. (0.167 mole) of 1,2-epoxybutane, together with 170 ml. (120 g., 1.67 mole) of

diethylamine, was sealed and heated at 100°C. for one week. The diethylamine was distilled off through a 45-cm. column of Raschig rings, to a pot temperature of 110°C., the residue transferred to a smaller flask, and 12.5 ml. of diethylene glycol monobutyl ether added. Vacuum fractionation through an 8-inch column of helices gave, after a small forerun, 23.3 g. (95%) of 1-diethylamino-2-butanol, B.P. 71.8-72.4°/20 mm., $\eta^{25}D$ 1.4271.

The hydrochloride, when prepared as above, had melting point 150.6-151.1°C. This was not lowered when mixed with a sample prepared from 1-diethylamino-2-butanol from 1-amino-2-butanol.

1-Ethylamino-2-butyl Hydrogen Sulfate*

A solution of 58.7 g. (0.50 mole) of 1-ethylamino-2-butanol in 100 ml. of water was titrated to the methyl orange end point with 33.07 ml. of 14.7N sulfuric acid (97% assay). A further 33 ml. was added and the water removed at aspirator vacuum on a steam bath. Five days at 1 mm. pressure and 120°C. (oil bath, resistance wire) were required to obtain a constant weight of glassy orange product.

N-Ethyl-1,2-iminobutane

In a 500-ml. apparatus similar to that used for 1,2-iminobutane was placed 98 g. (0.50 mole) of 1-ethylamino-2-butyl hydrogen sulfate and 150 ml. of water. At 0°C. there was added over 20 minutes a solution of 100 g. (1.75 mole) of potassium hydroxide in 100 ml. of water. Stirring was continued at room temperature for one-half hour and then heat was applied by means of an electric mantle; stirring was necessary to prevent bumping when boiling commenced

*The pure material was prepared by G. Dudek, according to the following directions by the author.

at 85°C. and solid potassium sulfate began to form. Distillation was continued to a pot temperature of 100°C., to collect 49 g. of distillate, which was then saturated with potassium hydroxide to give 2 phases. The much greater organic layer was separated and distilled through an 8-inch column of helices to give 29.9 g. (60%) of ammoniacal liquid, B.P. 91.0-92.1°C./741 mm., η^{25}D 1.4010.

1,2-Bis-ethylaminobutane

A 225-ml. ampoule (see footnote, p. 34) containing 12.0 g. (0.12 mole) of N-ethyl-1,2-iminobutane and 180 ml. (ca. 2.4 moles) of 70% aqueous ethylamine was sealed and heated at 120°C. for 16 days. The ethylamine was removed by distillation through a 45-cm. column of Raschig rings to a pot temperature of 99.5°C. Two phases resulted in the residue when hot, but they coalesced upon cooling. The solution was saturated with potassium hydroxide at 0°C., the organic layer (15.2 g.) separated, and the aqueous phase extracted with two 50-ml. portions of diethyl ether. The combined extracts were transferred to a 200-ml. flask and the ether distilled through an 8-inch column of helices until the pot temperature reached 110°C. A still base was added (10 ml. of diethylene glycol monobutyl ether) and vacuum fractionation at 20 mm. pressure gave 9.5 g. (55%) of 1,2-bis-ethylaminobutane, B.P. 73.0-73.8°C./20 mm. η^{25}D 1.4316. At least one more gram remained in the still base.

1,2-Bis-(N-ethyl-p-toluenesulfonamido)-butane

In a 25-ml. Erlenmeyer flask were placed 0.72 g. (0.0050 mole) of 1,2 bis-ethylaminobutane and 10 ml. of triethylamine. After cooling to 0°C. there was added in 5 portions, with stirring, 1.91 g.

(0.0100 mole) of p-toluenesulfonyl chloride. A white precipitate formed immediately. The reaction mixture was allowed to stand for 36 hours and was then acidified, with cooling and stirring, using 6N hydrochloric acid. A tan oil resulted, from which the aqueous layer was decanted. The oil was washed with fresh 6N hydrochloric acid and dried at 1 mm. pressure over sulfuric acid and potassium hydroxide. After several weeks it formed a tan solid. Seven recrystallizations from denatured ethanol gave colorless prisms, m.p. 87.8-88.6°C. Calculated for $C_{22}H_{32}N_2S_2O_4$: C 58.38, H 7.13, N 6.19, S 14.17. Found (E): C 58.53, H 7.03, N 6.17, S 13.60.

Neutral Oxalate of DL-threo-3-Amino-2-butanol

A solution of 0.85 g. (0.095 mole) of anhydrous oxalic acid in 20 ml. of dry diethyl ether was added slowly to a cooled solution of 1.65 g. (0.190 mole) of DL-threo-3-amino-2-butanol in 10 ml. of dry diethyl ether. The white precipitate which immediately formed was removed and dried in a vacuum desiccator. Seven recrystallizations from denatured ethanol gave colorless plates, m.p. 190.0-191.1°C. Calculated for $C_{10}H_{24}N_2O_6$: C 44.76, H 9.02, N 10.44. Found (E): C 44.71, H 8.83, N 10.13.

Neutral Oxalate of L(+)-erythro-3-Amino-2-butanol

This was prepared exactly as the DL-threo isomer. Four recrystallizations from 95% ethanol gave very thin flat colorless plates, m.p. 202.7-203.3°C. Calculated for $C_{10}H_{24}N_2O_6$: C 44.76, H 9.02, N 10.44. Found (E): C 45.40, H 8.90, N 11.13.

DL-threo-3-Diethylamino-2-butanol from DL-threo-3-Amino-2-butanol

In a 300-ml. round-bottomed flask were placed 8.9 g. (0.100 mole) of DL-threo-3-amino-2-butanol, 31.2 g. (0.200 mole) of ethyl

iodide and a solution of 25 g. (0.24 mole) of sodium carbonate in 100 ml. of water. The two-phase system was refluxed for 7 hours. Upon cooling the organic phase was less dense than the aqueous, which contained white crystals. The layers were separated and the organic layer (7.5 g.) was augmented with two 75-ml. portions of diethyl ether used to extract the aqueous phase. After the solution was dried over potassium hydroxide the ether was distilled off through an 8-inch column of helices to a pot temperature of 110°C. Fourteen milliliters of diethylene glycol monobutyl ether was added, and fractionation at 20 mm. pressure gave a 9.6 g. total yield, of which 7.5 g. (53%) was a central fraction of DL-threo-3-diethylamino-2-butanol, B.P. 71.0-71.2°C./20 mm., $\eta^{25}D$ 1.4240, d^{25} 0.843.

Hydrochloride of DL-threo-3-Diethylamino-2-butanol

To an ice-cold solution of 0.40 g. (0.0028 mole) of DL-threo-3-diethylamino-2-butanol in 10 ml. of dry benzene was added, with stirring, 10 ml. of 0.276M hydrogen chloride in benzene. A white precipitate resulted. After standing over night the solid was filtered off, rinsed with 20 ml. of dry benzene, and dried in a desiccator to give 0.45 g. (90%) of hydrochloride. After 3 recrystallizations from butanone it attained a constant melting point of 149.4-150.4°C. Calculated for $C_8H_{20}NClO$: C 52.88, H 11.10, N 7.71, Cl 19.51. Found (S): C 53.37, H 11.11, N 8.22, Cl 20.43.

L(+)-erythro-3-Diethylamino-2-butanol from L(+)-erythro-3-Amino-2-butanol

This was prepared from L(+)-erythro-3-amino-2-butanol in the same manner as the DL-threo isomer, except that the organic layer which formed after refluxing was very small. As a result the

aqueous phase was saturated with potassium hydroxide before separation and extraction. After a considerable forerun 5.1 g. (35%) of product was obtained, B.P. 83.7-84.9°C./20 mm., $\eta^{25}D$ 1.4377, d^{25} 0.861, $(\alpha)^{25}D$ +95.5° (α = +82.3°, pure liquid).

Hydrochloride of L(+)-erythro-3-Diethylamino-2-butanol

This was prepared exactly as the DL-threo isomer. Fifteen minutes passed before the hydrochloride began to crystallize from the ether solution. Three recrystallizations from butanone gave 60% of pure compound, m.p. 130.4-131.2°C. Calculated for $C_8H_{20}NClO$: C 52.88, H 11.10, N 7.71, Cl 19.51. Found (S): C 52.94, H 10.87, N 7.70, Cl 19.71.

DL-threo-3-Ethylamino-2-butanol

A stainless steel reaction tube containing 21 g. (0.29 mole) of cis-2,3-epoxybutane and 360 ml. (ca. 5 moles) of 70% aqueous ethylamine was heated at 100°C. for 7 days. The excess ethylamine was distilled through a 40-cm. column of Raschig rings, using ice water circulated by a centrifugal pump in the condensers. When the pot temperature reached 98°C. the distillation was stopped, and after cooling to 0°C. the residue was saturated with potassium hydroxide. The organic layer (33 g.) was removed and combined with 60 ml. of diethyl ether used to extract the aqueous phase. The ether was distilled off through a 40-cm. column of Raschig rings to a pot temperature of 100°C. Then 10 ml. of diethylene glycol monobutyl ether was added and fractionation continued at reduced pressure. A 29.0 g. (85%) fraction was collected, B.P. 69.3-70.2°C./20 mm., $\eta^{25}D$ 1.4366, d^{25} 0.879.

DL-threo-3-(N-Ethyl-p-toluenesulfonamido)-2-p-toluenesulfonoxybutane

A cold solution of 1.17 g. (0.0100 mole) of DL-threo-3-ethylamino-2-butanol in 8 ml. of pyridine was treated with 4.0 g. (0.021 mole) of p-toluenesulfonyl chloride. The resulting red solution darkened considerably upon standing for 24 hours. Acidification with 6N hydrochloric acid gave an oil which slowly solidified. The aqueous solution was poured off and the solid allowed to stand over 3N hydrochloric acid for 2 days, then filtered, washed and dried: 2.8 g. (66%). Four recrystallizations from 95% ethanol, after treatment with Norit, gave white rods, m.p. 111.1-111.5°C. Calculated for $C_{20}H_{27}NS_2O_5$: C 56.44, H 6.40, N 3.29, S 15.07. Found (E): C 56.48, H 6.29, N 3.27, S 14.97.

DL-threo-3-(N-Ethyl-p-nitrobenzamido)-2-p-nitrobenzoxybutane

To a solution of 0.58 g. (0.0050 mole) of DL-threo-3-ethylamino-2-butanol in 10 ml. of pyridine was added in portions 1.85 g. (0.0100 mole) of p-nitrobenzoyl chloride. The light yellow precipitate which formed was allowed to stand over night in the reaction mixture. Acidification with 6N hydrochloric acid gave over 1.5 g. (75%) of a pale yellow solid. Four recrystallizations from acetone gave very fine pale yellow needles, m.p. 167.2-167.9°C. Calculated for $C_{20}H_{21}N_3O_7$: C 57.82, H 5.10, N 10.12. Found (E): C 57.81, H 5.21, N 10.34.

DL-threo-3-Diethylamino-2-butanol from 3-Ethylamino-2-butanol

Seven and one-half grams (0.064 mole) of DL-threo-3-ethylamino-2-butanol was stirred at 0°C. with 10.5 g. (0.067 mole) of ethyl iodide. Two phases formed, so the reaction mixture was refluxed for 8 hours. Upon cooling a pink solid formed. After some abortive

attempts to purify this solid, there was added to it 5 ml. of water and 15 g. (0.26 mole) of potassium hydroxide. Two phases resulted, the lower one cloudy with precipitated potassium iodide. The organic layer was separated, added to 13 ml. of diethylene glycol monobutyl ether and fractionated through an 8-inch column of helices. Without any forerun 7.4 g. (80%) of product was obtained: B.P. 68.9-70.0°C./20 mm., $\eta^{25}D$ 1.4243.

Hydrochloride of DL-threo-3-Diethylamino-2-butanol above

This was prepared as previously described, m.p. 149.5-150.6°C. Mixed melting point with reference sample (m.p. 149.4-150.4°C.): 149.1-150.2°C.

L(+)-erythro-3-Ethylamino-2-butanol

This was prepared from D(+)-trans-2,3-epoxybutane in the same manner as the DL-threo isomer, yields of up to 84% being obtained. B.P. 69.2-69.5°C./20 mm., 70.3-70.7°C./21 mm., $\eta^{25}D$ 1.4386, d^{25} 0.888, m.p. 18-19°, $(\alpha)^{25}D$ + 31.2° (α = +27.73°, pure liquid).

L(+)-erythro-3-(N-Ethyl-p-toluenesulfonamido)-2-p-toluenesulfonoxybutane

All attempts to prepare this derivative as a crystalline solid failed. When 0.58 g. (0.0050 mole) of L(+)-erythro-3-ethylamino-2-butanol in 1.5 ml. of triethylamine was treated with 1.91 g. (0.0100 mole) of p-toluenesulfonyl chloride, allowed to stand over night and then acidified, a pale amber oil resulted which could not be induced to crystallize. $(\alpha)^{25}D$ +9.2° (α = +0.21°, c = 2.26, butanone).

L(-)-erythro-3-(N-Ethyl-p-nitrobenzamido)-2-p-nitrobenzoxybutane

This was prepared from L(+)-erythro-3-ethylamino-2-butanol exactly as was the DL-threo isomer, 6 recrystallizations from 95% ethanol giving small colorless rods, m.p. 117.0-117.6°C., $(\alpha)^{25}D$ -24.3° (α = -0.52°, c = 2.14, butanone). Calculated for $C_{20}H_{21}N_3O_7$: C 57.82, H 5.10, N 10.12. Found (E): C 57.85, H 5.27, N 9.79.

L(+)-erythro-3-Diethylamino-2-butanol from 3-Ethylamino-2-butanol

Five grams (0.043 mole) of L(+)-erythro-3-ethylamino-2-butanol and 7.0 g. (0.045 mole) of ethyl iodide were refluxed together for 90 minutes, and then worked up as described for the DL-threo isomer. A yield of 3.5 g. (56%) resulted: B.P. 81.8-83.0°C./20 mm., $\eta^{25}D$ 1.4378, $\alpha^{25}D$ = +78.99°.

Hydrochloride of L(+)-erythro-3-Diethylamino-2-butanol above

This was prepared as previously described: m.p. 130.2-131.2°C. Mixed melting point with reference sample (m.p. 130.4-131.2°C.): 130.3-131.1°C.

DL-threo-3-Ethylamino-2-butyl Hydrogen Sulfate

A solution of 21.3 g. (0.182 mole) of DL-threo-3-ethylamino-2-butanol in 50 ml. of water was titrated to the methyl orange end point with 19.8N sulfuric acid; 9.15 ml. was required, for an assay of 99.5%. A further 9.15 ml. was added, the water removed at aspirator vacuum on a steam bath, and the resulting syrup was subjected to a 1 mm. vacuum at 120°C. (oil bath heated by resistance wire). The removal of water, accompanied by crystallization, occurred slowly, and after 48 hours the solid was ground in a mortar, replaced in the drying apparatus, and brought to constant weight. A

white powder resulted, m.p. 197-199°C. (bath preheated to 190°C.).

cis-N-Ethyl-2, 3-iminobutane

In an apparatus identical to that used for N-ethyl-1, 2-iminobutane was placed a solution of 58.0 g. (0.294 mole) of DL-threo-3-ethylamino-2-butyl hydrogen sulfate in 125 ml. of water. With the solution kept at 5-10°C. by means of an ice bath, a solution of 75 g. (1.3 mole) of potassium hydroxide in 40 ml. of water was added. The stirring was continued and heat applied. At 75°C. crystallization of potassium sulfate began, quickly followed by distillation (complicated at first by foaming). Heating was continued until the pot temperature reached 104°C. The distillate was saturated with potassium hydroxide at 0°C., the organic layer separated and fractionated through a 24-inch column of helices. After a small forerun, 16.0 g. of cis-N-ethyl-2, 3-iminobutane was collected, B.P. 81.0-81.8°C./746 mm. The addition of 10 ml. of fractionated xylene allowed the collection of a further 5.0 g., B.P. 81.8-82.0°C. Total yield 21.0 g. (72%), $\eta^{25}D$ 1.3968, d^{25} 0.743.

L-erythro-3-Ethylamino-2-butyl Hydrogen Sulfate

This was prepared exactly as the DL-threo isomer. In a typical run, 20.6 g. (0.176 mole) of L-erythro-3-ethylamino-2-butanol (101% assay by titration) gave a constant weight of 33.9 g. (98%) of dry salt, m.p. 246.5-249°C. (dec.) (bath preheated to 190°C.).

L(+)-trans-N-Ethyl-2, 3-iminobutane

Application of the standard procedure to 33.5 g. (0.170 mole) of L-erythro-3-ethylamino-2-butyl hydrogen sulfate gave 12.7 g.

(73°/o) of L(+)-trans-N-ethyl-2, 3-iminobutane, B.P. 91.0-91.8°/ 745 mm.*, $\eta^{25}D$ 1.4042, d^{25} 0.760, $(\alpha)^{25}D$ +24.7° (α = + 18.75, pure liquid), $(\alpha)^{25}D$ +26.8° (α = +0.92°, c = 3.43, hexane).

DL-threo-2, 3-Bis-ethylaminobutane from cis-N-Ethyl-2, 3-iminobutane

A sealed ampoule (see footnote, p. 34) containing 5.5 g. (0.056 mole) of cis-N-ethyl-2, 3-iminobutane in 90 ml. (ca. 1.2 moles) of 70°/o aqueous ethylamine was heated at 120°C. for 3 weeks. The contents were transferred to a 200-ml. flask and the ethylamine distilled through a 45-cm. column of Raschig rings to a pot temperature of 100°C. Saturation of the distillate with potassium hydroxide at 0°C. led to the formation of 6.5 g. of an ammoniacal organic layer, which was augmented by 50 ml. of diethyl ether used to extract the aqueous phase. The ether was removed through an 8-inch column of helices, 10 ml. of diethylene glycol monobutyl ether added, and the fractionation continued at reduced pressure. Without any forerun, a fraction with boiling point 64.6-65.8°C./20 mm. was collected: 3.9 g. (48°/o), $\eta^{25}D$ 1.4299, d^{25} 0.809.

DL-threo-2, 3-Bis-(N-ethylacetamido)butane

A solution of 1.44 g. (0.0100 mole) of DL-threo-2, 3-bis-ethylaminobutane in 5 ml. of pyridine was treated at 0°C. with 3.5 g. (0.034 mole) of acetic anhydride and allowed to stand over night at room temperature. After several days in a vacuum desiccator over potassium hydroxide and sulfuric acid the material solidified. The amber solid was ground in a mortar and then redesiccated, to give 1.67 g. (73°/o)

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*It apparently forms an azeotrope with water, B.P. 81.9-82.2°/ 746 mm.

of dry product. Treatment with Norit and 3 recrystallizations from diisopropyl ether gave a white product, m.p. 68.3-69.6°C. Calculated for $C_{12}H_{24}N_2O_2$: C 63.12, H 10.60, N 12.27. Found (S): C 63.00, H 10.80, N 12.56.

DL-threo-2,3-Bis-(N-ethyl-p-toluenesulfonamido)butane

A solution of 0.72 g. (0.0050 mole) of DL-threo-2,3-bis-ethylaminobutane in 4 ml. of triethylamine was treated with 2.0 g. (0.0105 mole) of p-toluenesulfonyl chloride and the undissolved solid triturated. A further 3 ml. of triethylamine was added and the reaction mixture allowed to stand over night. The resulting gelatinous precipitate and liquid were spooned into 25 ml. of water and acidified carefully with 6N hydrochloric acid, filtered, and dried over potassium hydroxide. Recrystallization of this 2.2 g. (97%) of solid from denatured ethanol gave flat colorless plates, m.p. 135.8-136.7°C. Calculated for $C_{22}H_{32}N_2S_2O_4$: C 58.38, H 7.13, N 6.19, S 14.17. Found (S): C 58.53, H 7.08, N 6.26, S 14.64.

L(+)-threo-3-(N-Ethyl-p-toluenesulfonamido)-2-p-toluenesulfonamidobutane

A 0.40 g. (0.0010 mole) sample of L(-)-threo-2,3-di-p-toluenesulfonamidobutane was dissolved in a solution of 0.5 g. (0.01 mole) of potassium hydroxide in 10 ml. of 95% ethanol. To this solution was added 0.80 ml. (1.5 g., 0.01 mole) of ethyl iodide and the resulting solution refluxed for 4 hours. Another 1 ml. of ethyl iodide was then added, and refluxing was continued for a further 5 hours. The solvents were removed under aspirator

vacuum and the pale yellow dry residue treated with 10 ml. of water and 2 ml. of 4N potassium hydroxide solution. Twenty milliliters of diethyl ether was then added to dissolve the remaining solid, the layers were separated, and the ether phase was washed with 10 ml. of 1N potassium hydroxide and then with 5 ml. of dilute sodium thiosulfate solution. The ether was boiled from the resulting water-white solution and the solid residue recrystallized 6 times from denatured ethanol: m.p. 111.0-112.0°C., $(\alpha)^{25}D$ +2.2° (α = +0.025°, c = 1.13, butanone). Calculated for $C_{20}H_{28}N_2S_2O_4$: C 56.57, H 6.65, N 6.60, S 15.10. Found (E): C 58.11, H 7.04, N 6.51, S 14.76.

The analysis would seem to indicate contamination with 2,3-bis-(N-ethyl-p-toluenesulfonamido)butane. Nevertheless further treatment with ethyl iodide and potassium hydroxide failed to ethylate the remaining p-toluenesulfonamido group, but led instead to the recovery of starting material. The nonreactivity of the remaining group is probably due to its low acidity: L(+)-threo-3-(N-ethyl-p-toluenesulfonamido)-2-p-toluenesulfonamidobutane is practically insoluble in aqueous strong bases.

L(+)-threo-2,3-Bis-(N-ethyl-p-toluenesulfonamido)butane

To a solution of 0.1 g. (0.004 mole) of sodium metal in 10 ml. of absolute ethanol was added 0.20 g. (0.00050 mole) of L(+)-threo-3-(N-ethyl-p-toluenesulfonamido)-2-p-toluenesulfonamidobutane. The solvent was removed under vacuum and the solid residue dried to a white powder in a vacuum desiccator over sulfuric acid. This powder was added to 12 ml. (23 g., 0.15 mole) of ethyl iodide in a 75-ml. test tube, which was then placed in a stainless steel cylinder,

sealed, and heated at 100°C. (steam bath) for 8 hours. After the mixture had cooled a white solid and yellow liquid remained. The solid was filtered off and washed with 15 ml. of ethyl iodide. It proved to be completely soluble in water (sodium iodide). The ethyl iodide was removed from the filtrate under aspirator vacuum, to leave 0.23 g. (100%) of a yellow solid. Recrystallization from denatured ethanol, after treatment with Norit, gave 0.13 g. (60%) of L(+)-2, 3-bis-(N-ethyl-p-toluenesulfonamido)butane, m.p. 138.4-139.0°C., $(\alpha)^{25}D$ +12.1° (a = +0.55, c = 4.56, butanone).

The Resolution of DL-threo-2, 3-Bis-ethylaminobutane

To a 1-liter flask containing a solution of 24.0 g. (0.0638 mole) of L(-)-dibenzoyltartaric acid in 350 ml. of commercial absolute ethanol was added a solution of 4.55 g. (0.0316 mole) of DL-threo-2, 3-bis-ethylaminobutane in 100 ml. of absolute ethanol. The resulting solution had a rotation of -4.47°. Crystals began to form after 30 minutes. They were left undisturbed for 12 hours, then filtered off and washed with 300 ml. of ethanol to yield 8.0 g. (50% of the total) of white rods*. Calculated for neutral salt ($C_{26}H_{34}N_2O_8$): N 5.57. Calculated for acid salt ($C_{44}H_{48}N_2O_{16}$): N 3.25. Found (E): N 5.43. Cooling the mother liquor and washings at 5°C. over night led to the formation of a further 0.1 g. of

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*It is interesting to note that the neutral salt (acid:base = 1:1) of one enantiomer of the base separated when solutions of L(-)-dibenzoyltartaric acid and DL-threo-2, 3-bis-ethylaminobutane in in a 2:1 molar ratio were mixed. However, when the two reactants were mixed in a 1:1 molar ratio, two different crystalline forms (rods and almost spherical clusters of very small crystals) were evident, and they amounted to practically all of the solid material present.

salt, which was filtered off. Reducing the mother liquor to a volume of 150 ml. and allowing it to stand caused the further formation of an insignificant amount of solid.

The 8.0 g. of salt, with a specific rotation of -89° ($\alpha = -0.39^{\circ}$, $c = 0.44$, water), was recrystallized from 1.3 liter of methanol to yield 6.6 g. of colorless rods, with specific rotation -68° ($\alpha = -0.25^{\circ}$, $c = 0.367$, water). The rotation was unchanged after a second recrystallization, and a work up of the methanolic mother liquor yielded 0.5 g. of crystals with specific rotation -69° ($\alpha = -0.27^{\circ}$, $c = 0.398$, water). All portions with specific rotation $-69^{\circ} \pm 1^{\circ}$ were combined, dissolved in 45 ml. of water, and treated at 0°C. with a solution of 30 g. of potassium hydroxide in 40 ml. of water. An oily layer (1.8 g.) developed which was separated and then combined with 75 ml. of peroxide-free diethyl ether used to extract the aqueous phase in 3 portions. The solution was dried over potassium hydroxide, filtered, and the ether distilled off as the solution was added to a 20-ml. round bottomed flask. Distillation of the pale yellow residue at reduced pressure gave, with no forerun, 1.3 g. (57%) of ammoniacal liquid, B.P. $65.0-65.8^{\circ}/20$ mm., $\eta^{25}D$ 1.4302, d^{25} 0.781, $(\alpha)^{25}D$ $+106.0^{\circ}$ ($\alpha = +82.75$, pure liquid).

The original mother liquor was filtered and stripped to dryness, first at aspirator vacuum on a steam bath, and then at 1 mm. pressure in a desiccator over sulfuric acid. The gummy residue was transformed by the latter treatment into 19.0 g. of dry solid, which was ground to a powder and treated with four 250 ml. portions of sodium-dried diethyl ether to dissolve most of the excess free

acid. This left 14.8 g. of insoluble residue with a specific rotation of -88° (α = -0.41, c = 0.468, water). This was treated at 0°C. with a solution of 40 g. of potassium hydroxide in 100 ml. of water, and the resulting slurry was extracted with four 50 ml. portions of peroxide-free diethyl ether. The combined extracts were dried over potassium hydroxide and then added to 25 ml. of 2M hydrogen chloride in diethyl ether. The white precipitate which formed was allowed to stand for 3 hours and then the solvent was drawn off through a filter stick. Drying in a vacuum desiccator gave 2.8 g. (80%) of white solid, probably dihydrochloride, which was recrystallized twice from methanol, to obtain 1.7 g. of white prisms, with specific rotation -8.1° (α = -0.205°, c = 2.52, water). This was dissolved in 25 ml. of water and treated at 0°C. with 20 g. of potassium hydroxide, leading to the formation of a water-white oil, as well as some suspended potassium chloride. The oil was separated and then combined with 60 ml. of peroxide-free diethyl ether used to extract the aqueous phase. The ether was distilled off during addition to a 20-ml. round bottomed flask, until a water bath temperature of 60°C. was reached. Distillation at reduced pressure then gave 0.7 g. (65%) of a water-white ammoniacal liquid, B.P. 64.9-65.2°C./20 mm., $\eta^{25}D$ 1.4299, d^{25} 0.781, $(\alpha)^{25}D$ -103.7° (α = -80.97, pure liquid), $(\alpha)^{25}D$ -109° (α = -2.80°, c = 2.57, hexane).

L(+)- and D(-)-threo-2,3-Bis-(N-ethylacetamido)butanes

These were prepared in the same manner as the DL-threo isomer. That from L(+)-threo-2,3-bis-ethylaminobutane, after recrystallization from diisopropyl ether, had melting point

71.0-71.7°C., $(\alpha)^{25}D$ + 30° (a = +0.39, c = 1.30, butanone). That from D(-)-threo-2, 3-bis-ethylaminobutane had melting point 72.0-72.7°C., $(\alpha)^{25}D$ -25° (a = -0.36, c = 1.43, butanone).

L(+)- and D(-)-threo-2, 3-Bis-(N-ethyl-p-toluenesulfonamido)butane

These were prepared in good yield exactly as the DL-threo isomer, and were recrystallized from denatured ethanol to give colorless rods with constant melting point. The isomer from L(+)-threo-2, 3-bis-ethylaminobutane had melting point 138.7-139.5°C., $(\alpha)^{25}D$ +13.7° (a = +1.20°, c = 8.75, butanone); mixed melting point with L(+)-threo-2, 3-bis-(N-ethyl-p-toluenesulfonamido)butane (m.p. 138.4-139.0°C), p. 48: 137.7-138.8°C. The isomer from D(-)-threo-2, 3-bis-ethylaminobutane had melting point 138.5-139.5°C., $(\alpha)^{25}D$ -13.3° (a = -1.16°, c = 8.60, butanone); mixed melting point with L(+)-threo-2, 3-bis-(N-ethyl-p-toluenesulfonamido)butane: 126-136°C. Calculated for $C_{22}H_{32}N_2S_2O_4$: C 58.38, H 7.13, N 6.19, S 14.17. Found (E): C 58.49, H 7.12, N 6.19, S 14.13.

D(-)-threo-2, 3-Bis-ethylaminobutane and Zinc Chloride

To a solution of 0.034 g. (0.00024 mole) of D(-)-threo-2, 3-bis-ethylaminobutane in 2.0 ml. of 95% ethanol (a = -1.63°) was added 0.10 ml. of 2.5M zinc chloride (0.00025 mole) in 95% ethanol. The crystals which began to form after a short time were allowed to stand over night. The mother liquor (a = -0.25°) was removed and the crystals were rinsed with two 0.5 ml. portions of 95% ethanol and then dried, to give 0.0426 g. of colorless prisms, $(\alpha)^{25}D$ -71° (a = -0.56°, c = 0.790, N, N-dimethylformamide); they are soluble in N, N-dimethylformamide and dilute nitric acid,

but practically insoluble in water and most organic solvents. Calculated for $ZnC_8H_{20}N_2Cl_2$ ($ZnCl_2$ + one 2, 3-bis-ethylaminobutane): Chloride ion 25.3. Found by method of Swift (14): 26.0.

meso-2, 3-Bis-ethylaminobutane from L(+)-trans-N-Ethyl-2, 3-iminobutane

This was prepared in the same manner as the DL-threo isomer, 12.4 g. (0.125 mole) of L(+)-trans-N-ethyl-2, 3-iminobutane and 225 ml. (ca. 3 moles) of 70% aqueous ethylamine giving 14.7 g. of crude product. Fractionation gave, after a forerun of 2.0 g., 9.2 g. (51%) of meso-2, 3-bis-ethylaminobutane, B.P. 63.8-64.5°C./20 mm., $\alpha^{25}D$ +0.48°, d^{25} 0.806, $\eta^{25}D$ 1.4297.

meso-2, 3-Bis-(N-ethylacetamido)butane

To a cold solution of 0.72 g. (0.0050 mole) of meso-2, 3-bis-ethylaminobutane in 2 ml. of pyridine was added slowly 1.55 g. (0.0150 mole) of acetic anhydride. After standing for 6 hours the container was placed in a vacuum desiccator over sulfuric acid and potassium hydroxide, which was then evacuated to 1 mm. pressure. In 3 days a white solid had formed, 1.1 g. (97%) in weight, which in 7 recrystallizations from diisopropyl ether attained a melting point of 76.5-77.3°C., $\alpha^{25}D$ 0.00 (chloroform). Calculated for $C_{12}H_{24}N_2O_2$: C 63.12, H 10.60, N 12.27. Found (S): C 63.60, H 10.90, N 12.10.

meso-2, 3-Bis-(N-ethyl-p-toluenesulfonamido)butane

This was prepared in the same manner as the DL-threo isomer. The reaction mixture formed a hard cake which was triturated with 6N hydrochloric acid until acidic, then filtered and washed to give after desiccation 100% of white product. Six

recrystallizations from ethylene dichloride were required to attain a constant melting point of 241.8-243.3°C., $\alpha^{25}D$ 0.00. Calculated for $C_{22}H_{32}N_2S_2O_4$: C 58.38, H 7.13, N 6.19, S 14.17. Found (S): C 58.60, H 7.20, N 6.39, S 14.26.

meso-2,3-Butanediamine

A solution of 14.2 g. (0.20 mole) of L(-)-trans-2,3-iminobutane in 350 ml. (5.6 moles) of 15M ammonium hydroxide was sealed in an ampoule (see footnote, p. 34) and heated at 100°C. for 2 weeks. The ammonia was distilled off to a pot temperature of 98°C., the aqueous residue saturated at 0°C. with potassium hydroxide, and the organic layer separated (15.7 g.). It was combined with 40 ml. of diethyl ether used to extract the aqueous phase and dried over potassium hydroxide. The ether was removed through a 40-cm. column of Raschig rings, to a pot temperature of 102°C.; after the addition of 12.5 ml. of diethylene glycol monobutyl ether fractionation was continued at reduced pressure. A yield of 11.7 g. (67%) resulted, B.P. 56.1-60.5°C./60 mm., $\eta^{25}D$ 1.4438. Water was undoubtedly the major contaminant, as judged from the known hygroscopic property of the diamines (1).

DL-threo-2,3-Butanediamine

This was prepared from cis-2,3-iminobutane in exactly the same manner as the meso isomer was prepared from the L-trans-imine. A yield of 12.5 g. (71%) resulted, B.P. 55.3-59.3°C./60 mm., $\eta^{25}D$ 1.4428.

DL-threo-2,3-Di-p-toluenesulfonamidobutane

This was prepared from DL-threo-2,3-butanediamine by

the known procedure (1). After 2 recrystallizations from 2-propanol it had melting point 177.3-178.6°C. Lit.: 179.3-180.7°C. (after 6 recrystallizations).

DL-threo-3-(N-Ethyl-p-toluenesulfonamido)-2-p-toluenesulfonamidobutane from the Preceding

Forty one-hundredths of one gram (0.0010 mole) of DL-threo-2,3-di-p-toluenesulfonamidobutane was dissolved in a solution of 0.50 g. (0.0080 mole) of potassium hydroxide in 10 ml. of 95% ethanol. Five-tenths of one milliliter (0.9 g., 0.006 mole) of ethyl iodide was added and the solution refluxed for 5 hours, at the end of which time a further 0.5 ml. of ethyl iodide was added and refluxing was continued for 4 hours. The solvents were removed at aspirator vacuum and the pale yellow solid residue was partially dissolved in 12 ml. of 1N sodium hydroxide solution. The addition of 30 ml. of benzene dissolved the remainder, the layers were separated, and the organic layer dried over magnesium sulfate. Removal of the benzene under vacuum, followed by crystallization of the residue from ethanol-water gave colorless needles, m.p. 150.2-150.6°C.

DL-threo-2,3-Bis-(N-ethyl-p-toluenesulfonamido)butane from the Preceding

This was prepared exactly as was the L(+)-threo isomer from L(+)-threo-3-(N-ethyl-p-toluenesulfonamido)-2-p-toluenesulfonamidobutane. The product in this case was insoluble in the excess ethyl iodide, and was separated from the sodium iodide by treatment with water and extraction with benzene. The organic layer was dried over magnesium sulfate, evaporated, and the residue recrystallized from denatured ethanol to give a 53% yield of

DL-threo-2, 3-bis-(N-ethyl-p-toluenesulfonamido)butane, m. p. 134. 8-135. 7°C. Mixed melting point with DL-threo-2, 3-bis-(N-ethyl-p-toluenesulfonamido)butane from DL-threo-2, 3-bis-ethylaminobutane (m. p. 135. 8-136. 7°C.), p. 47: 134. 5-135. 6°C.

DL-threo-3-Ethylamino-2-aminobutane

An ampoule (see footnote, p. 34) containing 20 g. (0. 28 mole) of cis-2, 3-iminobutane and 400 ml. (ca. 6 moles) of 70% aqueous ethylamine was sealed and kept at 120° for 3 weeks. The ethylamine was removed by distillation through a 45-cm. column of helices, and the aqueous pot residue saturated with potassium hydroxide at 0°C. The yellow organic layer (18. 2 g.) was separated and augmented by 50 ml. of diethyl ether used to extract the aqueous phase. The solution was dried over potassium hydroxide and the ether removed at atmospheric pressure through an 8-inch column of helices. The addition of 7 ml. of diethylene glycol monobutyl ether and fractionation through the same column at reduced pressure gave, after a forerun amounting to 3 grams, 13. 5 g. (47%) of DL-threo-3-ethylamino-2-aminobutane, B. P. 82. 1-83. 3°C. / 100 mm., $\eta^{25}D$ 1. 4328, d^{25} 0. 816.

DL-threo-3-(N-Ethylacetamido)-2-acetamidobutane

To a cold solution of 1. 16 g. (0. 0100 mole) of DL-threo-3-ethylamino-2-aminobutane in 4 ml. of pyridine was added slowly 3. 06 g. (0. 0300 mole) of acetic anhydride. After standing at room temperature for several hours the reaction mixture was placed in a vacuum desiccator over potassium hydroxide and sulfuric acid,

which was then evacuated to 1 mm. pressure. After several days a light-colored solid formed, which was ground in a mortar and replaced in the desiccator until free of all odor: 1.9 g. (95%). Five recrystallizations from diisopropyl ether gave small white crystals, m.p. 80.4-81.0°C. Calculated for $C_{10}H_{20}N_2O_2$: C 59.97, H 10.07, N 13.99. Found (S): C 60.37, H 10.40, N 13.94.

DL-threo-3-(N-Ethyl-p-toluenesulfonamido)-2-p-toluenesulfonamidobutane

Fifty-eight hundredths of a gram (0.0050 mole) of DL-threo 3-ethylamino-2-aminobutane was treated in the cold with 1.91 g. (0.0100 mole) of p-toluenesulfonyl chloride and 15 ml. of triethylamine. After standing over night the white precipitate which formed was filtered off, washed with 20 ml. of water, and dried, to give 1.8 g. (85%) of white product. Four recrystallizations from denatured ethanol gave colorless needles, m.p. 150.6-151.6°C. Mixed melting point with DL-threo-3-(N-ethyl-p-toluenesulfonamido)-2-p-toluenesulfonamidobutane from the ethylation of DL-threo-2,3-di-p-toluenesulfonamidobutane (m.p. 150.2-150.6°C.) p. 55: 150.5-151.0°C. Calculated for $C_{20}H_{28}N_2S_2O_4$: C 56.57, H 6.65, N 6.60, S 15.10. Found (E): C 56.72, H 6.65, N 6.71, S 15.14.

DL-threo-2,3-Bis-ethylaminobutane from DL-threo-3-Ethylamino-2-aminobutane

A solution of 3.5 g. (0.030 mole) of DL-threo-3-ethylamino-2-aminobutane and 5.0 g. (0.032 mole) of ethyl iodide in 40 ml. of diisopropyl ether developed cloudiness after 20 minutes, to form

an oil which increased in amount for several days, and finally crystallized in part. The ether was removed by decantation and the oil was dried in a desiccator over sulfuric acid at 1 mm. pressure. When the amount of solid did not appreciably increase, it was treated with a solution of 10 g. of potassium hydroxide in 20 ml. of water. The resultant red oil was separated and combined with 50 ml. of diethyl ether used to extract the aqueous phase. Most of the ether was removed on a steam bath, 50 ml. of benzene was added, and the solution was refluxed over Norit for 30 minutes. Filtration by gravity (S and S no. 576) gave a yellow solution which was dried over potassium carbonate.

This solution was added slowly to a cooled excess of 2M hydrogen chloride in diethyl ether. The ether was decanted from the pasty mass formed, which was then dried in a desiccator and recrystallized from methanol after treatment with Norit: white prisms, m.p. 270°C. (dec.)

Treatment of 0.630 g. (0.0029 mole, as dihydrochloride) of this material with 0.900 g. (0.015 mole) of potassium hydroxide in 1 ml. of water led to the formation of a yellow oil, augmented by two 5 ml. portions of diethyl ether used to extract the pasty inorganic phase. After drying over potassium carbonate the ether was boiled off on a water bath to yield 0.460 g. of pale yellow oil.

DL-threo-2,3-Bis-(N-ethyl-p-toluenesulfonamido)butane from the Preceding

After an unsuccessful attempt to prepare this derivative directly from the hydrochloride, 0.460 g. (ca. 0.0029 mole) of

the crude DL-threo-2, 3-bis-ethylaminobutane was dissolved in 2 ml. of triethylamine and treated at 0°C. with 1.14 g. (0.0060 mole) of p-toluenesulfonyl chloride. A thick ivory-colored precipitate formed, along with some heat, when the reaction mixture was allowed to come to room temperature. Cooling was reapplied and a further 3 ml. of triethylamine added. After standing for 5 hours the mixture was warmed to 60°C. and treated with 2 ml. of water, then acidified with dilute hydrochloric acid and stirred to break up the lumps of solid. The white solid was filtered off, washed with water, and dried to give 1.1 g. (85%) of product. Two recrystallizations from denatured ethanol gave colorless plates, m.p. 135.5-136.3°C. Mixed melting point with DL-threo-2, 3-bis-(N-ethyl-p-toluenesulfonamido)-butane (m.p. 135.8-136.7°C.), p. 47: 135.6-136.5°C.

D(-)-erythro-3-Ethylamino-2-aminobutane

An ampoule (see footnote, p. 34) containing 21.3 g. (0.30 mole) of L(-)-trans-2, 3-iminobutane and 500 ml. (ca. 6 moles) of 70% aqueous ethylamine was sealed and heated at 120°C. for 16 days. The ethylamine was removed by distillation through a 45-cm. column of Raschig rings to a pot temperature of 100°C., and the residual aqueous solution saturated with potassium hydroxide. The organic layer (37 g.) which formed was augmented by two 50 ml. portions of diethyl ether used to extract the aqueous phase. The ether was distilled off through an 8-inch column of helices, 10 ml. of diethylene glycol monobutyl ether added, and the product distilled at reduced pressure to yield 23.0 g. (66%) of product,

B.P. 85.1-85.7°C./100 mm., d^{25} 0.823, $\eta^{25}D$ 1.4347, $(\alpha)^{25}D$ -36.7° (α = -30.24°, pure liquid).

D(+)-erythro-3-(N-Ethylacetamido)-2-acetamidobutane

The slow addition of 1.16 g. (0.0100 mole) of D(-)-erythro-3-ethylamino-2-aminobutane to a cold solution of 4.1 g. (0.040 mole) of acetic anhydride in 6 ml. of pyridine led to a red oil. It was allowed to stand for 24 hours, and was then desiccated at 1 mm. pressure over sulfuric acid and soda-lime. After 2 days solidification occurred, and the brown solid was ground in a mortar and redesiccated until odorless: 2.0 g. (100%). Treatment with Norit, followed by 5 recrystallizations from 10% benzene in diisopropyl ether gave colorless prisms, soluble in water and most organic solvents: m.p. 93.6-94.6°C., $(\alpha)^{25}D$ +7.1° (α = +0.24°, c = 3.40, butanone). Calculated for $C_{10}H_{20}N_2O_2$: C 59.97, H 10.07, N 13.99. Found (E): C 60.51, H 10.04, N 14.12.

D(-)-erythro-3-(N-Ethyl-p-toluenesulfonamido)-2-p-toluenesulfonamidobutane

A solution of 0.58 g. (0.0050 mole) of D(-)-erythro-3-ethylamino-2-aminobutane in 15 ml. of triethylamine was treated at 0°C. with 1.91 g. (0.0100 mole) of p-toluenesulfonyl chloride. After 3 days the liquid and gummy solid were treated with 10 ml. of water and then acidified with 6N hydrochloric acid to give, after filtration and drying, 1.67 g. (80%) of white solid. Eight recrystallizations from ethanol-water gave colorless prisms, m.p. 149.9-150.7°C., $(\alpha)^{25}D$ -23.8° (α = -1.19°, c = 5.04, butanone). Calculated for $C_{20}H_{28}N_2S_2O_4$: C 56.57, H 6.65, N 6.60, S 15.10.

Found (E): C 56.50, H 6.69, N 6.95, S 14.77.

L(+)-erythro-3-Ethylamino-2-aminobutane

A solution of 8.7 g. (0.088 mole) of L(+)-trans-N-ethyl-2,3-iminobutane in 170 ml. (2.7 moles) of concentrated ammonium hydroxide was sealed in an ampoule (see footnote, p. 34) and heated at 100°C. for 3 weeks. The ammonia was distilled off to a pot temperature of 99°C., and the residual aqueous solution was saturated with potassium hydroxide. The organic layer (8.7 g.) was removed and combined with 50 ml. of diethyl ether used to extract the aqueous phase. The ether was distilled off through an 8-inch column of helices to a pot temperature of 100°C. Ten milliliters of diethylene glycol monobutyl ether was then added, and the product distilled at reduced pressure. A total of 7.6 g. of water-white ammoniacal liquid, of which 5.2 g. (51%) was a central cut, was collected: B.P. 84.1-85.0°C./100 mm., $\eta^{25}D$ 1.4340, d^{25} 0.823, $(\alpha)^{25}D$ +37.2° (α = +30.58, pure liquid).

L(-)-erythro-3-(N-Ethylacetamido)-2-acetamidobutane

This was prepared in the same manner as the D(+)-erythro isomer. There was obtained after 4 recrystallizations from 10% benzene in diisopropyl ether almost colorless prisms, m.p. 93.9-94.6°C., $(\alpha)^{25}D$ -6.8° (α = -0.20°, c = 2.94, butanone).

L(+)-erythro-3-(N-Ethyl-p-toluenesulfonamido)-2-p-toluenesulfonamidobutane

This was prepared exactly as was the D(-)-erythro isomer, 0.58 g. (0.0050 mole) of L(+)-erythro-3-ethylamino-2-aminobutane giving 2.05 g. (97%) of solid derivative. Five recrystallizations from ethanol-water gave colorless prisms, m.p. 148.0-148.8°C.,

$(\alpha)^{25}D + 21.3^{\circ}$ ($\alpha = +0.64^{\circ}$, c = 2.99, butanone).

meso-2, 3-Bis-ethylaminobutane from D(-)-erythro-3-Ethylamino-2-aminobutane

This was prepared in the same manner as the DL-threo isomer was prepared from DL-threo-3-ethylamino-2-aminobutane, except that the hydrochloride was not purified, but simply treated with excess potassium hydroxide. Five and eight-tenths grams (0.050 mole) of D(-)-erythro-3-ethylamino-2-aminobutane gave 2.9 g. (40%) of meso-2, 3-bis-ethylaminobutane, B.P. 64.5-66.0°C./20 mm.

meso-2, 3-Bis-(N-ethyl-p-toluenesulfonamido)butane from the Preceding

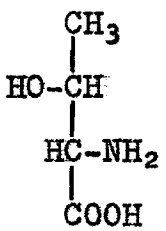
This was prepared by the method previously used, 0.72 g. (0.0050 mole) of amine yielding 2.05 g. (91%) of derivative. Two recrystallizations from ethylene dichloride, after treatment with Norit, gave colorless needles, m.p. 240.3-241.8°C. Mixed melting point with meso-2, 3-bis-(N-ethyl-p-toluenesulfonamido)butane (m.p. 241.8-243.3°C.), p. 53: 240.6-242.0°C.

II

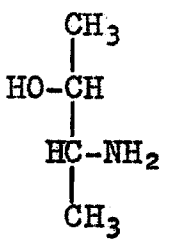
THE ATTEMPTED REDUCTION OF NATURALLY OCCURRING THREONINE TO 3-AMINO-2-BUTANOL

INTRODUCTION

The configuration of the essential amino acid L-threonine (D-threo-2-amino-3-hydroxybutanoic acid) has been established as threo by X-ray diffraction methods (15), and as L- at the 2-position by its reduction to L-2-aminobutanoic acid (16). A direct connection between naturally occurring threonine and one of the threo-3-amino-2-butanols, whose configurations are known with near certainty (1), would be satisfying.



L-Threonine



D-threo-
3-Amino-2-butanol

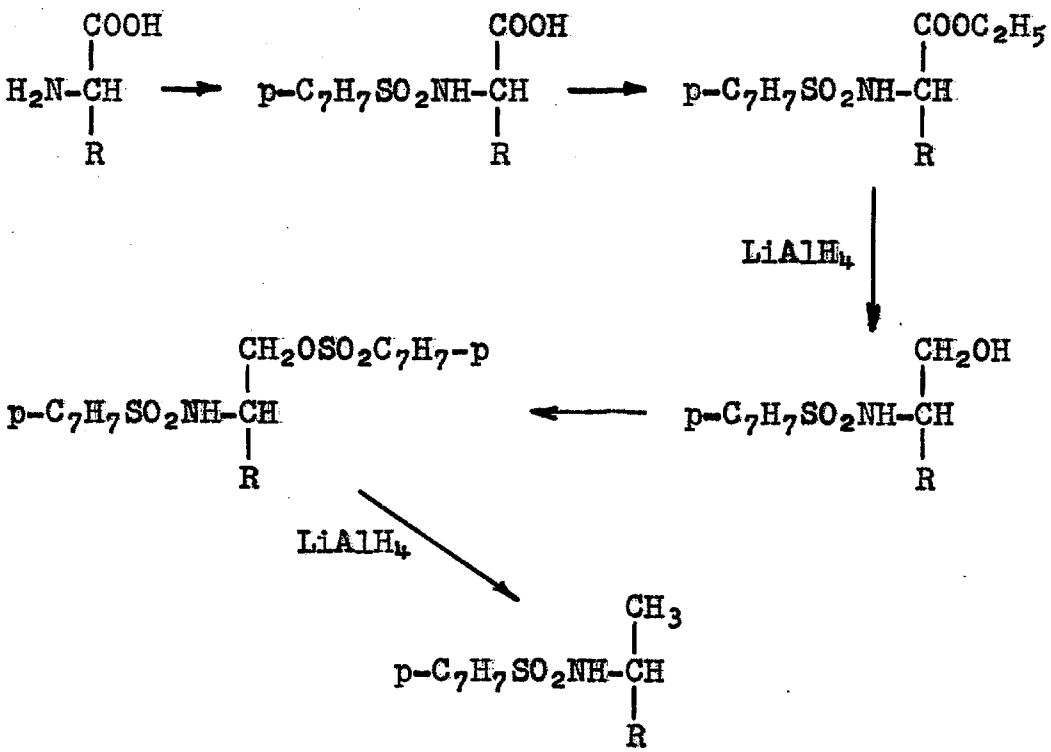
The problem in essence involves the reduction of a carboxyl group to a methyl group, and at first it was thought that a scheme of reactions involving the aldehyde as an intermediate could be used to effect this:

$$RCOOH \longrightarrow RCOCl \longrightarrow RCHO \longrightarrow RCH(SR')_2 \longrightarrow RCH_3$$

Some preliminary experiments along this line with phenylalanine were in fact carried out, but experience with and reflection upon the difficulties of preparing acid chlorides and aldehydes with two proximate functional groups caused the abandonment of this approach.

Attention then turned to the method utilized by Karrer and

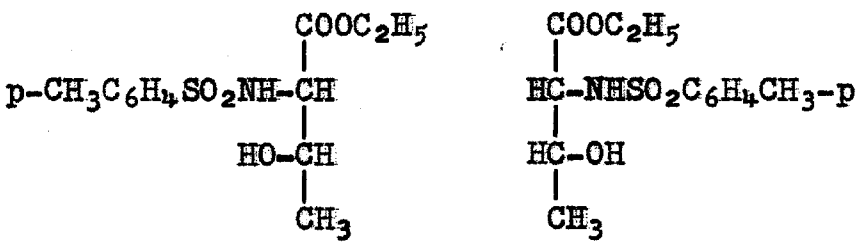
coworkers (17, 18) for the complete reduction of the carboxyl groups of other amino acids:



In order to be applied to a hydroxy amino acid, this procedure required modifications, so that the hydroxyl group on the 3- position would be unaffected by the treatment used to reduce the one derived from the carboxyl group. In the case of threonine this evidently had to be done by taking advantage of differences in the reactivity of the primary and secondary alcohol functions, a fact which necessitated that preliminary investigations involve a compound with the appropriate functional groups; DL-threonine was the most convenient substance available.

At first a commercial mixture of DL-threonine and DL-allothreonine was employed, to yield by p-toluenesulfonylation

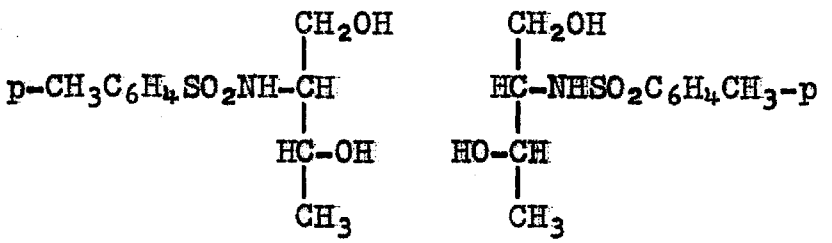
under Schotten-Baumann conditions (19), followed by esterification, an ethyl ester of N-p-toluenesulfonylthreonine; this later turned out to be, by a process of elimination, the derivative from DL-allothreonine, i.e., the erythro isomer.



N-p-Toluenesulfonyl-
DL-allothreonine
Ethyl Ester

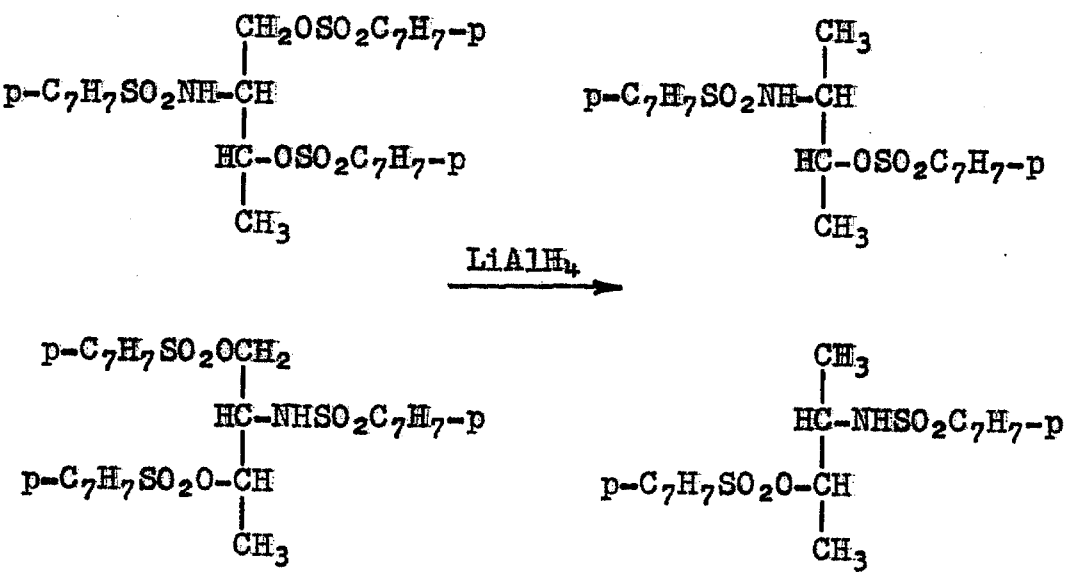
No crystalline product was isolable from the reduction of this compound with lithium aluminum hydride. In fact the isolation of pure N-p-toluenesulfonyl-DL-allothreonine ethyl ester was apparently a fortunate accident, as in subsequent preparations the product could not be freed of the DL-threo isomer.

It was then decided to synthesize pure DL-threonine, and this was done, according to the method of Pfister (20). Treatment of DL-threonine with p-toluenesulfonyl chloride, esterification, and reduction with lithium aluminum hydride by the method of Karrer (17, 18) gave DL-threo-2-p-toluenesulfonamido-1,3-butanediol as a brown oil which after several months solidified. An attempt to p-toluenesulfonylate exclusively the



DL-threo-
p-Toluenesulfonamido-
1,3-butanediol

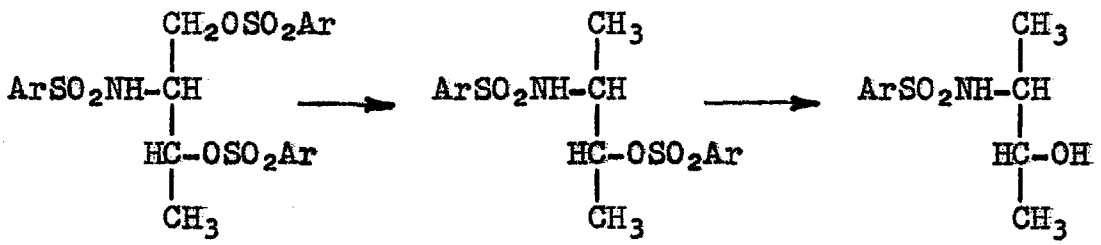
primary hydroxyl group of this compound failed, and it was decided to try to make the final reduction into the structurally specific step, by preparing DL-threo-2-p-toluenesulfonamido-1,3-di-p-toluenesulfonoxybutane and treating it with lithium aluminum hydride:



DL-threo-
2-p-Toluenesulfonamido-
1,3-di-p-toluene-
sulfonoxybutane

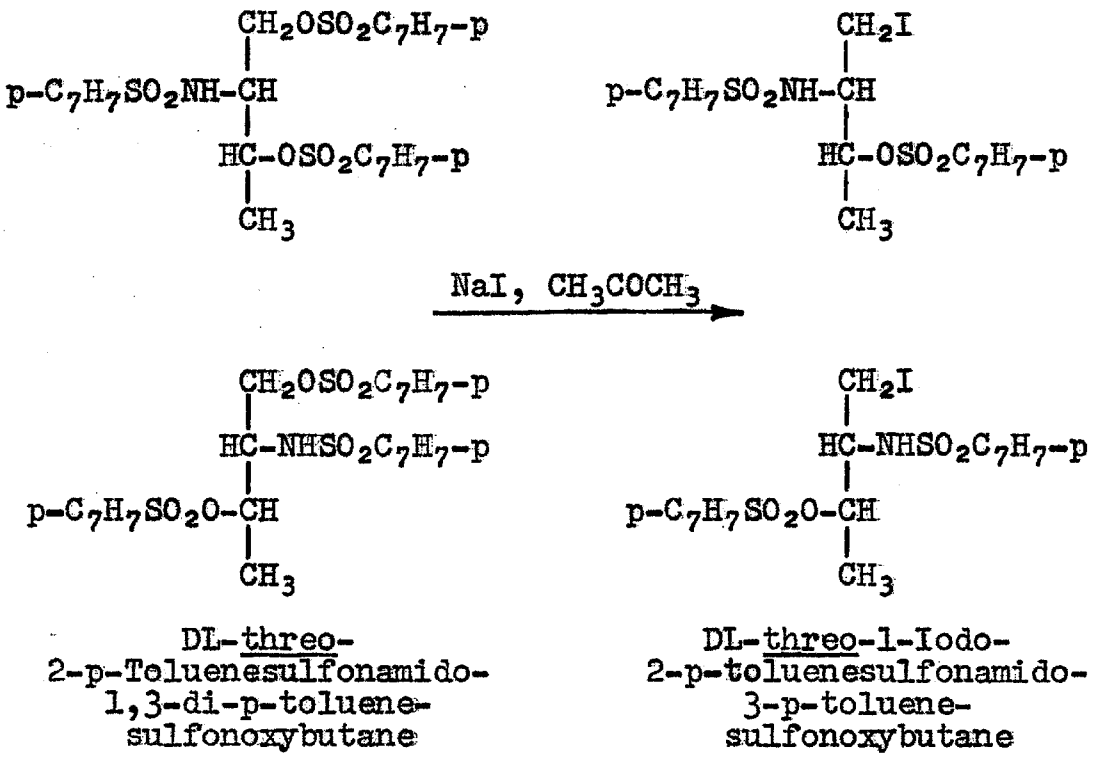
DL-threo-
3-p-Toluenesulfonamido-
2-p-toluene-
sulfonoxybutane

Lithium aluminum hydride has been found by workers with carbohydrates (21) to reduce primary arylsulfonates specifically, with the secondary groups being unaffected, or at worst, hydrolyzed to the alcohol:



Despite several attempts employing different reaction conditions, no solid product was obtained from this procedure, either before or after treatment with p-toluenesulfonyl chloride to re-esterify any free hydroxyl groups formed. Since the oils produced underwent no change when seeded with DL-threo-3-p-toluenesulfonamido-2-p-toluenesulfonoxybutane, it was evident that the reaction did not proceed in the expected manner.

Another reaction which is generally specific for primary groups as opposed to secondary is the reaction of sodium iodide in acetone with arylsulfonate esters (22). Since the tri-p-toluenesulfonyl derivative had already been prepared for use in the foregoing experiments, its reaction with sodium iodide in acetone was investigated:

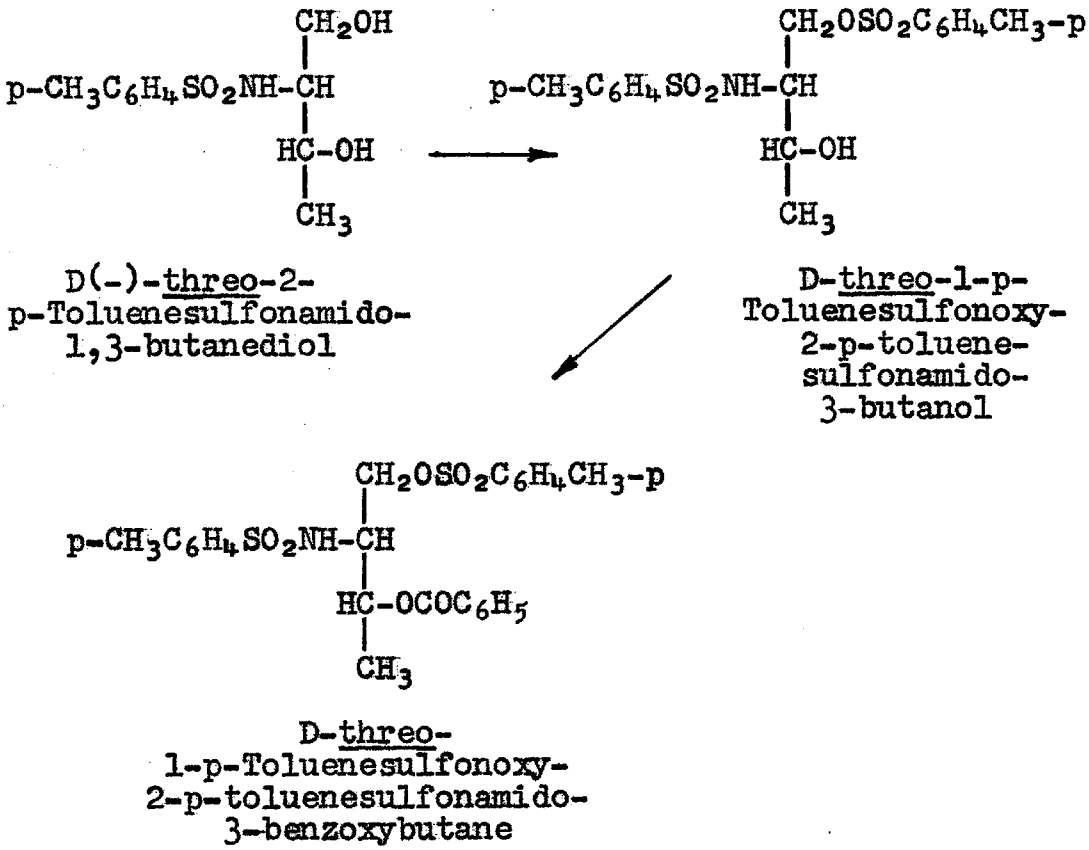


DL-threo-2-p-Toluenesulfonamido-1,3-di-p-toluenesulfonoxybutane

DL-threo-1-Iodo-2-p-toluenesulfonamido-3-p-toluenesulfonoxybutane

A glassy solid resulted, which upon hydrogenation over Raney nickel in weakly alkaline solution gave an uncrystallizable oil.

Simultaneously with these last experiments D(-)-threo-2-p-toluenesulfonamido-1,3-butanediol was prepared from natural L- threonine by the same series of reactions used with the DL- isomers. Once again the attempts to mono-p-toluenesulfonylate this compound failed to give a crystalline product, so the experiments were repeated and concluded by treatment of the reaction mixture with benzoyl chloride, hoping in this manner to increase the molecular weight sufficiently to obtain a crystalline product.



A solid was obtained in only one case, and it proved to be D(-)-threo-2-p-toluenesulfonamido-1,3-dibenzoxybutane. The completely p-toluenesulfonylated derivative, D-threo-2-p-toluenesulfonamido-1,3-toluenesulfonoxybutane was then prepared, and treated with sodium iodide in acetone. As in the case of the DL-isomer, a glassy solid was obtained.

All of the experiments with sodium iodide gave evidence which seems to indicate that a reaction occurred. On this basis and without evidence to the contrary, it is probable that reaction proceeded in the expected manner, but that time-consuming purifications are required. Unfortunately the necessary time was not available.

EXPERIMENTAL

Chloroform was freed of alcohol by being shaken 3 times with concentrated sulfuric acid, then with water, and finally was dried over powdered anhydrous calcium chloride.

Pyridine was dried by refluxing over potassium hydroxide and then fractionated, the forerun being discarded. It was stored over potassium hydroxide or barium oxide.

Tetrahydrofuran was dried by refluxing over sodium and then distilled from sodium. A final drying with lithium aluminum hydride (to the end of effervescence) was performed just before use.

Impure DL-threonine was 'DL-Threonine, with Allothreonine', a product of the Dow Chemical Company.

DL-Threonine hemihydrate was prepared in 30% overall yield according to the method of Pfister and coworkers (20). Its melting point was 230-231°C. (lit.: 229-230°C.).

L(+)-Threonine was obtained from the California Foundation for Biochemical Research. Its specific rotation was stated to be +28.1° (c = 2, water).

p-Toluenesulfonyl chloride was Eastman White Label material, recrystallized from hexane.

N-p-Toluenesulfonyl-DL-phenylalanine was prepared by the method of McChesney and Swann (19) from DL-phenylalanine prepared in the undergraduate laboratory course. Its melting point was 133-134°C. (lit.: 134-135°C.).

All melting points are corrected. Microanalyses are by A. Elek.

N-p-Toluenesulfonyl-DL-phenylalanine Ethyl Ester (Ethyl DL-2-p-Toluenesulfonamido-3-phenylpropanoate)

A solution of 15.0 g. (0.043 mole) of N-p-toluenesulfonyl-DL-phenylalanine in 200 ml. of absolute ethanol was saturated with dry hydrogen chloride at room temperature. It was heated to 50°C. for a short time, and then allowed to stand at room temperature for 3 days, during which time crystallization occurred. The volume was reduced to 60 ml. under aspirator vacuum and the solid filtered off and dried. Recrystallization from 95% ethanol gave 12 g. (74%) of colorless needles, m.p. 117-118°C. Calculated for $C_{18}H_{21}NSO_4$: C 62.23, H 6.09, N 4.03. Found: C 62.28, H 6.14, N 4.02.

Impure N-p-Toluenesulfonyl-DL-allothreonine (3-Hydroxy-2-p-toluenesulfonamidobutanoic Acid)

Twelve grams (0.10 mole) of commercial impure threonine was dissolved in a solution of 8.3 g. (0.21 mole) of sodium hydroxide in 25 ml. of water. This was shaken mechanically for 4 hours with a solution of 20 g. (0.105 mole) of p-toluenesulfonyl chloride in 60 ml. of diethyl ether. The layers were separated and the aqueous phase acidified to congo red with dilute hydrochloric acid. When the solution was allowed to stand over night 15.4 g. (56%) of white solid precipitated. Melting point after one recrystallization from water: 185-189°C.; lit. (23): melting point of DL-threo isomer, 180°C., of DL-erythro isomer (from DL-allothreonine), 198-199°C.

N-p-Toluenesulfonyl-DL-allothreonine Ethyl Ester (Ethyl DL-erythro-3-Hydroxy-2-p-toluenesulfonamidobutanoate)

A solution of 8.3 g. (0.030 mole) of impure N-p-toluenesulfonyl-DL-allothreonine in 120 ml. of absolute ethanol was saturated with gaseous hydrogen chloride at room temperature. The solvent was removed under aspirator vacuum on a steam bath, and the resulting solid recrystallized from dry diisopropyl ether to give 8.4 g. (92%) of product. Three recrystallizations gave a pure product as short needles, m.p. 70.3-71.0°C. Mixed melting point with N-p-toluenesulfonyl-DL-threonine ethyl ester (m.p. 83.6-84.6°C.): 70-74°C. (softens 64°C.). Calculated for $C_{13}H_{19}NSO_5$: C 51.81, H 6.35, N 4.65, S 10.64. Found: C 51.90, H 6.28, N 4.68, S 10.51.

N-p-Toluenesulfonyl-DL-threonine (DL-threo-3-Hydroxy-2-p-toluenesulfonamidobutanoic Acid)

A solution of 6.4 g. (0.050 mole) of DL-threonine hemihydrate in 50 ml. of 2.5M sodium hydroxide solution was shaken mechanically for 6 hours with a solution of 10.5 g. (0.055 mole) of p-toluenesulfonyl chloride in 85 ml. of diethyl ether. The layers were separated and the aqueous layer acidified to pH 2 with 6N hydrochloric acid. The resulting precipitate was filtered, washed and dried to give 10.4 g. (74%) of product.

N-p-Toluenesulfonyl-DL-threonine Ethyl Ester (Ethyl DL-threo 3-Hydroxy-2-p-toluenesulfonamidobutanoate)

A solution of 6.0 g. (0.022 mole) of N-p-toluenesulfonyl-DL-threonine in 100 ml. of absolute ethanol was saturated with gaseous hydrogen chloride at 0°C. After the solution had stood for 2 days at room temperature the ethanol, water, and hydrogen

chloride were removed under aspirator vacuum at 60°C. The residue solidified upon cooling and was evacuated in a desiccator over potassium hydroxide. Three recrystallizations from dry diisopropyl ether gave 4.1 g. (62%) of colorless needles, m.p. 83.6-84.6°C. An additional 0.9 g. (14%) was obtained from the mother liquors. Calculated for $C_{13}H_{19}NSO_5$: C 51.81, H 6.35, N 4.65, S 10.64. Found: C 52.23, H 6.30, N 4.80, S 10.63.

DL-threo-2-p-Toluenesulfonamido-1,3-butanediol

To a slurry-solution of 9.5 g. (0.25 mole) of lithium aluminum hydride in 150 ml. of dry tetrahydrofuran was added with stirring a solution of 7.2 g. (0.024 mole) of N-p-toluenesulfonyl-DL-threonine ethyl ester in 50 ml. of dry tetrahydrofuran. The temperature was kept near 25°C. during the addition and then the reaction mixture was refluxed for 24 hours. About two-thirds of the solvent was removed by distillation, and then 75 ml. of ethyl acetate was added slowly, followed by 150 ml. of 6N hydrochloric acid. The two-phase system was allowed to stand over night, and then was filtered by gravity (Whatman no. 1). The aqueous phase after separation was extracted with two 100 ml. portions of ethyl acetate. The combined extracts were dried over sodium sulfate, filtered, and then most of the solvent was removed under aspirator vacuum at 60°C. To the resulting 50 ml. of solution was added slowly 200 ml. of hexane, along with some seed crystals*. The

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*These were obtained from a preliminary experiment performed in much the same manner, except that the combined extracts were freed of as much solvent as possible, to give a brown oil which after several months desiccation and refrigeration solidified at room temperature.

resulting 4.0 g. (64%) of crystalline solid was washed with hexane and recrystallized from ethyl acetate several times to give white prisms, m.p. 122.5-123.5°C. Calculated for $C_{11}H_{17}NSO_4$: C 50.94, H 6.61, N 5.40, S 12.37. Found: C 50.38, H 6.84, N 5.54, S 12.59.

DL-threo-2-p-Toluenesulfonamido-1,3-di-p-toluenesulfonoxybutane

To a cooled solution of 0.52 g. (0.0020 mole) of DL-threo-2-p-toluenesulfonamido-1,3-butanediol in 0.9 ml. of pyridine was added in 10 portions 0.80 g. (0.0042 mole) of p-toluenesulfonyl chloride. Precipitation began within 15 minutes, and the reaction mixture, after standing over night, was treated with 2 ml. of water and then acidified with 6N hydrochloric acid. The resultant solid, after being filtered and dried, weighed 1.05 g. (93%). Its melting point after several recrystallizations from benzene was 137.1-137.6°C. Calculated for $C_{25}H_{29}NS_3O_8$: C 52.89, H 5.15, N 2.47, S 16.95. Found: C 55.39, H 5.25, N 2.41, S 15.34. The analysis would seem to indicate benzene of crystallization.

The Attempted Reduction of DL-threo-2-p-Toluenesulfonamido-1,3-di-p-toluenesulfonoxybutane with Lithium Aluminum Hydride

These attempted reductions were all run in refluxing tetrahydrofuran, followed by destruction of the excess reagent with ethyl acetate and extraction of the product. The results are tabulated.

Molar Ratio $LiAlH_4$ to Tritosylate	Time	Result
0.5 to 1	(THEORETICAL)	
0.7 to 1	9 hrs.	Starting material
1.25 to 1	8 hrs.	Oil
5 to 1	1 hr.	Oil
12 to 1	6 hrs.	Oil, after treatment with p-toluenesulfonyl chloride

The Reaction of DL-threo-2-p-Toluenesulfonamido-1, 3-di-p-toluenesulfonoxybutane with Sodium Iodide

An acetone solution containing 0.412 g. (0.00073 mole) of DL-threo-2-p-toluenesulfonamido-1, 3-di-p-toluenesulfonoxybutane and 0.115 g. (0.00077 mole) of sodium iodide in 30 ml. was refluxed for 24 hours. The precipitated sodium p-toluenesulfonate was filtered off (0.12 g., 80-90%) and the filtrate was stripped of acetone under aspirator vacuum, to give a mixture of solid and oil. This was extracted with dry diethyl ether, which left the solid undissolved. (The tritosylate was found to be practically insoluble in ether.) The ether was boiled from the extract and the residue desiccated at 1 mm. pressure over sulfuric acid and potassium hydroxide. A puffed-up biscuit of dry yellow solid resulted.

This was dissolved in dilute ethanolic sodium acetate and hydrogenated over Raney nickel for 45 minutes (36 p.s.i.). The mixture was filtered, the catalyst rinsed with ethanol, and the filtrate stripped of solvent under aspirator vacuum. The residue was extracted with benzene and the extracts freed of color by being shaken with sodium thiosulfate solution, then dried over magnesium sulfate and evaporated. None of the expected DL-threo-3-p-toluenesulfonamido-2-p-toluenesulfonoxybutane could be isolated from the resulting oil, although the latter gave a negative test for halogen after sodium fusion.

N-p-Toluenesulfonyl-L-threonine (D(+)-threo-3-Hydroxy-2-p-toluenesulfonamidobutanoic Acid)

This was prepared exactly as was the DL- isomer, 5.0 g. (0.042 mole) of L(+)-threonine yielding 7.7 g. (67%) of N-p-toluenesulfonyl-L(+)-threonine, m.p. 135-136°C., $(\alpha)^{25}D$ +10.9°

(α = +0.51, c = 4.69, butanone). Lit. (24): m.p. 136-137°C.

N-p-Toluenesulfonyl-L(+)-threonine Ethyl Ester (Ethyl D(+)-threo-3-Hydroxy-2-p-toluenesulfonamidobutanoate)

This was prepared exactly as was the DL- isomer, to give after recrystallization from dry diisopropyl ether an 80% yield of colorless needles. The melting point after 2 more recrystallizations was 107.5-108.1°C. $(\alpha)^{25}D$ -10.6° (α = -1.22°, c = 11.6, butanone). Calculated for $C_{13}H_{19}NSO_5$: C 51.81, H 6.35, N 4.65, S 10.64. Found: C 51.98, H 6.50, N 4.89, S 9.75.

D(-)-threo-2-p-Toluenesulfonamido-1,3-butanediol

This was prepared in the same manner as was the DL-threo isomer, 6.3 g. (0.0209 mole) of N-p-toluenesulfonyl-L(+)-threonine ethyl ester being reduced with 8.3 g. (0.22 mole) of lithium aluminum hydride to give 5.2 g. (96%) of brown oil, which required several weeks to solidify partially, and which was very difficult to purify. Eight recrystallizations from ethyl acetate after treatment with Norit were required to raise the melting point over 30 degrees to 97.5-98.3°C. $(\alpha)^{25}D$ -17° (α = -0.25°, c = 1.48, butanone). Calculated for $C_{11}H_{17}NSO_4$: C 50.94, H 6.61, N 5.40, S 12.37. Found: C 50.77, H 6.69, N 5.36, S 11.82.

It was later found that a convenient method of purifying the crude material was to form the potassium salt, which is sparingly soluble in 4N potassium hydroxide, and then to filter it and redissolve it in pure water. Acidification of the solution was followed by extraction with chloroform, in which the free compound is quite soluble. Evaporation of this extract then led to the solid product (60-75%) in condition suitable for final purification by recrystallization.

Attempted Mono-p-toluenesulfonylation of D(-)-threo-2-p-Toluenesulfonamido-1, 3-butanediol

This was attempted in pyridine or triethylamine, excesses of from 1 to 15% of p-toluenesulfonyl chloride being employed. The latter reagent was added either as a solid or as a chloroform solution. Some experiments were run at 0°C., some at room temperature, and still others at 50°C. In most cases the reaction solution was divided into 2 portions, one of which was then worked up with water and hydrochloric acid while the other was treated with excess benzoyl chloride, allowed to stand for several hours, and then worked up in similar manner. On the one occasion when a solid was obtained it proved to be D(-)-threo-2-p-toluenesulfonamido-1, 3-dibenzoxybutane, colorless needles from ethanol, m. p. 160.4-160.9°C., $(\alpha)^{25}D$ -41° (α = -0.16°, c = 0.39, butanone). Calculated for $C_{25}H_{25}NSO_6$: C 64.22, H 5.39, N 3.00, S 6.86. Found: C 64.21, H 5.41, N 3.02, S 6.37.

D-threo-2-p-Toluenesulfonamido-1, 3-di-p-toluenesulfonoxybutane

Application of the method employed for the DL-threo isomer to the preparation of this compound from D(-)-threo-2-p-toluenesulfonamido-1, 3-butanediol led to the isolation of a quantitative yield of crude product upon acidification of the reaction mixture. The material proved very soluble in most organic solvents, however, and had to be recrystallized from chloroform-carbon tetrachloride. Due to poor recovery and ease of oil formation this was not a very satisfactory system. The white solid had melting point 107.5-109°C. after one recrystallization.

The Reaction of D-threo-2-p-Toluenesulfonamido-1, 3-di-p-toluenesulfonoxybutane with Sodium Iodide

A solution of 0.351 g. (0.00062 mole) of D-threo-2-p-toluenesulfonamido-1, 3-di-p-toluenesulfonoxybutane and 0.103 g. (0.00069 mole) of sodium iodide in 15 ml. of acetone was refluxed for 3 hours. The sodium p-toluenesulfonate, which had begun to precipitate even before heat was applied, was removed, and it was observed that continued refluxing had no further effect. The acetone was boiled off on a steam bath and the residue extracted with benzene, leaving behind salts which were dissolved in water and extracted with benzene. The combined benzene extracts were treated with dilute sodium thiosulfate solution to remove the pink color, dried over magnesium sulfate and the solvent removed under aspirator vacuum. Two days over sulfuric acid, potassium hydroxide, and paraffin chips at 1 mm. pressure gave a biscuit of powdery solid, along with some sticky varnish-like material.

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PROPOSITIONS

1. Weizmann and coworkers (1) investigated the reaction of chloretone (2-trichloromethyl-2-propanol) with alkoxides to give 2-alkoxy-2-methylpropanoic acids. A mechanism was suggested, but a second possibility, though discounted, was not disproved.

It is proposed that studies be undertaken using an optically active isomer of 2-trichloromethyl-2-butanol to determine which mechanism is the correct one.

2. The catalytic hydrogenation of ethyl α-acetamido-acetoacetate to ethyl α-acetamido-β-hydroxybutyrate gives this product in nearly quantitative yield (2). However, the isomer corresponding to DL-allothreonine predominates to the extent of 80-85% of the total.

It is proposed that the reaction involves cis addition of hydrogen to the enolic double bond of ring structures resulting from hydrogen bonding between the oxygen and nitrogen atoms of the substrate or its anion.

3. A cyclic transition state (6-membered ring) is proposed for the addition reaction of phenylacetaldehyde to α,β-unsaturated carbonyl compounds (3).

4. It is proposed that the journal Chemical and Engineering News be relegated to the status of a trade journal, and that a new official organ for the American Chemical Society be published.

5. It is proposed that the general term 'alkylimino-' (methylimino-, ethylimino-, etc.) be accepted for the group R-N= , whether it be doubly bonded to a single atom (as in a Schiff base) or to a pair of atoms on a chain (thereby forming a heterocycle).

6. It is proposed that all normal reactions involving the opening of an ethyleneimine ring by a nucleophile (see this thesis, part I) involve attack upon an ethyleneimmonium ion, and that this explains the catalysis of such reactions by substances able to quaternize the ring nitrogen, i.e. Lewis acids.

7. It is proposed that the reaction of ethyleneimine compounds and ammonia or amines in the presence of chloride ion (4, 5) may occur via two steps: first, ring opening by the chloride ion (6), and second, displacement of chlorine by the ammonia or amine.

It is further proposed that a study of this reaction be made, using L(-)-trans-2, 3-iminobutane and aqueous ammonia in one case, anhydrous ammonia and ammonium chloride in the second. The proposed reaction should make its presence known by a greater dextrorotation of the product of the reaction involving chloride ion.

8. It is proposed that N-p-toluenesulfonyl-cis-2, 3-iminobutane and N-p-toluenesulfonyl-L-trans-2, 3-iminobutane (see this thesis, pp. 10, 11) be studied crystallographically, and it is further proposed that the former may show preference for an arrangement in the crystal which involves only

one of the two possible configurations at the nitrogen atom.

9. It has been reported (7) that acetaldehyde and ethyl chloroacetate undergo a glycidic ester condensation, although the yield was not stated. Contradictions have appeared in the literature concerning the mode of attack upon simple aliphatic glycidic esters by amines (8).

It is proposed that under conditions favoring S_N2 reactions nucleophilic attack by amines will be at the 2- position of ethyl 2, 3-epoxybutanoate, and that this constitutes a promising path to the preparation of pure DL-threonine and DL-allothreonine and some of their simple derivatives.

10. It has been found (9) that no ring opening occurs when the simple 2, 3-iminobutanes are treated with lithium aluminum hydride.

It is proposed that this is due to the formation of the anion by extraction of the proton from the nitrogen by hydride or aluminohydride ion. The anion is then not only unattractive to the nucleophiles present, but slightly less strained than the imine itself.

It is further proposed that if the N-ethyl-2, 3-iminobutanes be treated with lithium aluminum hydride they will undergo ring opening as do the epoxides, and give a direct path to the stereochemically pure N-alkyl-2-aminobutanes.

11. Nitrosyl chloride has been demonstrated to add to some representative alkenes (10, 11).

It is proposed that these nitroso chloro compounds will form ethyleneimines upon reduction in strongly basic media, and that this will constitute the most direct manner of obtaining imines from the corresponding alkenes.

12. A new method, primarily applicable to automatic titrimeters, is proposed for the estimation of the end point of potentiometric titrations. It involves the determination of titers corresponding to a series of potential values of uniform separation. The density of these titer values increases near the inflection point, and describes a continuous distribution which proves to be the first derivative of the original plot. The mode of this distribution is the best estimator for the end point titer, but in the more special case of a potential curve with an axis of symmetry through the inflection point (e.g. the titration of strong base with strong acid), the mean of the distribution is identical with the mode. The reliability of this estimator improves as the increment of potential difference between readings is decreased, and if readings distant from the end point are discarded. The latter operation also increases the applicability to less symmetric plots.

13. The methods used to collect all the combined oxygen of mineral samples into some form suitable for isotopic analysis have involved replacement by fluorine (12, 13) or reduction with graphite to form carbon monoxide (14). The former requires use of fluorine, while the latter is not universally applicable.

It is proposed that high temperature treatment with magnesium holds promise since magnesium is able to reduce silica and transition metal oxides; only group I and II oxides remaining. The reaction with carbon tetrachloride to form carbon monoxide and the metal chlorides could then be used (15).

14. The most specific reagents for the precipitation of zirconium are mandelic acid and some of its substituted derivatives (16). However, the method gives generally poor quantitative results when the precipitate is dried and weighed, necessitating ignition to ZrO_2. It is proposed that some easily reducible derivatives, such as p,p'-azomandelic acid be investigated as precipitating agents, since they can be determined volumetrically (17).

15. Optically active adsorbents have occasionally been used for the resolution of racemic compounds (18). Optically active developers have also been mentioned (19). It is proposed that the two treatments be combined into one method, since theoretically, if the enantiomorph which is less adsorbed is more soluble in the available form of the developer, the separation will be improved. The ethers and esters of active amyl alcohol and l-menthol, as well as the alcohols themselves, would constitute a useful set of solvents.

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