δ-Carbethoxyvaleroyl Chloride (VI).—Monethyl adipate obtained from Eastman Distillation Products was treated with excess thionyl chloride as described previously[18] to give on distillation a 91% yield of δ-carbethoxyvaleroyl chloride, b.p. 128–130° at 17 mm.

Acylation of Sodio Acetophenone with Acid Chloride VI to Form β-Diketone-ester VII.—A suspension of 0.30 mole of sodio acetophenone in 600 ml. of ether (essentially free from ammonia) was prepared as described above and cooled to −40°. To the stirred suspension was added 19.27 g. (0.10 mole) of δ-carbethoxyvaleroyl chloride (VI) in 50 ml. of dry ether and the reaction allowed to proceed for 1 hr.[19] at −30 to −40°. The reaction mixture was acidified and worked up as described above (see IV) to give on fractionation, 21.9 g. of recovered acetophenone, b.p. 106–107° at 39 mm., and 17.67 g. (64%) of 1-phenyl-7-carbethoxy-1,3-heptanedione (VII), b.p. 197–198° at 2.3 mm., $n^{25}D$ 1.5471. The product crystallized slowly to give a white solid, m.p. 34.5°.

Anal. Calcd. for $C_{16}H_{20}O_4$: C, 69.54; H, 7.30. Found: C, 69.68; H, 7.21.

This product was further identified by a positive red enol test with ferric chloride, by the formations of a gray copper chelate, m.p. 76.5–77°, and a yellow pyrimidol, m.p. 148.5–149°.[17]

A sample (0.04 mole) of VII was stirred and refluxed for 27 hr. with 0.08 mole of sodium ethoxide in 150 ml. of dry ether. The reaction mixture was acidified, washed with bicarbonate solution and dried. After removal of the ether, the viscous liquid residue gave a positive red enol test and a green copper chelate (stable up to 340°). The product was not identified.

(18) D. Papa, E. Schwenk and H. Hankin, THIS JOURNAL, **69**, 3021 (1947).

(19) Reaction times of 5 and 15 minutes gave yields of only 39 and 41% of VII, respectively.

Acylation of Sodio Cyclohexanone with Acid Chloride VI to Form β-Diketone-ester VIII.—A suspension of 0.60 mole of sodio cyclohexanone in 1.2 liters of ether was prepared essentially as described above (see IV) and cooled to −40°. To the stirred suspension was added 38.54 g. (0.20 mole) of δ-carbethoxyvaleroyl chloride (VI) in 100 ml. of dry ether and the reaction allowed to proceed for 30 minutes[7] at −30 to −40°. The reaction mixture was then acidified and worked up as described above (see IV). There was obtained 33.5 g. of recovered cyclohexanone, b.p. 74° at 53 mm., and 16.10 g. (32%) of 2-(δ-carbethoxyvaleroyl)-cyclohexanone (VIII), b.p. 152–154° at 0.7 mm., $n^{25}D$ 1.4906.

Anal. Calcd. for $C_{12}H_{18}O_4$: C, 66.11; H, 8.72. Found: C, 65.78; H, 8.78.

This product was further identified by a positive red enol test with ferric chloride and by the formation of a gray copper chelate, m.p. 107.5–108°.

Anal. Calcd. for $CuC_{28}H_{42}O_8$: Cu, 11.14; C, 58.98; H, 7.43. Found: Cu, 11.19; C, 59.30; H, 7.33.

Alkaline Cleavage of β-Diketone-ester VIII to Form Ketone Dicarboxylic Acid IX.—A mixture of 10.18 g. (0.040 mole) of 2-(δ-carbethoxyvaleroyl)-cyclohexanone (VIII) and 73 ml. (0.088 mole, 2 equivalents plus 10%) of 5% aqueous sodium hydroxide was refluxed for 2 hr. After cooling in an ice-bath, the alkaline reaction was extracted with ether. The aqueous alkaline layer was boiled for a short time in order to remove the dissolved ether and after cooling, the solution was acidified with 6 *M* hydrochloric acid. The precipitate was collected and washed several times with water. After recrystallization from chloroform and petroleum ether, 6.13 g. (63%) of 1,10-dicarboxydecanone-5 (IX), m.p. 114–114.5°, was obtained.

Anal. Calcd. for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25; neut. equiv., 122.1. Found: C, 59.05; H, 8.28; neut. equiv., 121.9.

DURHAM, NORTH CAROLINA

[CONTRIBUTION NO. 2132 FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY]

Stereochemistry of the Opening of the Imine Ring with Ethylamine[1,2]

BY ROBERT GHIRARDELLI[3] AND HOWARD J. LUCAS[4]

RECEIVED SEPTEMBER 4, 1956

Four openings of imine rings and one opening of an oxide ring have been found to occur in a *trans* manner. Of the first, three are reactions of ethylamine with L(−)-*trans*-2,3-iminobutane, L(+)-*trans*-N-ethyl-2,3-iminobutane and *cis*-N-ethyl-2,3-iminobutane, and one is the reaction of ammonia with L(+)-*trans*-N-ethyl-2,3-iminobutane. The *trans* opening of an oxide ring occurs in the reaction of ethylamine with D(+)-*trans*-2,3-epoxybutane. The configuration of DL-*threo*-2,3-bis-(ethylamino)-butane has been established as *threo* by resolution with (−)-dibenzoyltartaric acid. The configuration of the (+)-isomer has been established as L by relating it to L(+)-*threo*-2,3-diaminobutane. The configuration of (+)-*erythro*-3-ethylamino-2-butanol has been established by relating it to L(+)-*erythro*-3-amino-2-butanol. Zinc chloride forms a 1-to-1 complex with D(−)-*threo*-2,3-bis-(ethylamino)-butane. The enhancement of rotation in its formation suggests that it may have a cyclic structure, but its low solubility in organic solvents suggests a polymeric structure.

The isomeric N-ethyl-2,3-iminobutanes have been synthesized by methods which are strictly analogous to those described for the 2,3-iminobutanes[5] except that ammonia is replaced by ethylamine. In Figs. 1 and 2 are shown the steps in the synthesis of *cis*-N-ethyl-2,3-iminobutane and L-(+)-*trans*-N-ethyl-2,3-iminobutane, respectively. The openings of oxide rings by ethylamine and the closings of the N-ethylimine rings are depicted as *trans* openings and closings, respectively, similar to the former results.[5] A *trans* opening in Fig. 2 must be regarded as proven because the identity of the resulting amino alcohol has been established as L(+)-*erythro*-3-ethylamino-2-butanol. The single Walden inversions occurring during the ring openings and ring closings in Figs. 1 and 2 are shown at carbon atoms C-3.

Proof of *trans* Openings of Imine Rings by Ethylamine.—This is given by four independent results, as outlined in Figs. 3, 4, 5 and 6, respectively. In Fig. 3 *cis*-N-ethyl-2,3-iminobutane is converted into 2,3-bis-(ethylamino)-butane which is resolvable into (+)- and (−)-isomers. It therefore is the DL-*threo*-isomer. Carbon atom C-3 is inverted on the formation of the L-isomer and C-2 on that of the D.

(1) This research has been made possible by support extended the California Institute of Technology by the Office of Ordnance Research, United States Army, under Contract No. DA-04-495-Ord-410.

(2) Presented before the Organic Division at the 130th Meeting of the American Chemical Society at Atlantic City, N. J., September 19, 1956.

(3) Dow Chemical Co. Fellow, 1954–1955.

(4) To whom requests for reprints should be sent.

(5) F. H. Dickey, W. Fickett and H. J. Lucas, THIS JOURNAL, **74**, 944 (1952).

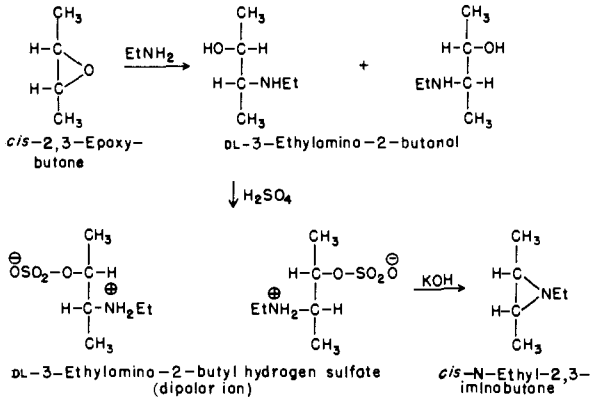

Fig. 1.—Synthesis of *cis*-N-ethyl-2,3-iminobutane.

In Fig. 4 optically active L(+)-*trans*-N-ethyl-2,3-iminobutane is converted into an inactive bis-ethylamine which is the *meso*-isomer, which is contaminated by a small amount of the (+)-isomer (+0.48°). A Walden inversion is involved in this

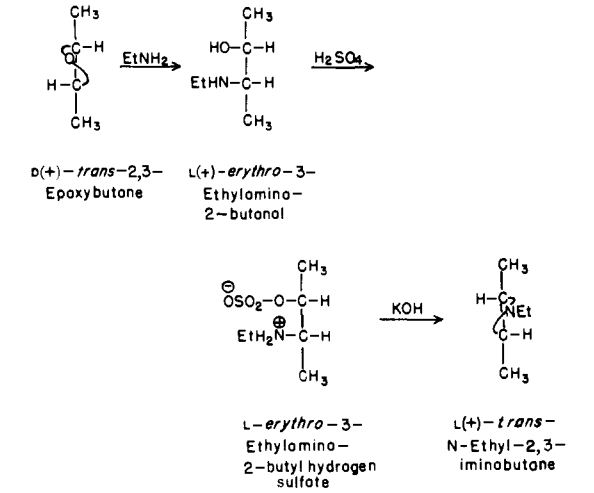

Fig. 2.—Synthesis of L(+)-*trans*-N-ethyl-2,3-iminobutane.

ring-opening process also. In Fig. 5 is shown the conversion of L(−)-*trans*-2,3-iminobutane by ethylamine to D(−)-*erythro*-2-amino-3-ethylaminobutane. Thus here also there is a *trans* opening of the imine ring.

Figure 6 is an outline of the synthesis of enantiomorphic *erythro*-2-amino-3-ethylaminobutanes from D(+)-*trans*-2,3-epoxybutane with exactly the same reagents but in a different order.

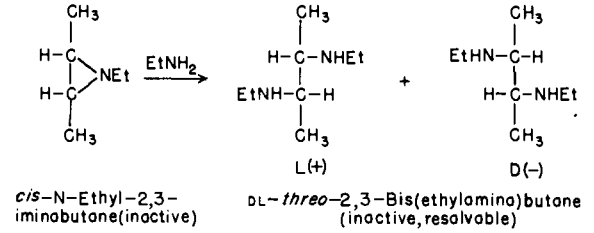

Fig. 3.—Ethylamine and *cis*-N-ethyl-2,3-iminobutane.

In the left hand path, D(+)-*trans*-2,3-epoxybutane is converted by ammonia into L(+)-*erythro*-3-amino-2-butanol, which with sulfuric acid yields the dipolar ion of L-*erythro*-3-amino-2-butyl hydrogen sulfate. When this is heated with aqueous potassium hydroxide, L(−)-*trans*-2,3-iminobutane is obtained. Its configuration has been established[5]

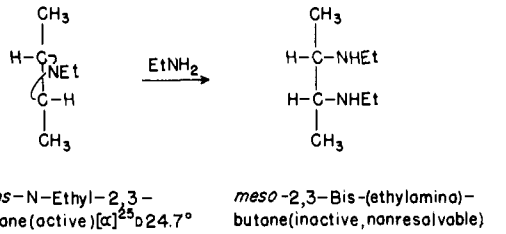

Fig. 4.—Ethylamine and L(+)-*trans*-N-ethyl-2,3-iminobutane.

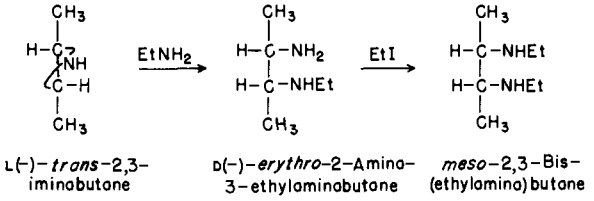

Fig. 5.—Ethylamine and L-(−)-*trans*-2,3-iminobutane.

as L. This compound is converted by ethylamine into D(−)-*erythro*-2-amino-3-ethylaminobutane, $[\alpha]^{25}D$ −36.7°.

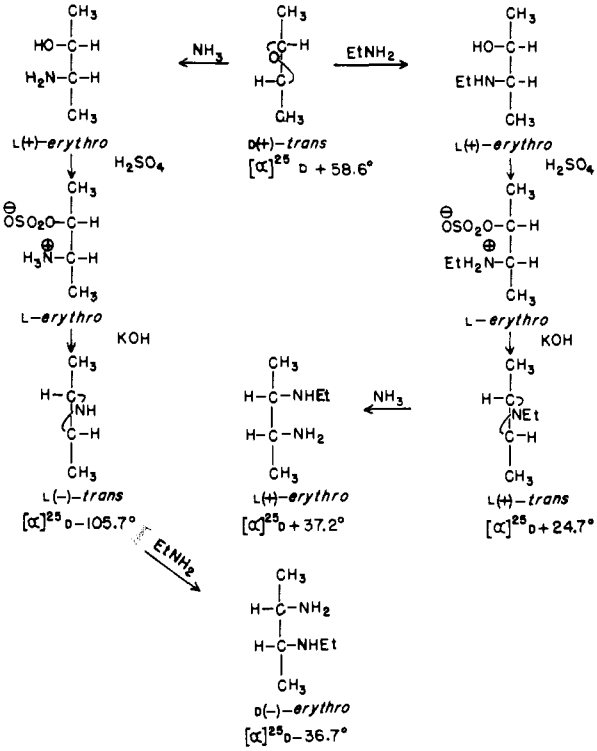

Fig. 6.—Synthesis of enantiomorphic 2-amino-3-ethylaminobutanes.

In the right hand path, the epoxide and ethylamine give L(+)-*erythro*-3-ethylamino-2-butanol (configuration established). This with sulfuric acid, then potassium hydroxide gives L(+)-*trans*-N-ethyl-2,3-iminobutane. Since this compound is formed analogously to L(−)-*trans*-2,3-iminobutane, the only difference being the use of ethylamine instead of ammonia, it is logical to assume

that it also has the L-configuration.[5] In the last step, in which ammonia reacts with L(+)-*trans*-N-ethyl-2,3-iminobutane, the product has a rotation which is opposite in sign to that of the product in the left hand path and is approximately the same in magnitude. This product is L(+)-*erythro*-2-amino-3-ethylaminobutane, $[\alpha]^{25}D$ + 37.2°. The two products are thus enantiomorphs, and their formation can only be accounted for on the basis of *trans* openings of the two imine rings by ethylamine. The only condition which would permit the formation of enantiomorphs by *cis* openings of the two imine rings would be opposite configurations of the two imines. Such a condition is highly improbable because it would be necessary for sulfuric acid or potassium hydroxide to cause a steric effect in the right hand path which is different from that in the left.

If in the last step each reaction had taken place by a *cis* opening of the ring of the respective imine, then the product in each case would have been L-*threo*-2-amino-3-ethylaminobutane, as shown in Fig. 7.

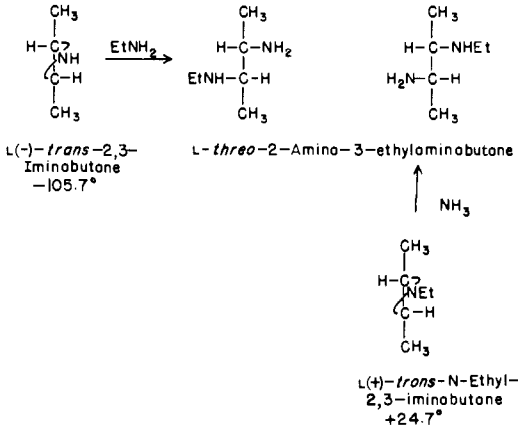

Fig. 7.—Predicted result if there were *cis* openings of the imine rings.

Configurations.—The configuration of DL-*threo*-2,3-bis-(ethylamino)-butane, established by resolution into (+)- and (−)-forms with (−)-dibenzoyltartaric acid, has been confirmed by relating it to DL-2,3-diaminobutane of known configuration.[5] The configuration of the (+)-isomer is known to be L(+)-2,3-bis-(ethylamino)-butane by its relation to L(+)-*threo*-2,3-diaminobutane, as shown in Fig. 8. The second ethylation step does not proceed in the presence of alcohol.

The configuration of *meso*-2,3-bis-(ethylamino)-butane can logically be assumed because of the non-identity of ditosyl and diacetyl derivatives of the two inactive bis-(ethylamino)-butanes. The configuration of D(−)-*erythro*-2-amino-3-ethylaminobutane, Fig. 6, has been established as *erythro* by relating it to *meso*-2,3-bis-(ethylamino)-butane. Since a Walden inversion takes place in its formation from L(−)-*trans*-2,3-iminobutane, it must belong to the D-family. The configuration of L(+)-*erythro*-3-ethylamino-2-butanol has been established by relating it to L(+)-*erythro*-3-amino-2-butanol of known configuration.[5]

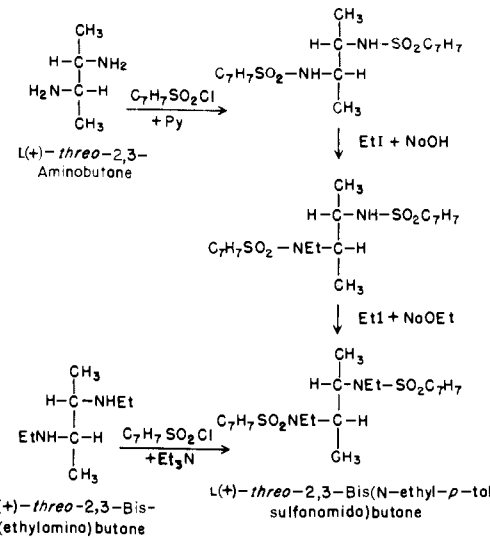

Fig. 8.—Proof that (+)-*threo*-2,3-bis-(ethylamino)-butane from the resolution has the L-configuration.

Coördination Complex.—Zinc chloride and D(−)-*threo*-2,3-bis-(ethylamino)-butane form a 1-to-1 complex, $[\alpha]^{25}D$ −71°. This is equivalent to a rotation of −138° on the basis of the bisethylamine content.

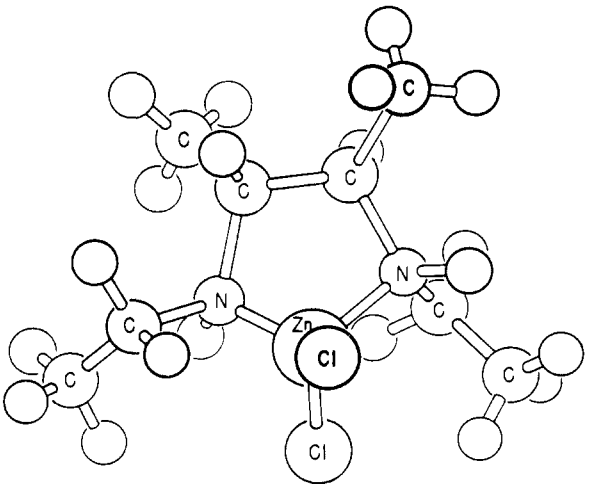

Fig. 9.—A possible structure of the coördination complex of zinc chloride with D(−)-*threo*-2,3-bis-(ethylamino)-butane.

In covalent compounds zinc may have four tetrahedral bonds or six octahedral bonds. Under anhydrous conditions there are four, and when water of crystallization is present, there may be six. Thus in zinc 8-hydroxyquinolinate dihydrate, composed of one zinc atom, two 8-hydroxyquinoline molecules and two water molecules there are six octahedral bonds,[6] but in the anhydrous molecule there are four bonds. These are tetrahedral bonds because zinc 8-hydroxyquinoline-5-sulfonic acid has been resolved.[7]

In the zinc chloride–D(−)-*threo*-2,3-bis-(ethylamino)-butane complex it is more than likely that

(6) L. L. Merritt, Jr., R. T. Cady and B. W. Mundy, *Acta Crystallographica*, **7**, 473 (1954).

(7) J. C. I. Liu and J. C. Bailar, Jr., THIS JOURNAL, **73**, 5432 (1951)

TABLE I

CONSTANTS OF SOME 2,3-DISUBSTITUTED BUTANES

Groups in position 2	Groups in position 3	Isomer	B.p., °C.	Mm.	$n^{25}D$	d^{25}	$[\alpha]^{25}D$	$\alpha^{25}D$ pure liquid
-OH	-NHEt	L(+)-*erythro*[a]	69.2–69.5	20	1.4387	0.888	+ 31.2°	+27.73°
-OH	-NHEt	DL-*threo*	69.3–70.2	20	1.4366	.879		
-OH	-NEt_2	L(+)-*erythro*	83.7–84.9	20	1.4377	.861	+95.5	+82.3
-OH	-NEt_2	DL-*threo*	71.0–71.2	20	1.4240	.843		
-NEt-		*cis*	81.0–81.8	746	1.3968	.743		
-NEt-		L(+)-*trans*	91.0–91.8	745	1.4042	.760	+24.7[d]	+18.75
-NH_2	-NH_2	DL-*threo*[b]	55.3–59.3	60	1.4428			
-NH_2	-NH_2	*meso*[c]	56.1–60.5	60	1.4438			
-NH_2	-NHEt	D(−)-*erythro*	85.1–85.7	100	1.4347	0.823	−36.7	−30.24
-NH_2	-NHEt	L(+)-*erythro*	84.1–85.0	100	1.4340	.823	+37.2	+30.58
-NH_2	-NHEt	DL-*threo*	82.1–83.3	100	1.4328	.816		
-NHEt	-NHEt	*meso*	63.8–64.5	20	1.4297	.806	+ 0.48	
-NHEt	-NHEt	DL-*threo*	64.6–65.8	20	1.4299	.809		
-NHEt	-NHEt	D(−)-*threo*	64.9–65.2	20	1.4299	.781	−103.7[e]	−80.97
-NHEt	-NHEt	L(+)-*threo*	65.0–65.8	20	1.4302	.781	+106.0	+82.75

[a] M.p. 18–19°. [b] Lit.,[5] 57.58° (60 mm.), 1.4408. [c] Lit.,[5] 59–60° (60 mm.), 1.4420. [d] $[\alpha]^{25}D$ +26.8° (α +0.92°, *c* 3.43, hexane). [e] $[\alpha]^{25}D$ −109° (α −2.80°, *c* 2.57, hexane).

TABLE II

CONSTANTS OF *p*-TOLUENESULFONYL AND ACETYL DERIVATIVES OF SOME 2,3-DISUBSTITUTED BUTANES

Groups in position 2	Groups in position 3	Isomer	M.p., °C. (cor.)	$[\alpha]^{25}D$	α	Concn., g./100 ml.[a]
-OTs	-NEtTs	L(+)-*erythro*		+9.2°	+0.21°	2.26
-OTs	-NEtTs	DL-*threo*	111.1–111.5			
-NTs-		*cis*	94.9–96.1			
-NTs-		L(−)-*trans*	78.4–79.4	−19.0	−0.68	3.59
-NHTs	-NEtTs	D(−)-*erythro*	149.9–150.7	−23.8	−1.19	5.04
-NHTs	-NEtTs	L(+)-*erythro*	148.0–148.8	+21.3	+0.64	2.99
-NHTs	-NEtTs	DL-*threo*	150.6–151.6			
-NHTs	-NEtTs	L(+)-*threo*	111.3–112.0	+2.2	+0.025	1.13
-NEtTs	-NEtTs	*meso*	241.8–243.3	0.0	0.0	0.80[b]
-NEtTs	-NEtTs	DL-*threo*	135.8–136.7			
-NEtTs	-NEtTs	D(−)-*threo*	138.5–139.5	−13.3	−1.16	8.60
-NEtTs	-NEtTs	L(+)-*threo*	138.7–139.5	+13.7	+1.20	8.75
-NHAc	-NEtAc	D(+)-*erythro*	93.6–94.6	+7.1	+0.24	3.40
-NHAc	-NEtAc	L(−)-*erythro*	93.9–94.6	−6.8	−0.20	2.94
-NHAc	-NEtAc	DL-*threo*	80.4–81.0			
-NEtAc	-NEtAc	*meso*	76.5–77.3	0.0	0.0	0.238
-NEtAc	-NEtAc	DL-*threo*	68.3–69.6			
-NEtAc	-NEtAc	D(−)-*threo*	72.0–72.7	−25	−0.36	1.43
-NEtAc	-NEtAc	L(+)-*threo*	71.0–71.7	+30	+0.39	1.30

[a] Butanone. [b] Chloroform.

there are four tetrahedral bonds, two from zinc to nitrogen and two from zinc to chlorine. It is possible that the complex may have the structure shown in Fig. 8, but its low solubility in organic solvents suggests that zinc forms intermolecular rather than intramolecular bonds to carbon.

Physical Constants.—Table I contains constants of 2,3-disubstituted butanes, Table II, solid ditosyl- and diacetyl-2,3-butane derivatives and Table III, miscellaneous solid 2,3-butane derivatives.

The most interesting constant is the specific rotation. The rotation of D(−)-*threo*-2,3-butanediol is −13.2°, D(−)-*threo*-3-amino-2-butanol is −17.05°, D(−)-*threo*-2,3-diaminobutane would be −29.5° and D(−)-*threo*-2,3-bis-(ethylamino)-butane is −103.7°. Thus, the tendency to cause negative rotation in the D-*threo*-series is in the order EtNH > NH_2 > OH. This is borne out in the L-*erythro*-series, when there is opposition between groups. The specific rotation of *meso*-2,3-dihydroxybutane is 0°, of L(+)-*erythro*-3-amino-2-butanol +0.85° (here the positive effect of amino in the 3-L-position outweighs the negative effect of hydroxyl in the 2 position), of L(+)-*erythro*-3-ethylamino-2-butanol +31.2°, and of L(+)-*erythro*-3-diethylamino-2-butanol +95.2°. Also the greater positive effect of ethylamino in the 3-position in the L-family is

TABLE III

MISCELLANEOUS DERIVATIVES OF SOME 2,3-DISUBSTITUTED BUTANES

Groups in position 2	Groups in position 3	Isomer	M.p., °C.	$[\alpha]^{25}D$
-OH	-NH_2·0.5$C_2H_2O_4$	L-*erythro*	202.7–203.2	
-OH	-NH_2·0.5$C_2H_2O_4$	DL-*threo*	190.0–191.1	
-OH	-NEt_2·HCl	L-*erythro*	130.4–131.2	
-OH	-NEt_2·HCl	DL-*threo*	149.4–150.4	
-OPnb[a]	-NEtPnb[a]	L(−)-*erythro*	117.0–117.6	−24.3°[b]
-OPnb[a]	-NEtPnb[a]	DL-*threo*	167.2–167.9	
-OSO_3^-	-NH_2Et^+	L-*erythro*	246.5–249[d]	
-OSO_3^-	-NH_2Et^+	DL-*threo*	197–199	
-NHEt	-NHEt·$ZnCl_2$	D(−)-*threo*		−71[c]

[a] *p*-Nitrobenzoyl. [b] α −0.52°, *c* 2.14, butanone. [c] α −0.56°, *c* 0.790, N,N-dimethylformamide. [d] Decomposition.

shown by *meso*-2,3-diaminobutane, 0°, and L(+)-*erythro*-2-amino-3-ethylaminobutane, +37.2°.

Tosylation tends to make the rotation at the 3-position in the D-*threo*-series more positive or less negative. In the *threo*-isomers, the rotation of D(−)-*threo*-2,3-butanediol is −13.2° and of D(+)-*threo*-2,3-ditosyloxybutane, +37.2°; also, of D-(−)-*threo*-2,3-diaminobutane, −104°, and of D-(+)-*threo*-2,3-ditosylamidobutane, +70°. Also, D-*threo*-2,3-bis-(ethylamino)-butane is −104° and D(−)-*threo*-2,3-bis-(tosylamido)-butane is −13.3°. In the L-family it should tend to make rotations more negative (less positive). The rotation of L(+)-*erythro*-3-ethylamino-2-butanol is +31.2°, and of L(+)-*erythro*-2-tosyloxy-3-N-ethyltosylamidobutane, + 9.2°; also of L(+)-*erythro*-2-amino-3-ethylaminobutane, +37.2°, and of L(+)-*erythro*-2-tosylamido-3-N-ethyltosylamidobutane, +21.3°.

In the ring compounds, the rotation of D(+)-*trans*-2,3-epoxybutane is +59°, of D(+)-*trans*-2,3-iminobutane, +106°, and of D(−)-*trans*-N-ethyl-2,3-iminobutane, −25°. Here the effect of ethyl substitution is just the opposite of that observed in the D-*threo*-series.

1,2-Butane Derivatives.—In order to conserve the supply of the more valuable 2,3-epoxybutanes, exploratory studies were made with 1,2-epoxybutane to ascertain conditions for carrying out various operations. The changes investigated in the series involving 1,2-iminobutane are: 1,2-epoxybutane $\xrightarrow{NH_3}$ 1-amino-2-butanol $\xrightarrow{H_2SO_4}$ 1-amino-2-butyl hydrogen sulfate $\xrightarrow{KOH}$ 1,2-iminobutane $\xrightarrow{NH_3}$ 1,2-diaminobutane, and 1,2-iminobutane $\xrightarrow{EtNH_2}$ 1-ethylamino-2-aminobutane. Those involving N-ethyl-1,2-iminobutane are: 1,2-epoxybutane $\xrightarrow{EtNH_2}$ 1-ethylamino-2-butanol $\xrightarrow{H_2SO_4}$ 1-ethylamino-2-butyl hydrogen sulfate $\xrightarrow{KOH}$ N-ethyl-1,2-iminobutane $\xrightarrow{EtNH_2}$ 1,2-bis-(ethylamino)-butane.

In the reaction of 1,2-epoxybutane with ammonia the product is predominatingly 1-amino-2-butanol.[8] For the purposes of preparing 1,2-iminobutane it is immaterial whether the product of the reaction is 1-amino-2-butanol or 2-amino-1-butanol. A similar statement holds for the synthesis of N-ethyl-1,2-iminobutane. However, in view of the results of others[8] and the fact that the product of the reaction of 1,2-epoxybutane with ethylamine is a solid, it is reasonable to conclude that this is almost completely if not entirely 1-ethylamino-2-butanol. Under basic conditions attack of a nucleophilic reagent on an unsymmetrical oxide takes place at a primary carbon atom in preference to a secondary or tertiary carbon atom.[8b,9] A large excess of ammonia (or an amine) is necessary because the resulting amino alcohol reacts readily with the epoxide.[5] It has been found that reaction proceeds better in aqueous solution than under anhydrous conditions.

The opening of the ring of 1,2-iminobutane, by analogy with that of 1,2-epoxybutane, is regarded as taking place almost entirely by attack at the primary carbon atom. Little or no reaction was observed by the action of anhydrous ethylamine alone, even when heated to 60° for several days. No attempt was made to carry out reactions under anhydrous conditions in the presence of a catalyst such as ammonium chloride or aluminum chloride, as used in reactions with ammonia[5,10,11] and amines,[11] because of the possibility that chloride ion might be an attacking reagent.

1-Diethylamino-2-butanol was prepared in three ways: (1) monoethylation of 1-ethylamino-2-butanol, from 1,2-epoxybutane and ethylamine; (2) diethylation of 1-amino-2-butanol, from 1,2-epoxybutane and ammonia; and (3) reaction of 1,2-epoxybutane with diethylamine. The properties of the three preparations and of their hydrochlorides agreed closely.

Summary on Preparations.—In the preparation and study of the different imines a number of ring openings have been investigated for the first time. These are: 1,2-epoxybutane with ethylamine and diethylamine, 1,2-iminobutane with ethylamine, N-ethyl-1,2-iminobutane with ethylamine, the 2,3-epoxybutanes with ethylamine, the 2,3-iminobutanes with ethylamine and the N-ethyl-2,3-iminobutanes with ammonia and ethylamine.

Some general conclusions can be drawn about the relative ease of opening three-membered rings. Ammonia is more reactive than ethylamine, and the latter is better than diethylamine. Reactions proceed more rapidly in aqueous solutions than under anhydrous conditions, as observed by others for 1,2-iminoethane.[12] Relative reactivities of ring compounds in decreasing order are: 1,2-epoxybutane, 2,3-epoxybutane, 1,2-iminobutane, 2,3-iminobutane, N-ethyl-1,2-iminobutane and N-ethyl-2,3-iminobutane. Heating usually is necessary with ethylamine and diethylamine, sometimes as high as 120° for as long as three weeks. Constants of the 1,2-disubstituted butanes are in Table IV.

TABLE IV

CONSTANTS OF SOME 1,2-DISUBSTITUTED BUTANES

Groups in position 1	2	M.p., °C.	B.p., °C.	Mm.	$n^{25}D$
-NH_2	-OH		82.0-83.0	20	1.4482
-NHBz	-OH	112.1-113.1[a]			
-NHPnb[b]	-OPnb[b]	119.2-120.2			
-NH_3^+	-OSO_3^-	224-226			
-NH_2·0.5$C_2H_2O_4$	-OH	195-196[c]			
-NH-			87.6-88.5[d]	743	1.4177[d]
-NHEt	-OH	30-33.5	78.0-79.2	20	
-NEtTs	-OTs	98.2-99.1			
-NEt_2	-OH		71.8-72.4	20	1.4281
-NEt_2·HCl	-OH	150.6-151.0			
-NEt-			91.0-92.1	741	1.4010
-NHEt	-NHEt		73.0-73.8	20	1.4316
-NEtTs	-NEtTs	87.8-88.6			

[a] Lit.,[25] 112-113.5°. [b] *p*-Nitrobenzoyl. [c] Lit.,[25] 196-200°. [d] Lit.,[23] b.p. 88-89°, $n^{25}D$ 1.4165.

(8) (a) M. de Montmollin and P. Matile, *Helv. Chim. Acta*, **7**, 106 (1924); (b) Stig Anderson, "The Reaction between Ethylene Oxide and Ammonia," Dissertation, Lund, 1955, p. 83.

(9) S. Winstein and R. B. Henderson, "Heterocyclic Compounds," Vol. 1, edited by R. C. Elderfield, John Wiley and Sons, Inc., New York, N. Y., 1950, p. 32.

(10) G. H. Coleman and J. E. Callen, THIS JOURNAL, **68**, 2006 (1946).

(11) L. B. Clapp, *ibid.*, **70**, 184 (1948).

(12) A. L. Wilson, U. S. Patents 2,318,729 and 2,318,730; *C. A.*, **37**, 5986 (1943); G. I. Braz and V. A. Skorodumov, *Compt. rend. acad. sci. URSS*, **55**, 315 (1947); *cf. C. A.*, **41**, 6527 (1947).

TABLE V

Groups in position 1	Groups in position 2	Isomer	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found
-NHPnb[a]	-OPnb[a]		55.81	56.61	4.42	4.62	10.85	11.08		
-NEtTs	-OTs		56.44	56.00	6.40	6.23	3.29	3.28	15.07	14.78
-NEtTs	-NEtTs		58.38	58.53	7.13	7.03	6.19	6.17	14.17	13.60
2	3									
-OH	$-NH_2 \cdot 0.5C_2H_2O_4$	L(+)-*erythro*	44.76	45.40	9.02	8.90	10.44	11.13		
-OH	$-NH_2 \cdot 0.5C_2H_2O_4$	DL-*threo*	44.76	44.71	9.02	8.83	10.44	10.13		
-OPnb[a]	-NEtPnb[a]	L(−)-*erythro*	57.82	57.85	5.10	5.27	10.12	9.79		
-OPnb[a]	-NEtPnb[a]	DL-*threo*	57.82	57.81	5.10	5.21	10.12	10.34		
-OH	$-NEt_2 \cdot HCl$	L(+)-*erythro*	52.88	52.94	11.10	10.87	7.71	7.70	19.51[b]	19.71[b]
-OH	$-NEt_2 \cdot HCl$	DL-*threo*	52.88	53.37	11.10	11.11	7.71	8.22	19.51[b]	20.43[b]
-OTs	-NEtTs	DL-*threo*	56.44	56.48	6.40	6.29	3.29	3.27	15.07	14.97
	-NTs-	*cis*	58.63	58.52	6.71	6.71	6.22	6.15	14.22	13.15
	-NTs-	L(−)-*trans*	58.63	58.83	6.71	6.99	6.22	6.58	14.22	14.27
-NHTs	-NEtTs	D(−)-*erythro*	56.57	56.50	6.65	6.69	6.60	6.95	15.10	14.77
-NHTs	-NEtTs	DL-*threo*	56.57	56.72	6.65	6.65	6.60	6.71	15.10	15.14
-NEtTs	-NEtTs	*meso*	58.38	58.60	7.13	7.20	6.19	6.39	14.17	14.26
-NEtTs	-NEtTs	DL-*threo*	58.38	58.53	7.13	7.08	6.19	6.26	14.17	14.64
-NEtTs	-NEtTs	L(+)-*threo*	58.38	58.49	7.13	7.12	6.19	6.19	14.17	14.13
-NHAc	-NEtAc	D(+)-*erythro*	59.97	60.51	10.07	10.04	13.99	14.12		
-NHAc	-NEtAc	DL-*threo*	59.97	60.37	10.07	10.40	13.99	13.94		
-NEtAc	-NEtAc	*meso*	63.12	63.60	10.60	10.90	12.27	12.10		
-NEtAc	-NEtAc	DL-*threo*	63.12	63.00	10.60	10.80	12.27	12.56		
-NHEt	$-NHEt \cdot ZnCl_2$	D(−)-*threo*							26.0[b]	25.3[b]

[a] *p*-Nitrobenzoyl. [b] Chlorine.

Experimental[13]

The starting materials were *meso*-2,3-butanediol, melting point range 0.3° or less in the temperature range,[14] 34.1–34.7°, purified by crystallization of industrial "butylene glycol"[15]; D(−)-*trans*-2,3-butanediol, b.p. 77.3–77.4° (10 mm.), $[\alpha]^{25}D$ −13.1°,[16,17] from distillation of "levo butylene glycol"[15]; and 1,2-epoxybutane, b.p. 62.2–62.3° (743 mm.), a center cut obtained by fractional distillation of "butylene oxide, straight chain isomers"[19] through a 40-cm. column of glass helices. The *meso*-glycol and the D(−)-glycol were converted to *cis*-2,3-epoxybutane and D(+)-2,3-epoxybutane, respectively.[14,17] From the 1,2-oxide the corresponding 1,2-imines and 1,2-diamines were prepared for exploratory purposes. The stereochemical studies were made with the 2,3-compounds. In this section only one example of a typical synthesis is given in detail. Yields are given for the different compounds so prepared and a note made of any significant change in directions. Physical constants are given in Tables I to IV and analyses in Table V.

Amino Alcohols.—The isomeric 3-amino-2-butanols were prepared as described earlier[5] except that L(+)-*erythro*-3-amino-2-butanol was distilled through a column of Raschig rings and was condensed by a slow stream of water to prevent solidification, b.p. 87.7–88.3° (40 mm.). 1-Amino-2-butanol, from 12 *M* aqueous ammonia and 1,2-epoxybutane (30-to-1 molar ratio) at room temperature for 2 weeks was obtained in 65% yield.

N-Ethylamino Alcohols, from Epoxides and Ethylamine.—The reactions involved and also the opening of imine rings by ethylamine and ammonia were in general carried out in 220-ml. stainless-steel tubes having threaded caps and Teflon gaskets. Some preparations were carried out in glass ampoules. A typical preparation (in this case in an ampoule) is that of DL-*threo*-3-ethylamino-2-butanol. A solution of 21 g. (0.29 mole) of *cis*-2,3-epoxybutane in 360 ml. (*ca.* 5 mole) of 70% aqueous ethylamine (a 30-to-1 molar ratio) was heated at 100° for 1 week. Unreacted ethylamine was removed by distillation through a cold 40-cm. column of Raschig rings to a pot temperature of 98°. The residue was cooled to 0° and saturated with potassium hydroxide. The upper phase (33 g.) was removed and combined with 50 ml. of ether used for extracting the lower phase. The ether solution was dried with solid potassium hydroxide, and ether was removed by distillation through a 40-cm. column of Raschig rings to a pot temperature of 100°. Then 10 ml. of diethylene glycol monobutyl ether[20] was added and distillation was continued at 20 mm. to give 29.0 g. (85%) at 69.3–70.2°.

Other compounds and yields were: L(+)-*erythro*-3-ethylamino-2-butanol, 84%, from D(+)-*trans*-2,3-epoxybutane, similarly; 1-ethylamino-2-butanol, 81%, from 1,2-epoxybutane and ethylamine (20-to-1 ratio) at 100° for 5 days; and 1-diethylamino-2-butanol, 95%, from 1,2-epoxybutane and diethylamine,[21] similarly.

Imines.—*cis*-2,3-Iminobutane and L(−)-2,3-iminobutane were prepared by the Wenker method,[5,22,23] and the products had properties agreeing closely with former values except that the observed rotation of the L(−)-imine was −83.28° instead of −80.37°. 1,2-Iminobutane was prepared similarly in 50% yield. The method for N-ethylimines is illustrated by the preparation of *cis*-N-ethyl-2,3-iminobutane. 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 19.8 *N* sulfuric acid; 9.15 ml. was required, giving an assay of 99.5%. An additional 9.15 ml. was added, and water was removed at aspirator vacuum on a steam-bath until the residue became a thick sirup, then at 1 mm. vacuum on an oil-bath at 120°. Crystallization took place slowly. After 48 hr. the solid was ground in a mortar. It was heated in the apparatus to constant weight. The residue was a white powder, m.p. 197–199° (bath preheated to 190°).

A solution of 58.0 g. (0.294 mole) of this sulfate in 125 ml. of water was placed in a 0.5-l. 3-necked flask equipped with:

(13) Microanalyses by A. Elek, Los Angeles, Calif., and G. Swinehart, Pasadena, Calif.

(14) H. J. Lucas and C. W. Gould, Jr., THIS JOURNAL, **63**, 2546 (1941), give m.p., 34.45–34.55°.

(15) Kindly supplied by the Celanese Corporation.

(16) A. C. Neish, *Can. J. Research*, **23B**, 10 (1945), gives −13.19°.

(17) H. J. Lucas and H. K. Garner, THIS JOURNAL, **70**, 990 (1948), give −13.17° and values of others in their Table I.

(18) Kindly supplied by the National Research Council of Canada through the courtesy of A. C. Neish and J. A. Wheat.

(19) Kindly supplied by the Dow Chemical Company; lit.[3a] value of 1,2-epoxybutane, 58.5–59°.

(20) Purified by fractional distillation through a 15-in. column of Raschig rings at 3 mm., b.p. 86.6–87.7° (120.9° at 20 mm.).

(21) Water was added to anhydrous diethylamine to produce an equimolar solution (about 80% in diethylamine).

(22) H. Wenker, THIS JOURNAL, **57**, 2329 (1935).

(23) G. D. Jones, *J. Org. Chem.*, **9**, 484 (1944).

(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. While the contents were maintained at 5–10° by means of an ice-bath a solution of 75 g. (1.3 moles) of potassium hydroxide in 40 ml. of water was added. Stirring was continued and heat was applied. At 75° crystallization of potassium sulfate began and distillation (complicated at first by foaming) followed rapidly. This was continued to a pot temperature of 104°. The distillate was saturated with potassium hydroxide. The organic layer was separated and fractionally distilled through a 2-ft. column of helices with xylene as still base for the last fourth; yield of *cis*-N-ethyl-2,3-iminobutane, 21.0 g. (72%); other compounds: N-ethyl-1,2-iminobutane, 60%, from 1-ethylamino-2-butanol; and L(+)-*trans*-N-ethyl-2,3-iminobutane, 73%, from L(+)-*erythro*-3-ethylamino-2-butanol.

Imines and Ammonia.—A solution of 14.2 g. (0.20 mole) of *cis*-2,3-iminobutane in 350 ml. (5.6 moles) of 15 *M* ammonium hydroxide (28-to-1 molar ratio) was heated at 100° for 2 weeks. The ammonia was distilled off to a pot temperature of 98°, and the aqueous residue was saturated at 0° with potassium hydroxide. The organic phase (15.7 g.) was combined with 40 ml. of ether used for extracting the aqueous phase and dried over solid potassium hydroxide. The ether was removed through a 40-cm. column of Raschig rings to a pot temperature of 102°, 12 ml. of diethylene glycol monobutyl ether[20] was added and 12.5 g. (71%) of DL-*threo*-2,3-diaminobutane was collected at 55.3–59.3° (60 mm.); other diamines: *meso*-2,3-diaminobutane, 67%, from L(−)-*trans*-2,3-iminobutane, in exactly the same manner; and L(+)-*erythro*-2-amino-3-ethylaminobutane, 51%, from L(+)-*trans*-N-ethyl-2,3-iminobutane (30-to-1), 100° for 3 weeks.

Imines and Ethylamine.—A solution of 21.3 g. (0.30 mole) of L(−)-*trans*-2,3-iminobutane in 500 ml. of 70% aqueous ethylamine (6 moles, 20-to-1 molar ratio) was heated at 120° for 16 days. The product, D(−)-*erythro*-2-amino-3-ethylaminobutane was removed as just described; yield 23.0 g. (66%); other compounds: 1,2-bis-(ethylamino)-butane, 55%, from N-ethyl-1,2-iminobutane, similarly; 2-amino-1-ethylaminobutane, 45%, from 1,2-iminobutane, similarly, but for 2 weeks; DL-*threo*-2-amino-3-ethylaminobutane, 47%, from *cis*-2,3-iminobutane, 22-to-1 at 120° for 3 weeks; *meso*-2,3-bis-(ethylamino)-butane, 51%, from L(+)-*trans*-N-ethyl-2,3-iminobutane, 22-to-1 at 100° for 3 weeks; and DL-*threo*-2,3-bis-(ethylamino)-butane, 48%, from *cis*-N-ethyl-2,3-iminobutane, similarly.

Resolution of DL-*threo*-2,3-Bis-(ethylamino)-butane.—To a solution of 4.55 g. (0.0316 mole) of DL-*threo*-2,3-bis-(ethylamino)-butane in 100 ml. of commercial absolute alcohol in a 1-l. flask was added a solution of 24.0 g. (0.0638 mole) of L(−)-dibenzoxysuccinic acid (dibenzoyltartaric acid),[24] $[\alpha]^{25}D$ −110° in 350 ml. of absolute alcohol. The observed rotation of the solution was −4.47°. Crystallization began in about 0.5 hr. After 12 hr. the solid was collected by filtration and washed with ethanol (300 ml.); yield 8.0 g. An additional 0.1 g. separated on cooling to 5°, $[\alpha]^{25}D$ −89° (α −0.39°, c 0.44, water).

Anal. Calcd. for neutral salt, $C_{26}H_{34}O_8N_2$: N, 5.57. Found: N, 5.43.

Recrystallization from 1.3 l. of methanol gave 6.6 g. (72%) of colorless rods, $[\alpha]^{25}D$ −68° (α 0.25°, *c* 0.367, water), unchanged after a second crystallization. The solid was decomposed by excess of concd. potassium hydroxide, and the organic phase was separated and combined with 75 ml. of peroxide-free absolute ether used in 3 portions for extracting the aqueous phase. The solution was dried with solid potassium hydroxide. Fractional distillation at 20 mm. gave 1.3 g. (58%) of L(+)-*threo*-2,3-bis-(ethylamino)-butane at 65.0–65.8°, $[\alpha]^{25}D$ +106.0°.

The original mother liquor was concentrated to 150 ml. at 50° (aspirator vacuum) and filtered from an insignificant amount of solid. The remaining solvent was removed, first at aspirator vacuum on a steam-bath, then at 1 mm. pressure over sulfuric acid in a desiccator. The last transformed the gummy residue to a dry solid; weight 19.0 g. This was ground to a powder and extracted with 1 l. of sodium-dried ethyl ether in 4 portions to remove excess dibenzoyltartaric acid. The residue, 14.8 g., had $[\alpha]^{25}D$ −88° (α −0.41, *c* 0.468, water). It was decomposed with excess concd. potassium hydroxide solution and dissolved into 100 ml. of peroxide-free ether. This, when added to 25 ml. of 2 *M* hydrogen chloride in peroxide-free ether, gave 2.8 g. (80%) of anhydrous colorless solid, presumably a dihydrochloride. Two crystallizations from methanol gave 1.7 g. of colorless prisms, $[\alpha]^{25}D$ −8.1° (α −0.205°, *c* 2.52, water). This yielded by the aforementioned treatment with potassium hydroxide 0.7 g. (30%) of a water-white ammoniacal liquid, D(−)-*threo*-2,3-bis-(ethylamino)-butane, b.p. 64.9–65.2° (20 mm.), $[\alpha]^{25}D$ −103.7°.

Ethylations.—Configurational relationships among some of the basic compounds were established by ethylations. When monoethylation was wanted, the base and ethyl iodide were in molar ratios usually without a solvent. Aqueous strong base was added after reaction has taken place, the liquid was extracted with ether, the ether dried with potassium hydroxide and the product recovered by fractional distillation at reduced pressure with diethylene glycol monobutyl ether[20] the still base. Yields were: 1-diethylamino-2-butanol, 64%, from 1-ethylamino-2-butanol and ethyl bromide (1-to-1) at room temperature for 3 hr.; DL-*threo*-3-diethylamino-2-butanol, 80%, from DL-*threo*-3-ethylamino-2-butanol and ethyl iodide (1-to-1.05), refluxed for 8 hr.; L(+)-*erythro*-3-diethylamino-2-butanol 56%, similarly except refluxed for 1.5 hr., from L(+)-*erythro*-3-ethylamino-2-butanol, which in turn resulted from the reaction of D(+)-*trans*-2,3-epoxybutane with ethylamine; *meso*-2,3-bis-(ethylamino)-butane, 40%, from D(−)-*erythro*-2-amino-3-ethylaminobutane, ethyl iodide (1-to-1) and isopropyl ether at room temperature for several days.

When diethylation was carried out, the organic base was refluxed with 2 moles of ethyl halide (usually iodide), sodium carbonate and water for 7 to 8 hr. Yields were 30 to 50% for 1-diethylamino-2-butanol from 1-amino-2-butanol; L(+)-*erythro*-3-diethylamino-2-butanol of known configuration, from L(+)-*erythro*-3-amino-2-butanol of known configuration (from D(−)-2,3-epoxybutane and ammonia)[5] and DL-*threo*-3-diethylamino-2-butanol, from DL-*threo*-3-amino-2-butanol.

Configurations.—The configuration of (+)-*threo*-2,3-bis-(ethylamino)-butane from the resolution was established as follows: some of the original tartrate of L(+)-*threo*-2,3-diaminobutane obtained by Fickett[5] in the resolution of DL-2,3-diaminobutane was converted into L(+)-*threo*-2,3-diaminobutane with potassium hydroxide by the usual procedure. The residual oil remaining after evaporation of the ether was tosylated with *p*-toluenesulfonyl chloride in pyridine to give L(−)-*threo*-2,3-bis-(*p*-toluenesulfonamido)-butane, m.p. 201.4–202.2°, $[\alpha]^{25}D$ −69.2°; previous values,[5] m.p. 201.1–202.8° $[\alpha]^{25}D$ −70.3°. Only monoethylation took place when this was heated with ethyl iodide and alcoholic sodium hydroxide to give L(+)-*threo*-2-*p*-toluenesulfonamido-3-N-ethyl-*p*-toluenesulfonamidobutane, $[\alpha]^{25}D$ +2.2°. This was converted to the sodium salt with sodium ethoxide (8-to-1 molar ratio) in ethanol, the solvent was evaporated and the dry solid was heated with ethyl iodide (30-to-1) for 8 hr. at 100° to give authentic L(+)-*threo*-2,3-bis-(N-ethyl-*p*-toluenesulfonamido)-butane, 60%, m.p. 138.4–139.0°, $[\alpha]^{25}D$ +12.1°.

Identification of (+)-2,3-bis-(ethylamino)-butane from the resolution as L was made through its (+)-ditosyl derivative, m.p. 138.7–139.5°, $[\alpha]^{25}D$ +13.7°, and confirmed by mixed melting point, 137.7–138.8°, with the authentic sample, m.p. 138.4–139.0°, $[\alpha]^{25}D$ +12.1°. The enantiomorphic (−)-ditosyl derivative, m.p. 138.5–139.5°, $[\alpha]^{25}D$ −13.3°, with the authentic sample gave m.p. 126–136°. The DL-*threo*-2,3-bis-(N-ethyl-*p*-toluenesulfonamido)-butane has m.p. 135.8–136.7°.

The configuration of the DL-*threo*-2,3-bis-(ethylamino)-butane, established by the resolution into (+)- and (−)-isomers, was confirmed by relating it to DL-2,3-diaminobutane (from *cis*-2,3-iminobutane and ammonia) through DL-*threo*-2,3-bis-(N-ethyl-*p*-toluenesulfonamido)-butane as follows: DL-*threo*-2,3-diaminobutane (I) (configuration known)[5] → DL-*threo*-2,3-bis-(*p*-toluenesulfonamido)-butane (II) → DL-*threo*-2-*p*-toluenesulfonamido-(3-N-ethyl-*p*-toluenesulfonamido)-butane (III) → DL-*threo*-2,3-bis-(N-ethyl-*p*-toluenesulfonamido)-butane (IV), m.p. 134.8–135.7°. The ditosyl derivative of the inactive bisethylamine from *cis*-N-ethyl-2,3-iminobutane and ethylamine had m.p. 135.8–136.7°, mixed m.p. of the two, 134.5–135.6°.

The configuration of D(−)-*erythro*-2-amino-3-ethylamino-

(24) C. L. Butler and L. H. Cretcher, THIS JOURNAL, **55**, 2605 (1933), give $[\alpha]^{25}D$ −115°.

butane (V) from L(−)-*trans*-2,3-iminobutane and ethylamine, Fig. 5, was established as *erythro* by ethylation to *meso*-2,3-bis-(ethylamino)-butane (VI). Ditosylation of VI gave *meso*-2,3-bis-(N-ethyl-*p*-toluenesulfonamido)-butane (VII), m.p. 240.3–241.8°, mixed m.p. 240.6–242.0°, with *meso*-2,3-bis-(N-ethyl-*p*-toluenesulfonamido)-butane, m.p. 241.8–243.3°, from the tosylation of *meso*-2,3-bisethylaminobutane. Since a Walden inversion is proven by the *erythro*-configuration, the compound must belong to the D-family.

The (+)-3-ethylamino-2-butanol from D(+)-*trans*-2,3-epoxybutane and ethylamine is L(+)-*erythro*-3-ethylamino-2-butanol by relationship with L(+)-*erythro*-3-diethylamino-2-butanol of known configuration, $[\alpha]^{25}D$ +95.5°. The hydrochloride of this had m.p. 130.4–131.2°. The (+)-3-diethylamino-2-butanol from monoethylation of (+)-3-ethylamino-2-butanol had $[\alpha]^{25}D$ +91.8°. Its hydrochloride had m.p. 130.2–131.2°, mixed m.p. with authentic sample, 130.3–131.1°.

Derivatives.—Diacetyl and ditosyl derivatives are prepared as previously described[5] except that triethylamine usually replaces pyridine. Darkening is much less, and during tosylation triethylammonium chloride usually crystallizes out. With imines this prevents any replacement reaction by chloride ion. In the preparation of *p*-nitrobenzoyl derivatives, *p*-nitrobenzoic acid is removed with aqueous sodium carbonate. The hydrochlorides are prepared by the addition of 2 *M* hydrogen chloride in absolute ether to a cold solution of the base in absolute ether. The salt precipitates. The oxalates are prepared by mixing ether solutions of the base and of anhydrous oxalic acid in equivalent amounts. The salt separates immediately, essentially quantitatively and quite pure.[25]

Zinc Chloride Complex.—To a solution of 0.034 g. (0.00024 mole) of D(−)-*threo*-2,3-bis-(ethylamino)-butane in 2.0 ml. of 95% ethanol (α −1.63°) was added 0.10 ml. of 2.5 *M* zinc chloride (0.00025 mole) in 95% ethanol. Crystallization occurred almost immediately. The mixture stood overnight, the mother liquor (α −0.25°) was removed. The crystals were washed with two 0.5-ml. portions of 95% ethanol and dried; weight of product, 0.0426 g. (0.00015 mole) of colorless prisms, soluble in N,N-dimethylformamide and dilute nitric acid, essentially insoluble in water and most organic solvents.

(25) M. G. Ettlinger, THIS JOURNAL, **72**, 4792 (1950).

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Polycarboxylic Esters as Mesylation Products of Phenolic Acids[1,2]

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Reaction of several hydroxybenzoic acids with methanesulfonyl chloride in pyridine has given complex products containing carboxylic esters, and in no instance was the methanesulfonic ester of the phenolic acid an isolable product. Trisalicylide was isolated as a crystalline mesylation product of salicylic acid.

The reaction of phenolic compounds with aromatic[3] and aliphatic[4] sulfonyl chlorides in pyridine to give sulfonic esters is well known. The nature of the products from phenolic acids in this reaction, however, has not been reported previously, although benzenesulfonic esters have been obtained in certain instances by reaction of benzenesulfonyl chloride with the phenolic acid in aqueous alkali.[5] The present paper demonstrates clearly that phenolic acids do not give simple sulfonic esters upon mesylation[6] in pyridine but instead complex products which contain polycarboxylic esters.

In Table I are given certain properties of the crude, water-insoluble mesylation products studied. The wide melting ranges are in distinct contrast to the sharp melting points usually observed for even crude mesylation products of simple phenols.[4] The slight solubility of all crude products in dilute sodium bicarbonate solution precludes the possibility that they are the simple mesyloxy acid, and this has been confirmed in the case of the monohydroxybenzoic acids by synthesis and characterization of the mesyloxy acid. Acidification of the bicarbonate extracts gave materials which melted over wide ranges. The infrared absorption spectra of all products show a prominent band in the region 1732–1755 cm.$^{-1}$, which is attributed to the presence of ester carbonyl groups.[7] A band in the vicinity of 1690 cm.$^{-1}$ is considered evidence for a carboxyl group in the mesylation products of *m*- and *p*-hydroxybenzoic and of 3,5-diiodo-4-hydroxybenzoic acids.[7] Definite bands in the latter

TABLE I

PROPERTIES OF CRUDE MESYLATION PRODUCTS

Phenolic acid reacted	Melting range, °C.	% soln., 5% $NaHCO_3$	Ester C=O, cm.$^{-1}$[a]	Sulfur, %
p-Hydroxybenzoic	175–250	8	1740	4.29[b]
m-Hydroxybenzoic	115–140	8	1732	3.90[b]
Salicylic	140–175	<1	1739	0.43[b]
3,5-Diiodo-4-hydroxybenzoic	>285	9	1743	0.78[c,d]
Gallic	110–250	2	1755	15.86[e,f]

[a] In Nujol mull. [b] Mesyloxybenzoic acids contain 14.83% S. [c] Mesyloxy acid contains 6.85% S. [d] 0.43% N present. [e] Trimesyloxy acid contains 23.78% S. [f] 1.66% N present.

(1) Taken in part from the M.S. Theses of Donald N. Thatcher, University of Nebraska, 1952, and Charles H. Hayes, University of Nebraska, 1955.

(2) Presented in part at the 16th Midwest Regional Meeting of the American Chemical Society, Omaha, Nebr., November 4, 1954; see Abstracts of Papers, p. 52.

(3) For leading references see (a) R. S. Tipson, *J. Org. Chem.*, **9**, 235 (1944); (b) R. S. Tipson, *Adv. in Carbohydrate Chem.*, **8**, 108 (1953); (c) D. D. Reynolds and W. O. Kenyon, THIS JOURNAL, **72**, 1597 (1950), and preceding papers.

(4) For leading references to mesyl esters, see J. H. Looker, *J. Org. Chem.*, **17**, 510 (1952).

(5) The benzenesulfonic ester of salicylic acid has been prepared thus by M. Georgesco, *Bul. soc. Romane Stiinte*, **8**, 668 (1899–1900); *Chem. Zentr.*, **71**, **I**, 543 (1900). There is a report that mesyl chloride does not appear to react to any extent with salicylic acid in 1 *N* sodium hydroxide: B. C. Saunders, G. J. Stacey and I. G. E. Wilding, *Biochem. J.*, **36**, 374 (1942).

(6) Mesyl (methanesulfonyl or methylsulfonyl) denotes the CH_3SO_2– group, mesyloxy (methane- or methylsulfonoxy, or methane- or methylsulfonyloxy) the CH_3SO_3– group, and mesylation a reaction with mesyl (methanesulfonyl) chloride; see reference 3b, p. 109.

(7) F. A. Miller in "Organic Chemistry," Vol. III, edited by H. Gilman, John Wiley and Sons, Inc., New York, N. Y., 1953, pp. 140–141, 143–150.