Optically Active *trans*-Cyclooctene from an Asymmetric Hofmann Elimination.

Resolution and Hofmann Degradation of N-*n*-Butyl-N-isobutyl-N-methylcyclooctylammonium Hydroxide[1a]

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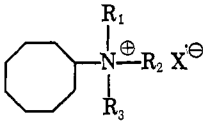
Abstract: Optically active *trans*-cyclooctene, $[\alpha]^{25}\text{D}$ $-6.28°$, was obtained in 1.4% optical yield from Hofmann degradation of (−)-N-*n*-butyl-N-isobutyl-N-methylcyclooctylammonium hydroxide, which was prepared by fractional crystallization of the corresponding (+)-10-camphorsulfonate. When (−)-N-*n*-butyl-N-isobutyl-N-methylcyclooctylammonium perchlorate was treated with potassium amide in liquid ammonia, (+)-*trans*-cyclooctene, $[\alpha]^{25}\text{D}$ $+10.87°$, was obtained in 2.4% optical yield. The optical purity of the resolved quaternary ammonium cation used in both of these decompositions was determined by the isotopic dilution method using nitrogen-15 as the isotopic label. Isolation of the racemic ^{15}N-enriched quaternary ammonium cation as its tetraphenylboron salt and determination of the isotopic dilution by mass spectrometry showed that the optical purity of the resolved material was 99.6% and that the degree of asymmetric induction obtained represented maximum values.

The molecular asymmetry of *trans*-cyclooctene has recently been demonstrated by the resolution of its two enantiomers *via* a platinum complex containing an optically active amine.[2] This resolution engendered interest in the possibility of preparing optically active *trans*-cyclooctene by an asymmetric Hofmann elimination of a resolved quaternary ammonium hydroxide of the type **1** in which the center of asymmetry is the tetravalent nitrogen atom. Several quaternary ammonium salts of the type $R_1R_2R_3R_4N^+X^-$ have been resolved.[3,4]



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1a, $R_1 = R_2 = R_3 = CH_3$; $X = OH^-$
b, $R_1 = CH_3$; $R_2 = CH_2Ph$; $R_3 = CH_2CH(CH_3)_2$; $X = OH^-$
c, $R_1 = CH_3$; $R_2 = CH_2CH(CH_3)_2$; $R_3 = CH_2(CH_2)_2CH_3$; $X = OH^-$
d, $R_1 = CH_3$; $R_2 = CH_2CH(CH_3)_2$; $R_3 = CH_2(CH_2)_2CH_3$; $X = I^-$
e, $R_1 = CH_3$; $R_2 = CH_2CH(CH_3)_2$; $R_3 = CH_2(CH_2)_2CH_3$; $X = ClO_4^-$
f, $R_1 = CH_3$; $R_2 = CH_2CH(CH_3)_2$; $R_3 = CH_2(CH_2)_2CH_3$; $X = BPh_4^-$

The preparation of optically active *cis,trans*-1,5-cyclooctadiene by an asymmetric Hofmann degradation of resolved N,N-dimethyl-*cis*-4-cycloocten-1-ylamine has been reported.[5] The resolution[6] of *cis,trans*-1,5-cyclooctadiene *via* a platinum complex containing an optically active amine has demonstrated that the asymmetric synthesis[5] afforded one enantiomer in about 80% optical purity.

Hofmann degradation of N,N,N-trimethylcyclooctylammonium hydroxide (**1a**) afforded an 89% yield of *trans*- and *cis*-cyclooctene in a 60:40 ratio.[7] However, the ratio of *cis*- and *trans*-cyclooctenes obtained by Hofmann degradation of N-cyclooctylammonium hydroxides has been found to depend on the substituents on the tetravalent nitrogen atom.[8] For instance, the pyrolysis of N-benzyl-N-isobutyl-N-methylcyclooctylammonium hydroxide (**1b**) gave isobutylene and *trans*- and *cis*-cyclooctenes in a ratio of 14:86. In the case of the quaternary ammonium hydroxide **1b**, thermal decomposition occurred at lower temperatures (80–90°) than the thermal decomposition of N,N,N-trimethylcyclooctylammonium hydroxide (105–120°). Thus the change in the ratio of the *cis*- and *trans*-cyclooctene obtained must have been due to different conformations of the cyclooctane ring rather than to thermal isomerization of the *trans*-cyclooctene first obtained to *cis*-cyclooctene.

After much exploratory work,[8] N-*n*-butyl-N-isobutyl-N-methylcyclooctylammonium hydroxide (**1c**) was found to be the best suited of the bases examined for the resolution and subsequent Hofmann elimination. The resolution of N-benzyl-N-isobutyl-N-methylcyclooctylammonium hydroxide (**1b**) could not be accomplished with a variety of optically active acids.

The preparation of N-*n*-butyl-N-isobutyl-N-methylcyclooctylammonium iodide (**1d**) is outlined below. N-Isobutylcyclooctylamine (**3**) was prepared from cyclooctanone (**2**) by condensation with isobutylamine and subsequent catalytic hydrogenation of the intermediate Schiff base. Acylation of the amine **3** with *n*-butyryl chloride and reduction of the resulting amide with lithium aluminum hydride gave N-*n*-butyl-N-isobutylcyclooctylamine (**4**) which was treated with methyl iodide to form N-*n*-butyl-N-isobutyl-N-methylcyclooctylammonium iodide (**1d**). The structure of

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(1) (a) Supported in part by Research Grants NSF-GP-1587 of the National Science Foundation and No. DA-ARO(D)31-124-G404 of the Army Research Office (Durham). (b) Deceased June 4, 1966. (c) To whom inquiries should be addressed: Central Research Department, E. I. du Pont de Nemours and Co., Wilmington, Del. 19898.

(2) A. C. Cope, C. R. Ganellin, H. W. Johnson, Jr., T. V. Van Auken, and H. J. S. Winkler, *J. Am. Chem. Soc.*, **85**, 3276 (1963).

(3) W. J. Pope and S. J. Peachy, *J. Chem. Soc. Trans.*, **75**, 1127 (1899).

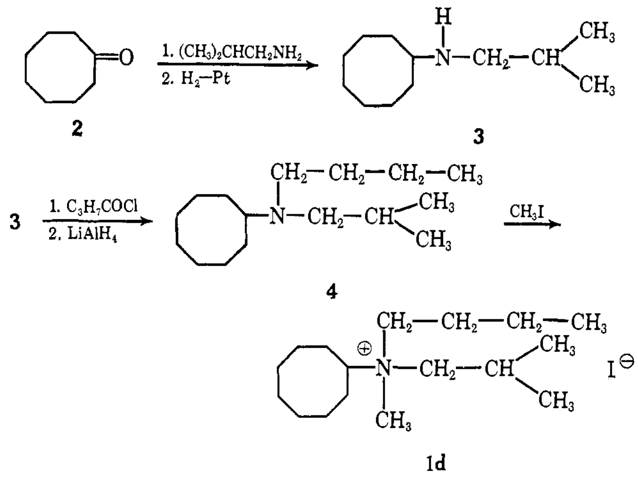
(4) H. O. Jones, *J. Chem. Soc.*, **83**, 1400 (1903).

(5) A. C. Cope, C. F. Howell, and A. Knowles, *J. Am. Chem. Soc.*, **84**, 3190 (1962).

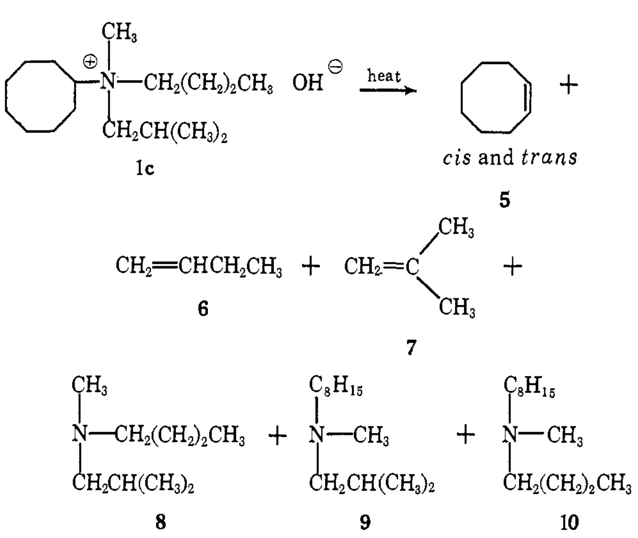
(6) (a) A. C. Cope, C. R. Ganellin, and H. W. Johnson, Jr., *ibid.*, **84**, 3191 (1962); (b) A. C. Cope, J. K. Hecht, H. W. Johnson, Jr., H. Keller, and H. J. S. Winkler, *ibid.*, in press.

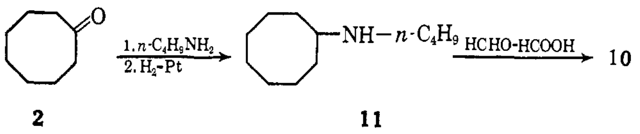
(7) A. C. Cope, R. A. Pike, and C. F. Spencer, *ibid.*, **75**, 3212 (1953).

(8) A. C. Cope, K. Banholzer, F. N. Jones, and H. Keller *ibid.*, **88**, 4700 (1966).



the methiodide **1d** was proved by Hofmann degradation of the corresponding hydroxide **1c**. The methiodide **1d** was converted to the hydroxide **1c** either by ion-exchange chromatography on Amberlite IRA-400 resin (OH form) or by treatment with a suspension of silver oxide in water. The hydroxide was concentrated to a syrup and decomposed at 55–80° and 0.5 mm. *cis*- and *trans*-cyclooctenes (**5**) were obtained in a 34:66 ratio as determined by gas chromatographic analysis. *trans*-Cyclooctene was isolated in 37% yield; its infrared spectrum, refractive index, and gas chromatographic retention time were identical with those of an authentic sample. *cis*-Cyclooctene was obtained in 19% yield and was identified by its gas chromatographic retention time. Butylene (**6**) and isobutylene (**7**) were not isolated. The amines **8**, **9**, and **10** were separated by preparative gas chromatography. Their molar ratio, 87.3:7.4:5.3, respectively, was calculated from the vapor phase chromatogram. The structure of amine **8** was confirmed by preparation of the known picrate and methiodide[9] and by mass spectrometry. N-Isobutyl-N-methylcyclooctylamine (**9**) was synthesized by Clarke–Eschweiler methylation of N-isobutylcyclooctylamine (**3**). Its identity with amine **9** was shown by comparison of the nuclear magnetic resonance spectra. Amine **10** was identified as N-*n*-butyl-N-methylcyclooctylamine by independent synthesis and comparison of the nuclear magnetic resonance spectra. N-*n*-Butylcyclooctylamine (**11**) was prepared by condensation of cyclooctanone (**2**) and *n*-butylamine and subsequent hydrogenation of the Schiff's base. Clarke–Eschweiler methylation of the amine **11** gave N-*n*-butyl-N-methylcyclooctylamine (**10**).





N-*n*-Butyl-N-isobutyl-N-methylcyclooctylammonium hydroxide (**1c**) was resolved by fractional crystallization of its (+)-10-camphorsulfonate. From the mixture of diastereoisomers a less soluble fraction was obtained, which was recrystallized to constant melting point and constant specific rotation. However, only a small change in the specific rotation was observed during this procedure. The more soluble fraction was obtained as an oil which could not be crystallized. The less soluble crystalline (+)-10-camphorsulfonate was converted to the corresponding N-*n*-butyl-N-isobutyl-N-methylcyclooctylammonium perchlorate (**1e**), $[\alpha]^{25}\mathrm{D}$ −1.65° (*c* 1.73, ethanol). Similar conversion of the more soluble (+)-10-camphorsulfonate (two different samples) led to perchlorates with $[\alpha]^{25}\mathrm{D}$ +0.81° (*c* 1.76, ethanol) and $[\alpha]^{25}\mathrm{D}$ +0.60° (*c* 3.18, ethanol). Samples of (+)- and (−)-N-*n*-butyl-N-isobutyl-N-methylcyclooctylammonium perchlorate (**1e**) were converted by ion-exchange chromatography on Amberlite IRA-400 resin (OH form) to the (+)- and (−)-hydroxides, respectively, which after removal of solvent were decomposed at 55–80° and 0.5–0.7 mm. The *trans*-cyclooctene formed during the reaction was isolated, and the specific rotation was determined. The results are listed in Table I. The purity of the *trans*-cyclooctene obtained from the different pyrolyses listed in Table I was determined by refractive index, infrared spectrum, and gas chromatographic analysis under conditions which separate *cis*- and *trans*-cyclooctenes. In all cases the optical activity disappeared completely when a sample of the *trans*-cyclooctene was converted to cyclooctane by catalytic hydrogenation.

The magnitude of the specific rotation of *trans*-cyclooctene obtained from perchlorate (*i.e.*, hydroxide) of the same optical purity, when decomposed thermally under nearly the same conditions, was found to depend on the amount of perchlorate (*i.e.*, hydroxide) which was decomposed. When equal amounts of the two enantiomeric perchlorates (runs 2 and 3) were decomposed *via* their hydroxides, the results were in good agreement with the expected values since the optical purity of the perchlorate used in run 3 was one-half that of the perchlorate used in run 2. Although the pyrolyses were carried out under nearly identical conditions, a longer time was required to complete the pyrolysis of the larger samples. If racemization of the quaternary base were occurring at the elevated temperatures, a change in the duration of the pyrolysis could have an effect on the optical purity of the product. No investigations were undertaken to prove the validity of this possibility or to determine what other factors may be contributing to this phenomenon. The resolved perchlorates did not undergo racemization when kept in

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(9) A. C. Cope, N. A. LeBel, H. H. Lee, and W. R. Moore, *J. Am. Chem. Soc.*, 79, 4720 (1957).

Table I. Results of Hofmann Degradations of the Resolved Perchlorates **1e**

	Perchlorate				*trans*-Cyclooctene		
Run	Amount decomposed, g	$[\alpha]^{25}D$ (EtOH), deg	% optical purity[a]	Pyrolysis conditions Temp, °C (mm)	% yield	$[\alpha]^{25}D$ (neat), deg	% induction[b]
1	4	−1.65	99.6	55–70 (0.7)	32	−5.01	1.1
2	3	−1.65	99.6	55–75 (0.5)	37.6	−6.28	1.4
3	3	+0.81	48.9	55–75 (0.55)	39	+3.04	0.7 (1.4)[c]
4	10	+0.81	48.9	60–80 (0.5)	37	+1.63	0.4 (0.7)[c]
5[d]	4	+0.60	36.3		32	−4.51	1.0 (2.7)[c]
6[d]	6	+0.60	36.3		27	−4.50	1.0 (2.7)[c]
7[d]	3.2	−1.65	99.6		33	+10.87	2.4

[a] Determined by the isotopic dilution method (see below). [b] Calculated based on $[\alpha]^{25}D$ ±458° (neat) for *trans*-cylcooctene.[1] [c] This value has been corrected for the optical purity of the starting perchlorate. [d] The perchlorate was decomposed at −40° with potassium amide in liquid ammonia.

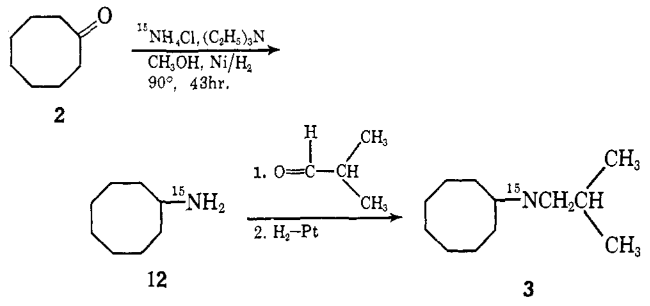
methanol solution for several days at room temperature or when recrystallized from boiling ethyl acetate or acetone–ethyl acetate. This dependence of the degree of asymmetric induction on the amount of hydroxide decomposed was circumvented when (+)- or (−)-N-*n*-butyl-N-isobutyl-N-methylcyclooctylammonium perchlorate (**1e**) was decomposed at −40° in liquid ammonia with potassium amide as base[10–12] (runs 5, 6, and 7 in Table I). Gas chromatographic analysis showed that *cis*- and *trans*-cyclooctenes were formed in a 34:66 ratio, respectively. The same ratio was observed for the thermal decomposition of N-*n*-butyl-N-isobutyl-N-methylcyclooctylammonium hydroxide (**1c**). The yield of *trans*-cyclooctene (33%) is also comparable to the yield obtained in the normal Hofmann procedure. The degree of asymmetric induction was greater than in the normal Hofmann procedure and was independent of the amount of perchlorate decomposed. However, the specific rotation of the *trans*-cyclooctene obtained was opposite in sign to that obtained when the same perchlorate (*i.e.*, hydroxide) was decomposed according to the normal Hofmann procedure. (−)-Perchlorate **1e** led to a slight excess of (−)-*trans*-cyclooctene when decomposed *via* the corresponding hydroxide according to the usual Hofmann conditions and to a slight excess of (+)-*trans*-cyclooctene when allowed to react with potassium amide in liquid ammonia. These facts indicate that the conformation of the cyclooctane ring and/or the conformation of the groups about the asymmetric nitrogen atom relative to the cyclooctane ring are different under these different reaction conditions if the mechanism is the same under these different conditions.

Determination of the Optical Purity of (−)-N-*n*-Butyl-N-isobutyl-N-methylcyclooctylammonium Perchlorate (1e) by the Isotopic Dilution Method. The degree of asymmetric induction obtained in the Hofmann degradation of (+)- and (−)-N-*n*-butyl-N-isobutyl-N-methylcyclooctylammonium perchlorates (**1e**) is dependent upon their optical purity. This was determined for (−)-N-*n*-butyl-N-isobutyl-N-methylcyclooctylammonium perchlorate (**1e**), $[\alpha]^{25}D$ −1.65°, by the isotopic dilution method[13,14] using nitrogen-15 as the isotopic label. In this method,[14] a known amount B of (−)-perchlorate **1e**, whose optical purity was to be determined, was mixed with a known amount X of racemic ^{15}N-labeled (atom % excess $^{15}N = C_0$) perchlorate of the same chemical species. From this mixture racemic material has to be isolated again by recrystallization. Depending on the degree of optical purity of the (−)-perchlorate **1e** the ^{15}N-content of the reisolated racemic material (atom % excess $^{15}N = C_\pm$) will be diluted. From the known quantities B and X and the determined values C_0 and $C_\pm$, the optical purity can be calculated by means of eq 1 and 2, and the relationship $B = R + E$, where R is the weight of racemate in B, and E is the weight of excess enantiomer in B.

$$C_\pm = \frac{1}{2}\left[\frac{(X)(C_0)}{2}\bigg/\left(E + \frac{X+R}{2}\right)\right] + \frac{1}{2}\left[\frac{(X)(C_0)}{2}\bigg/\frac{X+R}{2}\right] \quad (1)$$

$$\%\ \text{optical purity} = \frac{100E}{B} \quad (2)$$

Racemic N-*n*-butyl-N-isobutyl-N-methylcyclooctylammonium-^{15}N perchlorate (**1e**) was synthesized as



shown. Cyclooctanone (**2**) was converted to cyclooctylamine-^{15}N (**12**) by reductive amination with ammonia-^{15}N generated from ammonium-^{15}N chloride. Cyclooctylamine-^{15}N (**12**) was condensed with isobutyraldehyde; the intermediate Schiff base was converted by catalytic hydrogenation to N-isobutylcyclooctylamine-^{15}N (**3**). The preparation of N-*n*-butyl-N-isobutyl-N-methylcyclooctylammonium-^{15}N perchlorate (**1e**) was carried out as already described for the corresponding unlabeled compound.

All attempts to crystallize racemic perchlorate **1e** from a mixture of racemic perchlorate-^{15}N and (−)-perchlorate failed. Therefore a known amount of (−)-perchlorate **1e** was mixed with a known amount of the

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(10) G. Wittig and R. Polster, *Ann.*, **599**, 13 (1956); **612**, 102 (1958).

(11) G. Wittig and T. F. Burger, *ibid.*, **632**, 85 (1960).

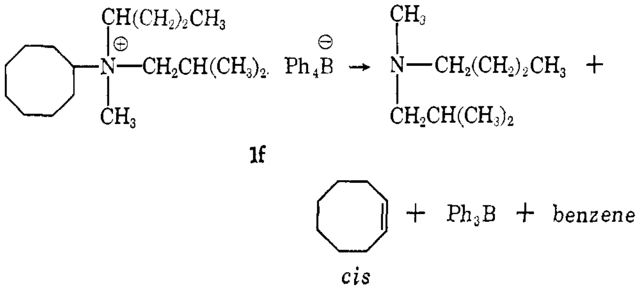
(12) J. Rabiant and G. Wittig, *Bull. Soc. Chim. France*, 798 (1957).

(13) S. Graff, D. Rittenberg, and G. L. Foster, *J. Biol. Chem.*, **133**, 745 (1940).

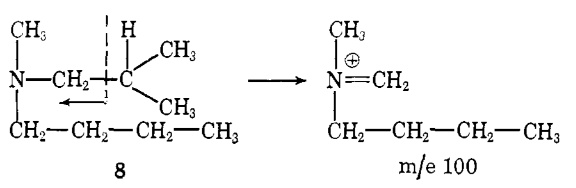
(14) J. A. Berson and D. A. Ben-Efraim, *J. Am. Chem. Soc.*, **81**, 4083 (1959).

corresponding labeled racemic perchlorate. A methanol–water solution of this mixture was converted to the corresponding hydroxide by ion-exchange chromatography. The eluted hydroxide was neutralized with dilute hydrochloric acid, and the chloride thus obtained was converted with sodium tetraphenylboron to the corresponding mixture of racemic and (−)-N-*n*-butyl-N-isobutyl-N-methylcyclooctylammonium-^{15}N tetraphenylboron (**1f**). Racemic material was obtained from this salt after 18 recrystallizations from ethyl acetate.[15] The crystalline material and the mother liquor of the final recrystallization showed no rotation. The melting point of the crystalline material and the atom % excess of nitrogen-15 remained constant after further recrystallizations.

Nitrogen-15 Determination by Mass Spectrometry. When N-*n*-butyl-N-isobutyl-N-methylcyclooctylammonium tetraphenylboron (**1f**) is heated to 160–210° at 40 mm, it undergoes decomposition. The lower boiling products, benzene, *cis*-cyclooctene, and N-isobutyl-N-methyl-*n*-butylamine (**8**), can be distilled; triphenylboron remains as residue. The distilled products were separated by preparative gas chromatography and identified by their infrared spectra. Triphenylboron was converted to its ammonia adduct[16] and identified by comparison of its infrared spectrum with that of an authentic sample and by its nuclear magnetic resonance spectrum.



The same thermal decomposition takes place when N-*n*-butyl-N-isobutyl-N-methylcyclooctylammonium tetraphenylboron (**1f**) is placed in a mass spectrometer and heated slowly. No molecular ion peak (*m/e* 574) is observed. However, in the region of lower mass to charge ratio, the superimposed spectra of *cis*-cyclooctene, benzene, and N-isobutyl-N-methyl-*n*-butylamine (**8**) can be detected. The most intense peak of the spectrum is found at *m/e* 100; this can be attributed to the favorable cleavage of N-isobutyl-N-methyl-*n*-butylamine (**8**). A repeated comparison of the region from *m/e* 99 to 102 in this spectrum with the same region in the spectrum of pure N-isobutyl-N-methyl-*n*-butylamine (**8**) showed that the two regions were completely identical. In both cases the peak height at *m/e* 101 was found to be 7.1% of the peak height at *m/e* 100 and therefore only due to the natural isotopic abundance (the calculated value is 7.09%).[17] The peak at *m/e* 102 (in theory 0.22% of the peak height at *m/e* 100) was not measurable and therefore was neglected. An equally small peak appeared at *m/e* 99 when the spectra were measured at an ionization potential of 80 ev, and this peak vanished completely when the ionization potential was lowered to 12 ev.



These results justified the direct use of N-*n*-butyl-N-isobutyl-N-methylcyclooctylammonium tetraphenylboron (**1f**) for the mass spectrometric ^{15}N determination instead of pure N-isobutyl-N-methyl-*n*-butylamine (**8**) obtained from a preceding thermal decomposition of the tetraphenylboron salt **1f**. To determine the atom % excess nitrogen-15 in N-*n*-butyl-N-isobutyl-N-methylcyclooctylammonium-^{15}N tetraphenylboron (**1f**) before (C_0) and after dilution ($C_\pm$), measurements were made of the peaks at *m/e* 100, 101, and 102 in the mass spectra of unlabeled tetraphenylboron salt **1f**, of undiluted tetraphenylboron-^{15}N salt **1f**, and of diluted tetraphenylboron-^{15}N salt obtained as racemic material from recrystallization of the mixture of (−)-tetraphenylboron salt **1f** and tetraphenylboron-^{15}N salt. The results of these measurements are listed in Table II. From the values listed in Table II, the atom % excess nitrogen-15 in the undiluted tetraphenylboron salt **1f** was calculated to be $C_0 = 38.7 \pm 0.3\%$, and for the diluted tetraphenylboron salt **1f**, $C_\pm = 23.1 \pm 0.2\%$. From eq 1, $E = 3.9837 \pm 0.0311$ g was calculated, which from eq 2 corresponds to an optical purity of 99.6 ± 0.8% for the (−)-N-*n*-butyl-N-isobutyl-N-methylcyclooctylammonium perchlorate (**1e**), $[\alpha]^{25}\mathrm{D}$ −1.65°. Based on these results, the percentages of asymmetric induction obtained from Hofmann eliminations using this material represent maximum values.

Table II. Mass Spectra of the Tetraphenylboron Salts **1f**

Salt	*m/e* 100	*m/e* 101	*m/e* 102
Tetraphenylboron-^{14}N	100	7.1 ± 0.07	
Tetraphenylboron-^{15}N			
undiluted	100	70.2 ± 0.4	4.6 ± 0.1
diluted	100	36.8 ± 0.3	2.5 ± 0.06

Experimental Section[18]

N-Isobutylcyclooctylamine (3).[19] A mixture of 25.6 g (0.20 mole) of cyclooctanone, 31 g (0.42 mole) of isobutylamine, 0.1 g of *p*-toluenesulfonic acid monohydrate, and 80 ml of benzene was heated at the reflux temperature for 18 hr. The water formed during the reaction (3.8 ml) was collected in a Dean–Stark trap. The resulting solution was distilled, giving 29.6 g (80%) of N-isobutylcyclooctanoneimine, bp 76–79° (1.2 mm).

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[15] A sample of the optically active tetraphenylboron salt **1f** did not undergo racemization when kept in boiling ethyl acetate for 3 hr.

[16] E. Krause, *Ber.*, **57**, 814 (1924).

[17] R. M. Silverstein and G. C. Basler, "Spectrometric Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1964.

[18] Melting points were determined on a Kofler hot stage. Melting points and boiling points are uncorrected. Analyses were performed by Dr. S. M. Nagy and by Scandinavian Microanalytical Laboratory, Herlev, Denmark. Optical rotations were determined with a Zeiss photoelectric precision polarimeter. The rotations measured at 546.1 and 577.8 mμ were used to calculate the values at the sodium D line (589.2 mμ). Mass spectra were measured with a Hitachi Perkin-Elmer Model RMU-6D mass spectrometer. Gas chromatographic analyses were performed on an F and M Model 720 instrument or in 180 × 0.8 cm Pyrex tubes packed with 48–100 mesh firebrick (Johns-Manville) which was coated with the appropriate stationary phase. Nmr spectra were measured on a Varian Associates A-60 instrument using tetramethylsilane as reference.

[19] British Patent 831,185 (March 23, 1960); *Chem. Abstr.*, **54**, 19543c (1960).

Anal. Calcd for $C_{12}H_{23}N$: C, 79.49; H, 12.77; N, 7.73. Found: C, 79.47; H, 12.67; N, 7.73.

A solution of 29.1 g (0.160 mole) of the imine in 75 ml of ethanol containing 0.2 g of prereduced platinum oxide was shaken with hydrogen at atmospheric pressure; 0.163 mole of hydrogen was absorbed. The mixture was filtered, and the filtrate was dissolved in 100 ml of 10% hydrochloric acid and extracted twice with ether. The amine was liberated by addition of solid sodium hydroxide and extracted three times with ether. After removal of ether from the dried solution, the residue was distilled, giving 26.1 g (89%) of N-isobutylcyclooctylamine (**3**), bp 72.0–72.5° (0.9 mm), $n^{25}\mathrm{D}$ 1.4642.

Anal. Calcd for $C_{12}H_{25}N$: C, 78.61; H, 13.75; N, 7.64. Found: C, 78.80; H, 13.96; N, 7.35.

In a later experiment the imine was reduced without purification to give the amine **3** in 79% yield.

The hydrochloride was prepared from a sample of the amine **3** and ethanolic hydrogen chloride and was recrystallized twice from 20:1 acetone–ethanol, mp 182.0–182.5° (a phase change occurred at about 150°). In later experiments, the entire amine product was purified by recrystallization of the hydrochloride.

Anal. Calcd for $C_{23}H_{26}ClN$: C, 65.57; H, 11.92; N, 6.37. Found: C, 65.40; H, 11.74; N, 6.55.

N-*n*-Butyl-N-isobutylcyclooctylamine (4). To a stirred solution of 146 g (0.8 mole) of N-isobutylcyclooctylamine (**3**) in a mixture of 640 ml of benzene and 640 ml of pyridine, 172 g (1.6 moles) of butyryl chloride was added slowly. Heat was evolved, and after a few minutes pyridine hydrochloride precipitated. The reaction mixture was stirred at the reflux temperature for 2 hr, cooled to room temperature, and poured into 800 ml of ice–water. The organic layer was separated, washed with 18% hydrochloric acid, saturated aqueous sodium bicarbonate solution, and water, and then dried with magnesium sulfate. Distillation afforded 109 g (94%) of N-cyclooctyl-N-isobutylbutyramide, bp 119–121° (0.15 mm), $n^{30}\mathrm{D}$ 1.4795.

Anal. Calcd for $C_{16}H_{31}NO$: C, 75.83; H, 12.33; N, 5.53. Found: C, 75.93; H, 12.42; N, 5.68.

A solution of the amide (189.2 g, 0.75 mole) in 350 ml of anhydrous ether was added to a stirred suspension of 29.4 g (0.77 mole) of lithium aluminum hydride in 1100 ml of anhydrous ether. The addition was performed at such a rate that the reaction mixture boiled gently. The mixture was heated at the reflux temperature for 4.5 hr, cooled to room temperature, and decomposed with water. The ether layer was separated, and the aqueous layer was extracted twice with ether. The combined ether extracts were dried with sodium sulfate and distilled to give 157.9 g (89%) of N-*n*-butyl-N-isobutylcyclooctylamine (**4**), bp 96–98° (0.19 mm), $n^{25}\mathrm{D}$ 1.4655.

Anal. Calcd for $C_{16}H_{33}N$: C, 80.26; H, 13.89; N, 5.85. Found: C, 80.42; H, 13.87; N, 5.78.

Treatment of a sample of the amine **4** with 35% perchloric acid afforded the amine perchlorate, which after three recrystallizations from ethyl acetate had mp 106.5–107.5°.

Anal. Calcd for $C_{16}H_{33}ClNO_4$: C, 56.54; H, 10.08; N, 4.12. Found: C, 56.57; H, 9.94; N, 4.12.

N-*n*-Butyl-N-isobutyl-N-methylcyclooctylammonium Iodide (1d). A solution of 62.3 g (0.26 mole) of N-*n*-butyl-N-isobutylcyclooctylamine (**4**) and 88 g (0.62 mole) of methyl iodide in 200 ml of dimethylformamide was stirred for 6 hr at 80°. The solvent was removed at 25 mm and 75° bath temperature with a rotary evaporator. The remaining oil was dissolved in 75 ml of acetone and 600 ml of ether was added. An oil formed which crystallized overnight at 0°. A quantitative yield of slightly yellow material, mp 114°, was obtained which was recrystallized from 300 ml of ethyl acetate–acetone (2:1) to give 97.8 g (99%) of colorless crystals, mp 115.0–115.5°.

Anal. Calcd for $C_{17}H_{36}IN$: C, 53.53; H, 9.54; N, 3.67. Found: C, 53.54; H, 9.37; N, 3.83.

N-*n*-Butyl-N-isobutyl-N-methylcyclooctylammonium Perchlorate (1e). A mixture of 0.93 g of iodide **1d** and 20 ml of 35% perchloric acid was stirred for 0.5 hr. The resulting solid was dissolved in chloroform, and the solution was washed twice with 35% perchloric acid. (When the perchlorate was prepared from N-*n*-butyl-N-isobutyl-N-methylcyclooctylammonium (+)-10-camphorsulfonate as mentioned later, the chloroform layer was washed with aqueous sodium bicarbonate and water in addition to 35% perchloric acid.) The chloroform layer was dried with magnesium sulfate and evaporated. The residue was recrystallized five times from ethyl acetate, giving 0.18 g of the perchlorate **1e**. When a solution of this perchlorate in ethyl acetate was cooled to −25°, and the sides of the container were scratched, small crystals melting at 89–90° rapidly precipitated. When such a solution was kept at −25° for 24 hr, large crystals melting at 124–125° separated. The two forms were interconverted by dissolving one in ethyl acetate and recrystallizing in the way that gave the other.

Anal. Calcd for $C_{17}H_{36}ClNO_4$: C, 57.69; H, 10.25; N, 3.96. Found: C, 57.88; H, 10.35; N, 3.66.

N-*n*-Butyl-N-isobutyl-N-methylcyclooctylammonium (+)-10-Camphorsulfonate. A solution of 250.8 g (0.65 mole) of the quaternary ammonium iodide **1d** in a mixture of 300 ml of water and 375 ml of ethanol was stirred with 150 g of silver oxide for 2 hr at 25°. The solid material was collected on a filter and washed twice with a mixture of ethanol–water (1:1); the wash solutions were combined with the filtrate and neutralized with a solution of 153 g (0.65 mole) of (+)-10-camphorsulfonic acid (Eastman Chemical Co.), $[\alpha]^{25}\mathrm{D}$ +23.07° (*c* 28, water) [lit.[20] $[\alpha]^{25}\mathrm{D}$ +23.11° (*c* 28, water)]. From the resulting solution, the solvent was evaporated under reduced pressure (the last traces of the solvent were removed at 40° bath temperature and 1 mm or less), giving 309.3 g (97%) of a viscous oil. From a solution of this oil in ethyl acetate 155.1 g of crystalline material was obtained in three crops. The remaining mother liquor gave no more crystals. The solvent was evaporated, and the remaining oil was considered as the more soluble fraction.

The crystalline material, mp 80–100°, was fractionally crystallized from acetone at −20° five times until the melting point and the specific rotation remained constant. The less soluble (+)-10-camphorsulfonate (55.1 g) had mp 110.5–111.0°, $[\alpha]^{25}\mathrm{D}$ +20.43° (*c* 1.34, ethanol).

Anal. Calcd for $C_{27}H_{51}NO_4S$: C, 66.76; H, 10.58; N, 2.88. Found: C, 66.62; H, 10.61; N, 2.73.

(−)-N-*n*-Butyl-N-isobutyl-N-methylcyclooctylammonium Perchlorate (1e). The less soluble (+)-10-camphorsulfonate (52.5 g, 0.108 mole) was converted to the perchlorate as described above for the preparation of the racemic perchlorate **1e**. The (−)-perchlorate (36.5 g, 95%) had mp 91–93°; α^{25}_{578} (obsd) −0.030°, α^{25}_{546} (obsd) −0.035°, $[\alpha]^{25}\mathrm{D}$ −1.65° (*c* 1.73, ethanol).

Anal. Calcd for $C_{17}H_{36}ClNO_4$: C, 57.69; H, 10.25; N, 3.96. Found: C, 57.54; H, 10.11; N, 4.22.

Two different fractions of the more soluble (+)-10-camphorsulfonate were similarly converted to the corresponding (+)-perchlorates **1e**, mp 91–92°; α^{25}_{578} (obsd) +0.015°, α^{25}_{546} (obsd) +0.0175°, $[\alpha]^{25}\mathrm{D}$ +0.81° (*c* 1.76, ethanol); and α^{25}_{578} (obsd) +0.020°, α^{25}_{546} (obsd) +0.0225°, $[\alpha]^{25}\mathrm{D}$ +0.60° (*c* 3.18, ethanol). No change in rotation could be observed when samples of these optically active perchlorates were kept in methanol solution for 7 days at room temperature or when recrystallized several times from hot ethyl acetate.

Pyrolysis of (+)-N-*n*-Butyl-N-isobutyl-N-methylcyclooctylammonium Hydroxide (1c). A solution of 10.0 g (0.028 mole) of (+)-perchlorate **1e**, $[\alpha]^{25}\mathrm{D}$ +0.81°, in 66 ml of 40% aqueous methanol was passed through a 36 × 2.4 cm column of Amberlite IRA 400 ion-exchange resin (OH form). This resin was prepared from the chloride form by elution with 5% aqueous sodium hydroxide until the eluate was free of chloride ions, then washed with 40% methanol to neutrality. The column was eluted with 40% methanol until the eluate was neutral. A sample of the eluate had a positive rotation. The solvent was removed from the eluate at 25 mm and a maximum bath temperature of 30°. The remaining oil was dried for several hours at 20° and 1 mm or less. The oil (8.8 g) was decomposed at 60–80° (0.5 mm) in a 100-ml round-bottomed flask. The distillate was collected in two cold traps. The first trap, cooled with acetone–Dry Ice, contained all of the amines and the cyclooctenes; the second trap, cooled with liquid nitrogen, contained butylene and isobutylene. The contents of the first trap were made acidic with 10 ml of 10% hydrochloric acid and extracted with 20 ml of pentane. The pentane layer was washed with aqueous sodium bicarbonate and water. A sample of the pentane extract had a positive rotation. Analysis of the pentane extract by gas chromatography [4-methyl-4-nitropimelonitrile (NMPN), 65°] showedt hat *cis*- and *trans*-cyclooctenes were present in a 34:66 ratio. The pentane solution was extracted with six 25-ml portions of a solution of 20% (by weight) aqueous silver nitrate.[7] The combined silver nitrate extracts were washed carefully with pentane and poured into 100 ml of concentrated ammonium hydroxide containing cracked ice. The ammonia mixture was extracted with three 25-ml portions of pentane, and the combined extracts were dried with sodium sulfate. A sample of the pentane solution had a positive rotation. The pentane was re-

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[20] E. M. Richards and T. M. Lowry, *J. Chem. Soc.*, 1503 (1925).

moved by distillation through a spinning-band column[2] at 30° bath temperature and 500 mm. The remaining liquid was distilled at room temperature and 3 mm into a trap cooled to −30°, giving 1.16 g (37%) of *trans*-cyclooctene. Gas chromatographic analysis (NMPN, 65°) showed that no *cis*-cyclooctene or pentane was present. No impurity could be detected when the *trans*-cyclooctene was analyzed by gas chromatography (10-ft column of 30% silicone grease on Chromosorb W 80–100, linear temperature programming 100–200°). The infrared spectrum and refractive index ($n^{25}\text{D}$ 1.4738) were in agreement with the reported values.[7] The olefin had the following rotations: $\alpha^{25}{}_{578}$ (obsd) +1.445°, $\alpha^{25}{}_{546}$ (obsd) +1.665°, $[\alpha]^{25}\text{D}$ +1.63° (neat, $d^{25}{}_4$ 0.8456)[7]; $\alpha^{25}{}_{578}$ (obsd) +0.050°, $\alpha^{25}{}_{546}$ (obsd) +0.055°, $[\alpha]^{25}\text{D}$ +1.87° (*c* 2.57, pentane); and $\alpha^{25}{}_{578}$ (obsd) +0.035°, $\alpha^{25}{}_{546}$ (obsd) +0.045°, $[\alpha]^{25}\text{D}$ +1.68° (*c* 1.91, acetic acid). From the ratio of *cis*- and *trans*-cyclooctene obtained by gas chromatography and from the yield of *trans*-cyclooctene, the yield of *cis*-cyclooctene (19%) and the over-all yield of cyclooctenes (56%) were calculated. All Hofmann eliminations listed in Table I were performed similarly. In the case of the racemic quaternary ammonium iodide **1d**, this was converted to the corresponding hydroxide with silver oxide in water.

Hydrogenation of Optically Active *trans*-Cyclooctene. A solution of 178.1 mg of the optically active *trans*-cyclooctene in 8 ml of acetic acid containing 60 mg of prereduced platinum oxide as catalyst was shaken with hydrogen; the quantitative amount of hydrogen was absorbed. The catalyst was removed by filtration; the filtrate was found to have no rotation.

Analysis of the Amine Fraction of the Hofmann Pyrolysis. The aqueous layer obtained after acidification of the Hofmann reaction products was treated with excess solid sodium hydroxide. The liberated amines were extracted with ether; the ether extracts were dried with magnesium sulfate. Gas chromatographic analysis of the ether extracts (8-ft column of 20% silicone rubber on Chromosorb W, linear program from 100–190°) showed three peaks with areas in the ratio 83.5:9.87:7.0 in order of their elution. Samples of each of the three amines were collected and identified as amines **8**, **9**, and **10**, respectively.

Identification of N-Isobutyl-N-methyl-*n*-butylamine (8). A sample of the first fraction of the above gas chromatogram was converted to the picrate, mp 51.0–54.5° (lit.[9] mp 51–54°). A second sample was converted to the methiodide, which after five recrystallizations from acetone–ether melted at 170.5–171.0° (lit.[9] mp 176.6–178.4°).

N-Isobutyl-N-methylcyclooctylamine (9). A mixture of 10.1 g (0.055 mole) of N-isobutylcyclooctylamine (**3**), 25 g of 90% formic acid, and 12 g of 30% formaldehyde was heated on a steam bath for 12 hr. The reaction mixture was worked up as described,[21] giving 9.7 g (89 %) of N-isobutyl-N-methylcyclooctylamine (**9**), bp 84.0–85.5° (1.3 mm). The nmr spectrum of this amine confirmed the structure and was identical with that of the second peak of the gas chromatogram.

Anal. Calcd for $C_{13}H_{27}N$: C, 79.11; H, 13.79; N, 7.10. Found: C, 78.96; H, 13.49; N, 7.12.

N-*n*-Butylcyclooctylamine (11). N-*n*-Butylcyclooctanone imine, bp 86–88° (0.9 mm), was prepared as described above for the preparation of N-isobutylcyclooctanone imine.

Anal. Calcd for $C_{12}H_{23}N$: C, 79.49; H, 12.79; N, 7.73. Found: C, 79.42; H, 12.79; N, 7.58.

The imine was converted to the amine by catalytic hydrogenation as described. The product was isolated in 80% yield as the hydrochloride, which, after two recrystallizations from acetone–ethanol, melted at 227.0–228.5° (a phase change occurred at 140–180°).

Anal. Calcd for $C_{12}H_{26}ClN$: C, 65.57; H, 11.92; N, 6.32. Found: C, 65.26; H, 12.01; N, 6.40.

The free amine, bp 84–85° (0.85 mm), was recovered quantitatively from the hydrochloride.

Anal. Calcd for $C_{12}H_{25}N$: C, 78.61; H, 13.75; N, 7.64. Found: C, 78.40; H, 13.76; N, 7.88.

N-*n*-Butyl-N-methylcyclooctylamine (10). Clarke–Eschweiler methylation of amine **11** as described for amine **3** gave N-*n*-butyl-N-methylcyclooctylamine (**10**), bp 74° (1.2 mm), in 70% yield.

Anal. Calcd for $C_{13}H_{27}N$: C, 79.11; H, 13.79; N, 7.10. Found: C, 79.30; H, 13.96; N, 7.34.

The nmr spectrum of this amine confirmed its structure and was identical with that of the third peak of the gas chromatogram.

Hofmann-Type Elimination of (−)-N-*n*-Butyl-N-isobutyl-N-methylcyclooctylammonium Perchlorate (1e) in Liquid Ammonia. To a solution of 160 ml of liquid ammonia (−40°) containing a few crystals of ferric nitrate, 1.75 g (0.045 g-atom) of potassium was added. The solution was stirred until a gray color appeared; then 3.178 g (0.0091 mole) of (−)-perchlorate **1e**, $[\alpha]^{25}\text{D}$ −1.65°, was added in small portions. The solution was stirred for 4 hr at −35 to −40°. Pentane (50 ml) was added to the reaction mixture, and the excess potassium amide was destroyed with solid ammonium chloride. The ammonia was allowed to evaporate, 100 ml of water was added, and the solution was made acidic with 10% hydrochloric acid. The pentane layer was separated, and the aqueous phase was extracted with two 50-ml portions of pentane. The combined pentane layers were washed with 10% hydrochloric acid and then with water until neutral. The pentane solution had a positive rotation. Analysis of the pentane solution by gas chromatography (NMPN, 65°) showed a 34:66 mixture of *cis*- and *trans*-cyclooctenes from which *trans*-cyclooctene (0.331 g, 33%) was isolated as described above. The infrared spectrum and refractive index, $n^{25}\text{D}$ 1.4740, were identical with the reported values.[7] Analysis by gas chromatography (NMPN, 65°; 2-ft silicone rubber, 100–200°) indicated that the *trans*-cyclooctene was pure. The olefin had the following rotations: $\alpha^{25}{}_{578}$ (obsd) +1.930°, $\alpha^{25}{}_{546}$ (obsd) +2.225°, $[\alpha]^{25}\text{D}$ +10.87° (neat, $d^{25}{}_4$ 0.8456[7]); $\alpha^{25}{}_{578}$ (obsd) +0.555°, $\alpha^{25}{}_{546}$ (obsd) +0.640°, $[\alpha]^{25}\text{D}$ +10.40° (*c* 5.08, pentane). A solution of the above *trans*-cyclooctene in acetic acid showed no rotation after catalytic hydrogenation.

Cyclooctylamine-^{15}N (12). A mixture of 3.5808 g (0.06643 mole) of ammonium-^{15}N chloride (40.5 atom % enrichment), 8.3845 g (0.06643 mole) of cyclooctanone (**2**), 18 ml of methanol, and 1 g of Raney nickel was placed in an autoclave. Triethylamine (13.5 g, 0.13 mole) was added to this mixture, and the autoclave was closed quickly. The mixture was shaken with hydrogen at 1500 psi at 90° for 43 hr. The catalyst was removed by filtration, and the filtrate was concentrated by distillation through a 30-cm column packed with steel helices. The remaining liquid was made acidic with 10% hydrochloric acid while the mixture was cooled in an ice bath. The acidic solution was washed with four 50-ml portions of ether, and then was made basic with solid sodium hydroxide and extracted with ether. The ether solution was dried with solid sodium hydroxide and distilled, giving 7.45 g (88%) of cyclooctylamine-^{15}N, bp 95° (30 mm), $n^{25}\text{D}$ 1.4782 (lit.[22] $n^{23.5}\text{D}$ 1.4802). Analysis by gas chromatography (2-ft silicone rubber, 120°) showed that the product had a retention time identical with that of an authentic, unlabeled sample.

N-Isobutylcyclooctylamine-^{15}N (3). To a stirred solution of 7.45 g (0.058 mole) of cyclooctylamine-^{15}N (**12**) and 20 mg of *p*-toluenesulfonic acid monohydrate in 35 ml of benzene, 4.25 g (0.059 mole) of isobutyraldehyde was added dropwise. An immediate reaction occurred at room temperature with formation of water. The mixture was heated at the reflux temperature for 14 hr, and the water formed was collected in a Dean–Stark trap. Most of the solvent was removed by distillation through a Vigreux column. The remaining liquid was dissolved in 25 ml of methanol and reduced catalytically at atmospheric pressure with prereduced platinum oxide. The hydrogen uptake was quantitative. The catalyst was removed by filtration, and the filtrate was concentrated and distilled, giving 9.74 g (91%) of N-isobutylcyclooctylamine-^{15}N (**3**), bp 93–94° (4 mm), $n^{20}\text{D}$ 1.4652.

From this amine **3**, N-*n*-butyl-N-isobutyl-N-methylcyclooctylammonium-^{15}N perchlorate (**1e**) was prepared as described above for the corresponding unlabeled compound. The melting point and infrared spectrum were identical with that of the unlabeled compound. The perchlorate-^{15}N contained 38.7 atom % excess nitrogen-15 (as determined by mass spectrometry, see below).

Anal. Calcd for $C_{17}H_{36}Cl^{15}NO_4$: C, 57.62; H, 10.24; N, 4.07. Found: C, 57.54; H, 10.13; N, 3.89.

N-*n*-Butyl-N-isobutyl-N-methylcyclooctylammonium Tetraphenylboron (1f). A solution of 0.7 g (1.98 mmoles) of N-*n*-butyl-N-isobutyl-N-methylcyclooctylammonium perchlorate (**1e**) in 5 ml of 50% aqueous methanol was passed through a 30 × 2 cm column of Amberlite IRA-400 ion-exchange resin (OH form). The column was eluted with 50% aqueous methanol until the eluate was neutral. The eluate was then neutralized with 10% hydrochloric acid, and a solution of 1 g (2.9 mmoles) of sodium tetraphenylboron in 15 ml of water was added. The milky solution was evaporated to dryness,

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(21) M. L. Moore, *Org. Reactions*, **5**, 323 (1949).

(22) P. T. Moore, Ph.D. Thesis, Massachusetts Institute of Technology, 1959.

and the residue was extracted with 150 ml of methylene chloride. The methylene chloride solution was washed with water, dried with sodium sulfate, and evaporated to dryness. The crude product, obtained in quantitative yield, was recrystallized from 35 ml of ethyl acetate to give 0.99 g (87%) of colorless crystals, mp 156.0–157.5°.

Anal. Calcd for $C_{44}H_{56}BN$: C, 85.83; H, 9.84; N, 2.44. Found: C, 86.10; H, 9.81; N, 2.38.

Thermal Decomposition of N-*n*-Butyl-N-isobutyl-N-methylcyclooctylammonium Tetraphenylboron (1f). A sample of the tetraphenylboron salt **1f** was heated under a nitrogen atmosphere at 40 mm in a flask connected to a trap cooled in acetone–Dry Ice. The temperature was raised slowly to 210°; decomposition started at about 180° bath temperature. The temperature was kept at 210° for 2 hr while colorless liquid condensed in the trap leaving a slightly yellow oil in the reaction flask. The contents of the trap were made acidic with 10% hydrochloric acid and extracted with ether. Analysis of the ether extract by gas chromatography (8-ft 3% silicone rubber on Chromosorb W, 100°) showed two products which were collected and identified by their retention times and their infrared spectra as benzene and *cis*-cyclooctene. Analysis by gas chromatography (NMPN, 65°) showed that no *trans*-cyclooctene was present. The aqueous layer was made basic with solid sodium hydroxide and extracted with ether. Gas chromatographic analysis (8-ft 3% silicone rubber on Chromosorb W, 100–200°) showed only one product which was collected and identified by its infrared spectrum as N-isobutyl-N-methyl-*n*-butylamine (**8**).

The triphenylboron remaining in the flask was dissolved in anhydrous ether in an atmosphere of nitrogen, and dry ammonia was bubbled into the solution. Colorless needles formed which, after recrystallization from benzene, melted at 216° (sealed tube) (lit.[16] mp 216°). The ammonia addition product of triphenylboron was identified by its nmr spectrum (CD_3SOCD_3), τ 4.47 (broad singlet) and 2.85 (unresolved multiplet), and by comparison of the infrared spectrum (KBr pellet) with that of an authentic sample.[16]

Isotopic Dilution Method. A solution of 3.9983 g of (−)-N-*n*-butyl-N-isobutyl-N-methylcyclooctylammonium perchlorate (**1e**), $[\alpha]^{25}\mathrm{D}$ −1.65°, and 2.0007 g of the racemic labeled perchlorate-^{15}N **1e** in 100 ml of 40% methanol was passed through a 36 × 2.4 cm column of Amberlite IRA-400 ion-exchange resin (OH form) as described. The eluate was neutralized with 10% hydrochloric acid and combined with a solution of 7.8 g of sodium tetraphenylboron in 50 ml of water. The milky mixture was evaporated to dryness, and the residue was extracted with 100 ml of methylene chloride. The methylene chloride solution was washed with 25 ml of water, dried with sodium sulfate, and evaporated to dryness to give 10 g of crude product. Crystallization of the crude product from a mixture of 200 ml of ethyl acetate and 10 ml of acetone gave 8.46 g of colorless crystals, $[\alpha]^{25}_{435}$ −1.14° (*c* 3.08, acetone), mp 148–151°. A 6.514-g sample of this material was dissolved in 900 ml of hot ethyl acetate[23] and cooled slowly to 27° over a period of 20 hr. The crystals formed, 2.900 g, $[\alpha]^{25}_{436}$ −1.36° (*c* 3.12, acetone), were collected quickly on a filter, and the mother liquor was allowed to stand for 2 days at 25°. The crystals obtained from the mother liquor, $[\alpha]^{26}_{436}$ −0.88° (*c* 3.91, acetone), were recrystallized 17 times from ethyl acetate until neither the crystalline product nor the mother liquor showed a rotation.[24] After two further recrystallizations, 0.295 g of racemic material, mp 156.0–157.5°, was obtained which contained 23.1 atom % excess of nitrogen-15 as determined by mass spectrometry (see below). After two further recrystallizations, 0.254 g of material was obtained, mp 156.0–157.5°, which contained 23.1 atom % excess nitrogen-15.

Nitrogen-15 Determination by Mass Spectrometry. Mass Spectrum of N-Isobutyl-N-methyl-*n*-butylamine (8). The mass spectrum of N-isobutyl-N-methyl-*n*-butylamine (**8**) at 80 ev had the most intense peak at *m/e* 100 and a peak at *m/e* 101 due to the natural isotopic abundance. The peaks at *m/e* 99 and 102 were too small to be measured. The peak at *m/e* 99 disappeared completely when the ionization potential was lowered to 12 ev. The region of *m/e* 99–102 was scanned 15 times at 80 ev for each measurement; the peak height at *m/e* 101 was expressed as a percentage of the peak height at *m/e* 100. The average value for *m/e* 101 was determined to be 7.1%.

Determination of C_0 and $C_\pm$. Mass Spectrum of N-*n*-Butyl-N-isobutyl-N-methylcyclooctylammonium-^{15}N Tetraphenylboron (1f). A sample of the tetraphenylboron salt **1f** was placed in the mass spectrometer and heated slowly. The region of the spectrum at *m/e* 99–102 was scanned 15 times at an ionization potential of 80 ev. This procedure was repeated three times, and the mean value for *m/e* 101, expressed as a percentage of the peak height at *m/e* 100, was determined to be 7.1%. The region of the spectrum at *m/e* 99–102 was identical with that of the pure amine **8**.

Mass Spectrum of N-*n*-Butyl-N-isobutyl-N-methylcyclooctylammonium-^{15}N Tetraphenylboron (1f). Exactly the same procedure was repeated for the undiluted tetraphenylboron-^{15}N salt **1f**, which was prepared from the corresponding perchlorate-^{15}N **1e**, and the diluted tetraphenylboron-^{15}N salt. The mean values are listed in Table III. From these values the atom % excess of nitrogen-15 for the undiluted tetraphenylboron-^{15}N salt **1f**, C_0 = 38.8%, and for the diluted tetraphenylboron-^{15}N salt **1f**, $C_\pm$ = 23.1%, were calculated.

Table III. Mass Spectra of the Tetraphenylboron Salts **1f**

Salt	— Peak height at *m/e* — 100	101	102
Tetraphenylboron-^{14}N	100	7.1	
Tetraphenylboron-^{15}N undiluted	100	70.2	4.7
Tetraphenylboron-^{15}N diluted	100	36.7	2.5

A second determination of C_0 and $C_\pm$ was carried out on a sample which had been recrystallized two additional times exactly as described, but the ionization potential was lowered to 12 ev. This reduced the fragmentation drastically, but the peak at *m/e* 100 still remained very intense. The small peak at *m/e* 99, which was neglected in the determination above, vanished completely. Again the spectra of the three tetraphenylboron salts were measured under the same conditions, scanning the region of the spectrum at *m/e* 99–102 30 times for each sample. The mean values and their standard deviations are listed in Table II. The atom % excess of nitrogen-15 was calculated from these data: C_0 = 38.7 ± 0.3% for the undiluted tetraphenylboron-^{15}N salt **1f**, and $C_\pm$ = 23.1 ± 0.2% for the diluted tetraphenylboron-^{15}N salt **1f**. From these values, E = 3.9837 ± 0.0311 g[25] was obtained from eq 1 and the optical purity, 99.6 ± 0.8%, of the (−)-N-*n*-butyl-N-isobutyl-N-methylcyclooctylammonium perchlorate, $[\alpha]^{25}\mathrm{D}$ −1.65°, was obtained from eq 2.

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[23] A sample of the optically active (−)-tetraphenylboron salt **1f** did not show any change in specific rotation when boiled in ethyl acetate for 3 hr.

[24] During the recrystallizations, the material isolated from the mother liquor always showed a higher specific rotation than the crystallized material.

[25] The error a of E was calculated from the partial differential of eq 1

$$a^2 = [\partial E/\partial(C_0/C_\pm)]^2 r^2 = \frac{(X^2 + BX)^2 r^2}{4[(X + B)^2 - (X^2 + BX)(C_0/C_\pm)]}$$

where r is the error of $C_0/C_\pm$. The weighing error was neglected.