[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, ILLINOIS INSTITUTE OF TECHNOLOGY]

Cyclohexenimine (7-Azabicyclo[4.1.0]heptane) and the Stereochemistry of Ethylenimine Ring-closure and Opening[1]

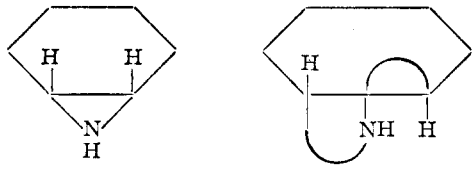
BY OLDEN E. PARIS AND PAUL E. FANTA[2]

RECEIVED NOVEMBER 28, 1951

Cyclohexenimine has been prepared by the treatment of *d,l-trans*-2-aminocyclohexanol with sulfuric acid to form a *trans*-sulfate ester, which in turn was cyclized by treatment with sodium hydroxide. The imine was characterized by the preparation of a number of derivatives not involving the opening of the three-membered ring. The imine ring was readily opened by hydrolysis in the presence of perchloric acid to form the *trans*-aminoalcohol and by treatment with dry hydrogen chloride in ether to give the *trans*-chloroamine. The ring-closure and opening reactions of cyclohexenimine have thus been shown to occur with inversion at the substituted carbon atom.

The stereochemistry of the formation and opening of the three-membered ring in cyclohexene oxide has been the object of detailed study.[3] The six- and three-membered rings are capable of fusion only in the *cis*-configuration; and the oxide is produced by dehydrohalogenation only of the *trans*-chlorohydrin, so that the ring closure must occur with Walden inversion. Furthermore, opening of the ring also has been shown to occur with inversion.

We have found that the formation and ring-opening reactions of cyclohexenimine are stereochemically analogous to the corresponding reactions of cyclohexene oxide.[4] From a consideration of models, it is evident that cyclohexenimine also can exist only in the *cis* and not in the prohibitively strained *trans* configuration.



cis *trans* (impossible)

Cyclohexenimine was prepared by the general method of Wenker,[5] *i.e.*, the *trans*-aminoalcohol I was heated with sulfuric acid to produce the sulfate ester II (with retention of configuration)[6] which in turn was cyclized with sodium hydroxide. The ring-closure is considered to occur with inversion at the carbon undergoing nucleophilic displacement as depicted by formulas III → IV → V. The imine (V) is a colorless liquid having a strong, unpleasant ammoniacal odor.

Hydrolysis of the *trans*-sulfate ester II by heating with dilute hydrochloric acid gave the *trans*-amino alcohol I,[7] showing that the reaction occurred by cleavage of the sulfur–oxygen bond with retention of configuration at the carbon atom.

The same amino alcohol was obtained by the hydrolysis of cyclohexenimine in hot, dilute perchloric acid. This reaction undoubtedly occurred through the formation of the immonium ion (as in formula IV), followed by nucleophilic displacement by water at one of the bridge carbon atoms.

Ring-opening of the imine with dry hydrogen chloride in ether likewise occurred with inversion, to give *d,l-trans*-2-chlorocyclohexylamine (VI). This compound was isolated but not characterized by analysis. On standing at room temperature for several days, it partly decomposed to form a deposit of the crystalline hydrochloride, VII. On treatment with aqueous sodium hydroxide and benzoyl chloride both VI and VII yielded the previously reported[8] *d,l-trans*-2-benzamidocyclohexyl chloride (VIII).

Treatment of *d,l-trans*-2-aminocyclohexanol hydrochloride, (IX) with phosphorus pentachloride gave a *d,l*-2-chlorocyclohexylamine (X) which has been assigned the *cis*-configuration.[9] The halogen atom of this molecule was rather inert, and was not removed by long refluxing with silver acetate.[9a] When X was refluxed with aqueous sodium hydroxide, both dehydrohalogenation and deamination occurred and cyclohexanone was formed. This reaction probably occurred through a *trans*-

(1) The work reported in this paper was supported by a Frederick Gardner Cottrell grant of the Research Corporation and was presented in part before the Division of Organic Chemistry at the 117th National Meeting of the American Chemical Society in Philadelphia, Penna., April 12, 1950.

(2) To whom inquiries regarding this article should be sent.

(3) For a general discussion of ethylene oxide chemistry see S. Winstein and R. B. Henderson in "Heterocyclic Compounds," Vol. I, edited by R. C. Elderfield, John Wiley and Sons, Inc., New York, N. Y., 1950, p. 1.

(4) During the preparation of this manuscript, F. H. Dickey, W. Fickett and H. J. Lucas presented a paper before the XIIth International Congress of Pure and Applied Chemistry, New York, N. Y., September 11, 1951, in which they established that one Walden inversion is associated with the ring openings and closings of 2,3-dimethylethylenimine. Their paper was subsequently published in THIS JOURNAL, **74**, 944 (1952), and should be consulted for a thorough discussion of the analogy between the openings and closings of epoxide and ethylenimine rings.

(5) A recent review of the chemistry of ethylenimine has been given by J. S. Fruton in "Heterocyclic Compounds," Vol. I, edited by R. C. Elderfield, John Wiley and Sons, Inc., New York, N. Y., 1950, p. 61.

(6) N. C. Deno and M. S. Newman (THIS JOURNAL, **72**, 3852 (1950)) have shown that the esterification of sulfuric acid by primary and secondary alcohols to form alkyl acid sulfates proceeds predominantly by a bimolecular displacement reaction with no alkyl-oxygen fission.

(7) S. Lieberman, L. B. Hariton and D. K. Fukushima (*ibid.*, **70**, 1427 (1948)) have shown that secondary alkyl sulfates such as cholesterol sulfate, are hydrolyzed by aqueous acid solution with retention of configuration indicating that these compounds react by a rupture of the S–OR linkage.

(8) W. S. Johnson and E. N. Schubert, *ibid.*, **72**, 2187 (1950).

(9) (a) G. E. McCasland, R. K. Clark, Jr., and H. E. Carter (*ibid.*, **71**, 637 (1949)) point out that in the treatment of *d,l-trans*-2-aminocyclohexanol hydrochloride with phosphorus pentachloride the normal displacement (with inversion) of hydroxyl by chlorine might be expected to result, since participation by the neighboring positively charged ammonium ion seems improbable. (b) The formation of cyclohexanone by the fusion of *cis*-2-chlorocyclohexylamine with ethylmagnesium bromide (presumably followed by treatment with water) has been reported by M. Mousseron and F. Winternitz, *Compt. rend.*, **221**, 201 (1945). They present evidence for the intermediate formation of an enamine structure corresponding to XI in the hydrolysis of certain substituted 2-chlorocycloalkylamines.

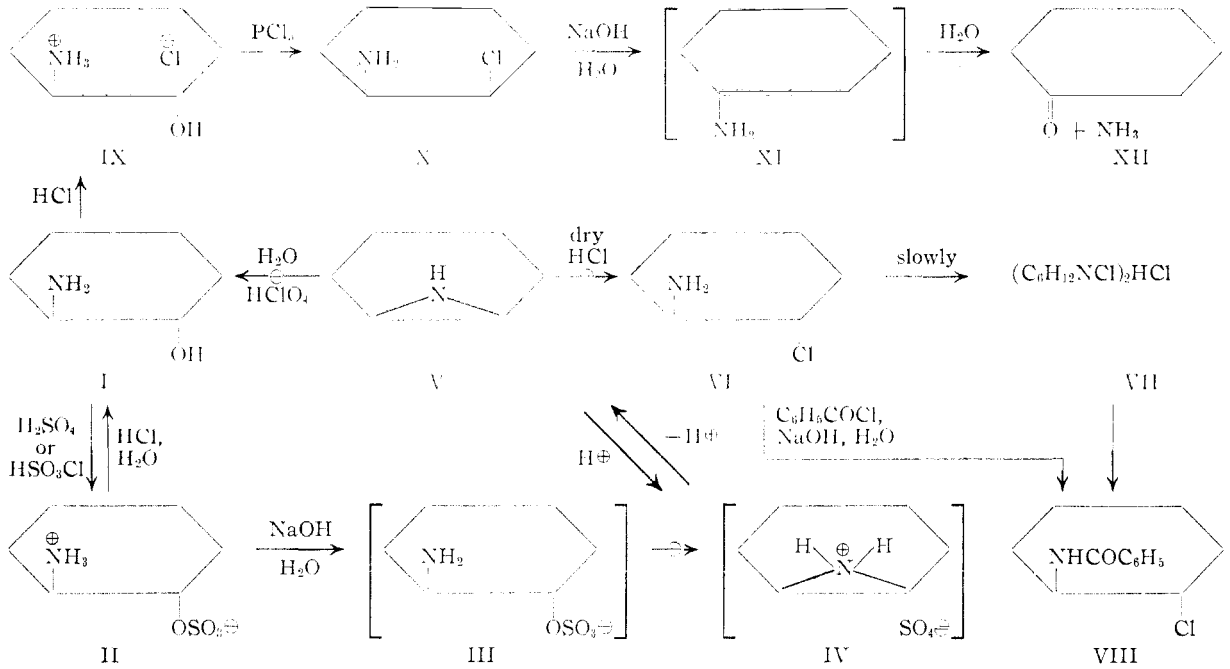
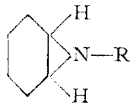


Fig. 1.— ⟶ reactions which occur without inversion; —⊖⟶ reactions which occur with inversion; substances not isolated are in brackets.

elimination of hydrogen chloride to yield 1-aminocyclohexene (XI) which then tautomerized and was hydrolyzed to the ketone.[9b] The result is exactly analogous to the reaction of *cis*-2-chlorocyclohexanol with sodium hydroxide, which produces cyclohexanone but no cyclohexene oxide.[3]

It was hoped that the Wenker synthesis of cyclohexenimine could be improved by the use of *d,l-trans*-2-aminocyclohexyl *p*-toluenesulfonate (XIII) in place of the sulfate ester II. However, attempts to prepare XIII by the treatment of *d,l-trans*-2-aminocyclohexanol with *p*-toluenesulfonyl chloride in pyridine resulted in the formation of *d,l-trans*-2-*p*-toluenesulfonamidocyclohexyl *p*-toluenesulfonate (XIV). Treatment of XIV with hot, concentrated sodium hydroxide solution did not yield cyclohexenimine.

Cyclohexenimine was further characterized by the preparation of a number of derivatives which did not involve the opening of the three-membered ring. It reacted with phenyl isothiocyanate to yield the phenylthiourea, Va. On refluxing with acrylonitrile, cyclohexenimine formed a β-cyanoethyl derivative, Vb, which was reduced catalytically to the γ-aminopropyl derivative, Vc. The latter compound was not analyzed, but was converted to a crystalline benzenesulfonamide, Vd. The *n*-butyl derivative, Ve, was obtained by refluxing cyclohexenimine with a mixture of *n*-butyl bromide and sodium bicarbonate.



V, R = H
Va, R = $CSNHC_6H_5$
Vb, R = CH_2CH_2CN
Vc, R = $CH_2CH_2CH_2NH_2$
Vd, R = $CH_2CH_2CH_2NHSO_2C_6H_5$
Ve, R = $CH_2CH_2CH_2CH_3$

In the present work there was no indication of the presence of stereoisomers of the predicted type[10] in which the N-substituent may be either *cis* or *trans* to the angular hydrogen atoms.

Infrared Spectra.—The infrared absorption spectrum of cyclohexenimine, Fig. 2, clearly shows a band corresponding to the NH stretching frequency at 3.1 μ which is absent in the spectrum of the N-butyl derivative, Fig. 3.

Toxicity of Cyclohexenimine.—Early in the course of this research, one of the authors (O.E.P.) inhaled a high concentration of cyclohexenimine vapor after accidental breakage of a distillation apparatus. Headache, chills and a fever lasting about 30 hours resulted. Thereafter an increasingly marked sensitivity to traces of the material was observed. Even careful manipulation of small amounts of the compound generally resulted in an itching rash and blisters on the hands and face. No abnormality of the blood count accompanied these symptoms.[11] The senior author (P.E.F.) experienced no such hypersensitivity after exposure to low concentrations of the vapor.

Experimental[12]

d,l-trans-**2-Aminocyclohexanol** (I) was prepared by the procedure described in the literature.[13] See reference 9 for a discussion of the configuration.

d,l-trans-**2-Aminocyclohexanol Sulfate.**—A solution of 3.45 g. (0.03 mole) of *d,l-trans*-2-aminocyclohexanol in 10

(10) J. F. Kincaid and F. C. Henriques, Jr., THIS JOURNAL, **62**, 1474 (1940).

(11) G. D. Jones, A. Langsjoen, M. M. C. Neumann and J. Zomlefer, *J. Org. Chem.*, **9**, 125 (1944), reported that continued inhalation of ethylenimine vapor resulted in a prolonged reduction of the white corpuscle and platelet count.

(12) Analyses marked (S.M.N.) are by S. M. Nagy of Massachusetts Institute of Technology. All other analyses are by Micro-Tech Laboratories, Skokie, Illinois. Melting points are uncorrected unless otherwise indicated. Infrared absorption spectra were determined by Samuel P. Sadtler and Sons, Inc., Philadelphia, Pennsylvania.

(13) N. A. B. Wilson and J. Read, *J. Chem. Soc.*, 1269 (1935).

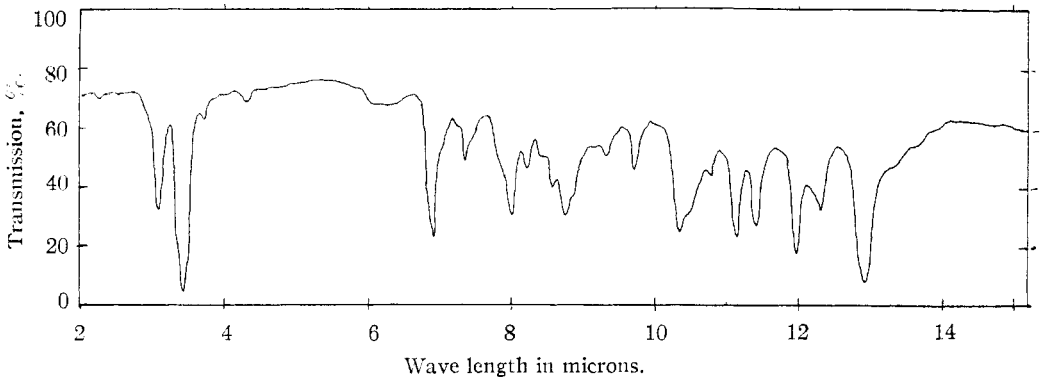


Fig. 2.—Infrared absorption spectrum of cyclohexenimine (V); pure liquid, 0.01 mm. thickness.

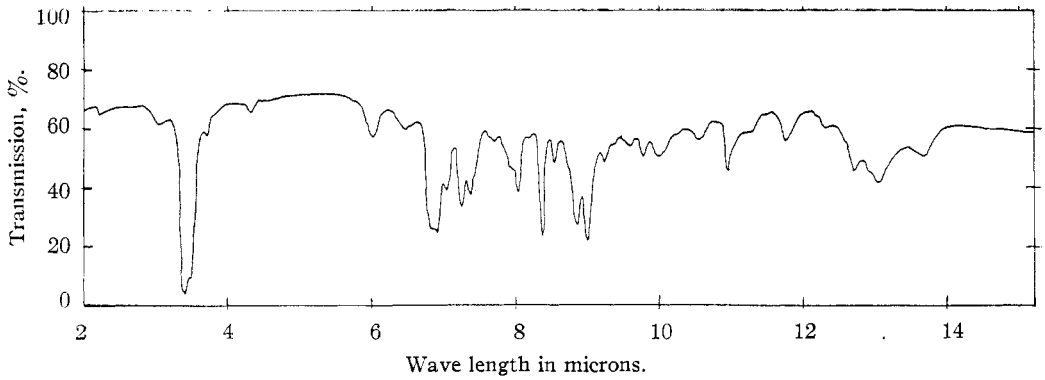


Fig. 3.—Infrared absorption spectrum of *n*-butylcyclohexenimine (Ve); pure liquid, 0.01 mm. thickness.

ml. of water was cooled and mixed with 3.10 g. (0.03 mole) of 95% sulfuric acid. Evaporation on the steam-bath at 20 mm. pressure gave a white, solid residue which was recrystallized from 95% alcohol. It formed lustrous, white plates which melted at 288.5–289.5° with vigorous decomposition.

Anal. (S.M.N.) Calcd. for $(C_6H_{13}ON)_2H_2SO_4$: C, 43.88; H, 8.59; S, 9.76. Found: C, 43.74; H, 8.59; S, 9.71.

An aqueous solution of this material gave an immediate precipitate with barium chloride solution. This experiment shows that a relatively higher temperature and low pressure are required for the formation of the sulfate ester in the first step of the Wenker synthesis.

***d,l-trans*-2-Aminocyclohexylsulfuric Acid (II).**—The salt described above was heated for two hours at 230° and 0.1 mm. pressure. The product was a hard, gray solid which was recrystallized from 50% aqueous alcohol. The pure ester was obtained in the form of fine, white, granular crystals which melted at 304–305° with decomposition.

Anal. (S.M.N.) Calcd. for $C_6H_{13}O_4NS$: C, 36.91; H, 6.71. Found: C, 37.21; H, 6.84.

An aqueous solution of the pure material gave no precipitate with barium chloride.

Acid Hydrolysis of *d,l-trans*-2-Aminocyclohexylsulfuric Acid.—A solution of 1.95 g. of the recrystallized ester and 2.50 g. of barium chloride dihydrate in 30 ml. of water was heated to the boiling point. The solution remained clear. The addition of 10 ml. of concentrated hydrochloric acid immediately caused a turbidity. After heating for two hours on the steam-bath the solution was filtered and the filtrate was made basic by the addition of an excess of solid sodium hydroxide. The resulting solution was extracted with two 50-ml. portions of ether. Evaporation of the ether extracts gave a 70% yield of *d,l-trans*-2-aminocyclohexanol, m.p. 68–69°, mixed m.p. with an authentic sample unchanged. The melting point of a mixture of approximately equal amounts of *d,l-cis*- and *d,l-trans*-2-aminocyclohexanol was depressed nearly 20°.[14]

Cyclohexenimine (7-Azabicyclo[4.1.0]heptane) (V). Procedure A.—Seventy grams of *d,l-trans*-2-aminocyclohexanol was converted to *d,l-trans*-2-aminocyclohexylsulfuric acid by the procedure described above. To minimize charring in large scale runs, 5% less than the theoretical quantity of sulfuric acid was used and the initial mixing of acid and aminoalcohol was carried out with good cooling and stirring. The hard cake of crude product was refluxed for two hours with 400 ml. of 20% aqueous sodium hydroxide solution. A dark, oily layer separated and was transferred to a distilling flask. The fraction boiling at 100–200° was dried over sodium hydroxide pellets and redistilled through a short column. The yield was 17.8 g. (28%) of colorless liquid having a strong, unpleasant ammoniacal odor; b.p. 149–150°; $n^{20}D$ 1.4800; d^{27}_{27} 0.9484. On standing in the refrigerator it formed colorless prisms, m.p. 20–21°.

Anal. Calcd. for $C_6H_{11}N$: C, 74.17; H, 11.42; N, 14.42. Found: C, 73.94; H, 11.23; N, 14.28.

The phenylthiourea was prepared by the usual procedure.[15] Upon recrystallization from alcohol it formed white plates which melted at 180°.

Anal. Calcd. for $C_{13}H_{16}N_2S$: C, 67.20; H, 6.94. Found: C, 67.17; H, 6.88.

Procedure B.—A solution of 98 g. of *d,l-trans*-2-aminocyclohexanol in 500 ml. of dry carbon tetrachloride was stirred with efficient cooling while 60 ml. (one equivalent) of chlorosulfonic acid was added dropwise during the course of two hours. The solvent was removed by decantation and the gummy, white precipitate was dissolved (caution) in 500 ml. of 20% aqueous sodium hydroxide solution. The solution was refluxed for two hours and then steam distilled. The distillate was saturated with sodium hydroxide and the non-aqueous phase which separated was dried over sodium hydroxide pellets and fractionally distilled, giving 28.5 g. (35% yield) of cyclohexenimine, b.p. 60–70° (30 mm.), $n^{24}D$ 1.4804.

Acid-catalyzed Hydrolysis of Cyclohexenimine.—A solution of 1.00 g. of cyclohexenimine and 4 ml. of 72% per-

(14) The *d,l-cis*-2-aminocyclohexanol used in this determination was prepared from a sample of the hydrochloride furnished by Dr. G. E. McCasland of the University of Toronto.

(15) R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," 3rd Edition, John Wiley and Sons, Inc., New York, N. Y., 1948, p. 179.

chloric acid in 40 ml. of water was heated on the steam-bath for two hours. The solution was made basic by the addition of an excess of solid sodium hydroxide and extracted with three 20-ml. portions of ether. Evaporation of the ether extracts gave a 52% yield of *d,l-trans*-2-aminocyclohexanol, which was identified by melting point and mixed melting point with an authentic sample.

d,l-trans-**2-Chlorocyclohexylamine (VI).**—Dry hydrogen chloride was passed into a cold solution of 10 g. of cyclohexenimine in 100 ml. of dry ether until no further precipitation occurred. The solid formed is presumably the hydrochloride of VI. An excess of cold 10% aqueous sodium hydroxide solution was added to the ether suspension and the mixture was shaken thoroughly. The ethereal layer was dried briefly over solid sodium hydroxide and distilled, giving a colorless oil; b.p. 69° (12 mm.); $n^{25}D$ 1.4850. Upon shaking with benzoyl chloride and excess aqueous sodium hydroxide solution, the freshly distilled material was converted to the previously reported *d,l-trans*-2-**benzamidocyclohexyl chloride (VIII).**[8,16]

Compound VII.—No analytical data were obtained for VI, because on standing at room temperature for a few days the clear liquid changed to a mixture of colorless crystals and oil. The crystalline material was collected on a filter and washed with ether. Its analysis corresponds to a salt containing two molecules of VI and one molecule of hydrogen chloride.

Anal. Calcd. for $(C_6H_{12}NCl)_2HCl$: C, 47.45; H, 8.30; N, 9.23. Found: C, 47.31; H, 8.76; N, 9.44.

On treatment with benzoyl chloride and aqueous sodium hydroxide VII also yielded *d,l-trans*-2-benzamidocyclohexyl chloride.

d,l-cis-**2-Chlorocyclohexylamine (X)** was prepared by the procedure described in the literature.[17]

Alkaline Hydrolysis of *d,l-cis*-2-Chlorocyclohexylamine.—A mixture of two grams of the chloroamine and 20 ml. of 33% aqueous potassium hydroxide was refluxed for 10 hours; at the end of this time the odor of ammonia was no longer noted at the top of the condenser. The non-aqueous phase was removed and dissolved in a small amount of alcohol, to which was added an ether extract of the aqueous phase of the reaction mixture. The ether was boiled off and the residual alcoholic solution was treated with an excess of 2,4-dinitrophenylhydrazine in 2 *N* hydrochloric acid. Two and fifteen-hundreths grams of slightly impure cyclohexanone 2,4-dinitrophenylhydrazone was obtained, m.p. 153–155°, mixed m.p. with an authentic sample melting at 157° was 155–156°. This represents the conversion of at least 52% of the chloroamine to cyclohexanone.

N-(β-Cyanoethyl)-cyclohexenimine or 7-(2-Cyanoethyl)-7-azabicyclo[4.1.0]heptane (Vb).—A mixture of 10.5 ml. of cyclohexenimine and 30 ml. of acrylonitrile was refluxed for four hours and fractionally distilled under vacuum, giving 12.8 g. (82%) of colorless liquid; b.p. 132–133.5° (25 mm.); $n^{20}D$ 1.4762; d^{20}_{20} 0.9796.

Anal. Calcd. for $C_9H_{14}N_2$: N, 18.65. Found: N, 18.64.

Addition of a few drops of Vb to a saturated alcoholic solution of picrolonic acid gave a yellow precipitate of the **picrolonate,** which melted at 136° without recrystallization.

Anal. Calcd. for $C_{19}H_{22}O_5N_6$: C, 55.06; H, 5.35. Found: C, 55.25; H, 5.48.

N-(γ-Aminopropyl)-cyclohexenimine or 7-(3-Aminopropyl)-7-azabicyclo[4.1.0] heptane (Vc) was obtained in 55% yield by the catalytic reduction of Vb below 90°, using Raney nickel catalyst and alcohol saturated with ammonia as solvent. The amine boiled at 105° (45 mm.); $n^{20}D$ 1.4859. The sample was not analyzed, but was converted by the usual procedure[18] to the **benzenesulfonamide (Vd)** which melted at 103–104° after crystallization from alcohol.

Anal. Calcd. for $C_{15}H_{22}O_2N_2S$: C, 61.19; H, 7.53. Found: C, 61.03; H, 7.41.

N-*n*-Butylcyclohexenimine or 7-*n*-Butyl-7-azabicyclo[4.1.0]heptane (Ve).—A mixture of 4 ml. of cyclohexenimine, 40 ml. of *n*-butyl bromide and 5 g. of sodium bicarbonate was refluxed for five hours. The solid was removed by decantation and the liquid was fractionally distilled. About 2 g. of product was obtained, b.p. 100–102° (50 mm.); $n^{23}D$ 1.4588. The sample was not analyzed, but addition of a few drops of it to a saturated alcoholic solution of picric acid yielded an analytically pure **picrate,** m.p. 140–141° without recrystallization.

Anal. Calcd. for $C_{16}H_{22}O_7N_4$: C, 50.26; H, 5.80; N, 14.70. Found: C, 50.14; H, 5.85; N, 14.70.

d,l-trans-**2-*p*-Toluenesulfonamidocyclohexyl *p*-Toluenesulfonate (XIV).**—Treatment of *d,l-trans*-2-aminocyclohexanol with two equivalents of *p*-toluenesulfonyl chloride in pyridine, followed by washing with dilute sulfuric acid and recrystallization from benzene–ligroin yielded a product melting at 136–140°. A slightly less pure sample of the same material was obtained when one equivalent of *p*-toluenesulfonyl chloride was used in the reaction. An analytically pure sample, m.p. 149–151°, was obtained by further recrystallization from benzene–ligroin.

Anal. Calcd. for $C_{20}H_{26}O_5NS_2$: C, 56.71; H, 5.95; S, 15.14. Found: C, 56.52; H, 5.91; S, 15.03.

CHICAGO 16, ILLINOIS

(16) The identification by determination of melting point and mixed melting point with an authentic sample was carried out at the University of Wisconsin under the supervision of Dr. W. S. Johnson.

(17) A. E. Osterberg and E. C. Kendall, THIS JOURNAL, **42**, 2616 (1920).

(18) See reference 15, p. 178.