ethylene glycol, 6.9 g of the mixture of **25** and **27**, and 6.0 g of hydrazine hydrate, at 210° for 3 hr. The mixture was diluted with water, neutralized, and extracted three times with ether to give 1.7 g (about 30% yield) of an oil, bp 110–112° (2 mm). Gas chromatography on column A (see above) separated, with difficulty, **(−)-2-methyl-2-ethylpentanoic acid (26)** from its isomer **28, 3-methyl-3-ethylpentanoic acid.** The ir spectrum of **26** was identical with that of authentic material, made after Prout.[26] The mixture of **26** and **28** was used in the next step, in which 1.4 g of the mixture (0.01 mol) was treated with 3 ml of thionyl chloride at room temperature for 18 hr. After heating to reflux for 2 hr, the thionyl chloride was removed *in vacuo*, 0.5 g of activated sodium azide and 3 ml of xylene were added, the solution was heated to 80°, and another 0.5 g of sodium azide was added. After 5 hr, the temperature was raised to 180°. The filtrate was stirred for 12 hr with 4 ml of concentrated hydrochloric acid at about 80° and cooled, the aqueous layer separated, and the organic solution extracted once with hydrochloric acid. From the aqueous layers, the amine was liberated by base, extracted into ether, and acylated with ethyl chloroformate and sodium hydroxide. Analysis on column A readily separated **3** from its (optically inactive) isomer **29, 3-carbomethoxyaminomethyl-3-methylpentane.** Compound **3** was recognized by its retention time, spectra, and optical activity; compound **29** had the following spectra: ir NH 3450 (sharp), 3350 (broad); C=O 1720 cm^{-1}; nmr OCH_2CH_3 δ 4.03 (q, 2.0), $-CH_2$NHCOOEt 2.97 (d, 2.0), NH about 5 (very broad), other protons 0.5–1.5 (16.2). The rotation of **3** was found to be $[\alpha]^{25}\text{D}$ −0.837° (homogeneous). It being 49% optically pure, the maximum rotation should be $[\alpha]^{25}\text{D}$ −1.708°, and **3** obtained with full retention from 79% optically active (+)-(*S*)-3-methylhexane should have a $[\alpha]^{25}\text{D}$ of +1.35° (compare Table VI).

Acknowledgments. We are greatly indebted to the National Science Foundation for support of this work, and to the National Institutes of Health for a predoctoral fellowship to J. M. S.

Stereochemical Studies. VIII. Asymmetric Selection *via* Elimination. Assignment of Nitrogen Chirality by Pyrolytic Elimination in Optically Active Amine Oxides[1]

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Contribution from the Department of Chemistry, University of South Carolina, Columbia, South Carolina 29208. Received March 20, 1969

Abstract: The four possible optically active stereoisomeric N-methyl-N-neopentyl-4-methylcyclohexylamine oxides were individually prepared. The stereomeric secondary amines, *cis*- and *trans*-N-neopentyl-4-methylcyclohexylamines (**3** and **4**), obtained by reductive amination procedures, were separated and converted to the corresponding tertiary amines (**8** and **9**) by N-methylation. The *cis*- and *trans*-amine oxides (**10** and **11**) were obtained by oxidation of **8** and **9** with peracetic acid. A consistent correlation of nmr signal envelope shapes at each synthesis stage provided the basis for assignment of stereochemistry to these compounds. Resolution of the amine oxides gave the four optically active stereoisomers in undetermined enantiomeric purity. Each optically active amine oxide underwent asymmetrically selective pyrolytic elimination to optically active 4-methylcyclohexene of known configuration. Thus, the (−)-*cis*- and (+)-*trans*-amine oxides each gave (−)-(*S*) olefin, while the (+)-(*R*) olefin was the predominant enantiomer obtained from pyrolysis of the (+)-*cis*- and (−)-*trans*-amine oxides. These results, plus the reasonable assumption that neopentyl is bulkier than methyl, allowed for definition of nitrogen chirality in each of the amine oxides by a transition-state argument.

Although asymmetric selectivity[3] was observed during pyrolyses of optically active esters,[4] reliable interpretation regarding configurational correlations could not be made because of the low optical yields and because of a general lack of understanding of the factors governing conformational relationships in the carbalkoxy group. Unlike this situation, interpretation of the very high levels of asymmetric selectivity observed during pyrolyses of optically active sulfoxides[5] was straightforward because of the absence of these conformational questions. It was, therefore, of considerable interest to investigate pyrolyses of suitable optically active amine oxides, for, based upon the generally accepted view of the transition state,[6] here too no conformational questions would be involved. An additional point of interest lay in the realization that, with a reliable model of the transition state for the *syn* pyrolytic amine oxide process, and with a knowledge of the configurational details of other moieties present, the chirality at nitrogen could be uniquely defined. The system chosen for this undertaking was N-methyl-N-neopentyl-4-methylcyclohexylamine oxide, and we report herein on the synthesis of each of the four possible configurational isomers, stereochemical assignments (4-methylcyclohexyl group), individual pyrolyses, and transition-state analyses leading to specification of nitrogen chiralities.[7]

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(1) (a) Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for financial support of this research. (b) Presented in part at the 155th National Meeting of the American Chemical Society, San Francisco, Calif., April 1968; see, Abstracts, No. P31.

(2) Taken in part from the dissertation submitted by F-L. L. to the Graduate School, University of South Carolina, 1966, in partial fulfillment of the requirements for the Ph.D. degree.

(3) Any reaction or process that gives, either directly or indirectly, enantiomers in unequal amounts.

(4) S. I. Goldberg and F.-L. Lam, *J. Org. Chem.*, **31**, 2336 (1966).

(5) S. I. Goldberg and M. S. Sahli, *ibid.*, **32**, 2059 (1967).

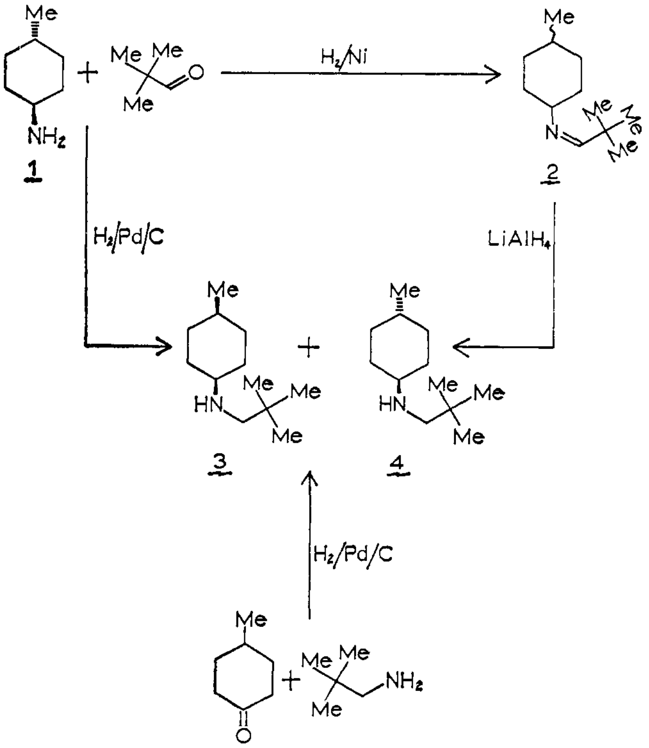
(6) A. C. Cope and E. R. Trumbull, *Org. Reactions*, **11**, 317 (1960).

(7) During the early stages of the present investigation, G. Berti and G. Bellucci [*Tetrahedron Letters*, 3853 (1964)] reported that an optically active N-methyl-N-phenyl-4-methylcyclohexylamine oxide gave optically active 4-methylcyclohexene upon pyrolysis. No attempt was made by these authors to analyze their results under the concept presented herein.

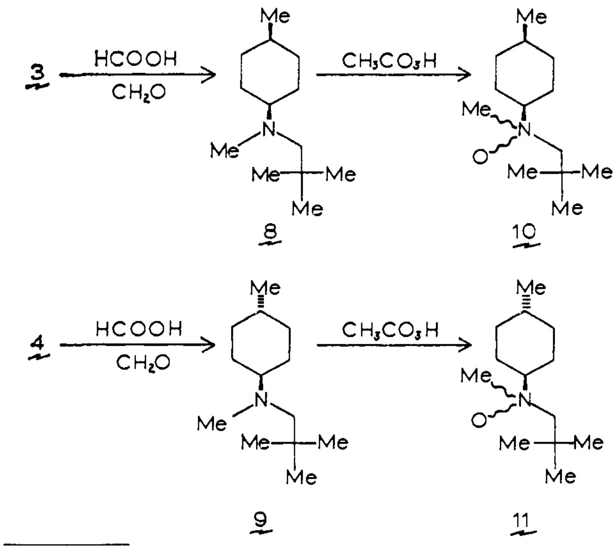
Results

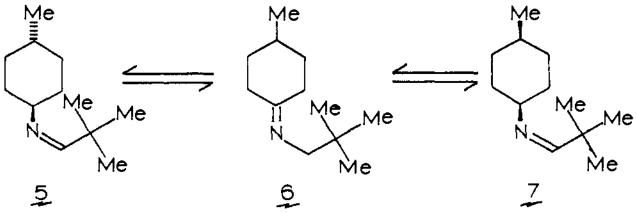
Preparation of the stereomeric amine oxides is outlined in Schemes I and II. Attempted reductive amination of *trans*-4-methylcyclohexylamine (**1**)[8] with pivaldehyde in the presence of Raney nickel gave only the imine, 2,2-dimethyl-1-(4-methylcyclohexylimino)propane (**2**), which was reduced by lithium aluminum hydride to a mixture of the secondary amines, *cis*- and *trans*-N-neopentyl-4-methylcyclohexylamines (**3** and **4**, 43 and 57%, respectively). This same mixture of **3** and **4** was obtained directly with the use of a 5% palladium on charcoal catalyst, and from reductive amination of 4-methylcyclohexanone and neopentylamine. Although the point was not investigated, these observations are probably best explained in terms of an equilibrium involving the tautomeric imines, **5**, **6**, and **7**.

Scheme I



Scheme II





In any case, formation of **3** and **4** in almost equal amounts provided an unanticipated source of the stereomeric secondary amines, which were individually converted to the tertiary amines, **8** and **9**, by Eschweiler–Clarke methylation, followed by oxidation (peracetic acid) to the corresponding amine oxides, **10** and **11**.[9]

The assignments of cyclohexyl stereochemistry (*cis* or *trans*) throughout the series of transformations were based on the relative shapes of the nmr signal envelopes due to the cyclohexyl protons. Briefly, since a disubstituted cyclohexane with its substituents oriented diequatorially will exist almost exclusively in an essentially rigid chair conformation, and since axial and equatorial protons give different chemical shifts with complex spin–spin interactions, it is to be expected that the signal envelopes in such cases will be significantly broader than those of the corresponding nondiequatorial isomers.[10–13] The nmr spectra determined from the *cis*- and *trans*-amine oxides, **10** and **11**, are given in Figures 1 and 2, respectively.

Accumulated in Table I are the physical constants determined from the stereomeric cyclohexanes. It is of interest to note that the nmr-based stereochemical assignments correlate with the modern statement of the von Auwers–Skita rule[14] which designates the isomer with the higher physical constants as the one of higher enthalpy. The observed reversal in glpc elution order in going from the secondary amines (*cis* faster) to the tertiary amines (*cis* slower) appears to corroborate ear-

Table I. Some Physical Properties of Stereomeric Pairs of Amine Derivatives

Compd	Glpc retention time, min	n^{20}D	Bp, °C (mm)	Mp, °C
		Secondary Amines		
cis-**3**	23.8	1.4480		Liquid
trans-**4**	26.8	1.4458		Liquid
		Tertiary Amines		
cis-**8**	36.2	1.4569	90–91 (4.5)	Liquid
trans-**9**	32.4	1.4527	88–89 (4.5)	Liquid
		Amine Oxides		
cis-**10**				52–53
trans-**11**				Liquid

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[8] D. R. Smith, M. Maienthal, and J. Tipton, *J. Org. Chem.*, **17**, 294 (1952).

[9] The anomalous chemical shifts present in the nmr spectra determined from these and other neopentyl compounds have been previously noted [S. I. Goldberg, F-L. Lam, and J. E. Davis, *J. Org. Chem.*, **32**, 1658 (1968)].

[10] S. Brownstein and R. Miller, *ibid.*, **24**, 1886 (1959).

[11] J. Musher and R. E. Richards, *Proc. Chem. Soc.*, 230 (1958); F. A. Jensen and B. H. Beck, *Tetrahedron Letters*, 4523 (1966); J. T. Gerig and J. D. Roberts, *J. Amer. Chem. Soc.*, **88**, 2791 (1966); W. L. F. Armarego, *J. Chem. Soc.*, *C*, 337 (1967).

[12] A. C. Cope and R. B. Kinnel, *J. Amer. Chem. Soc.*, **88**, 752 (1966).

[13] For a collection of nmr spectra, including those of compounds **3**, **4**, **8**, and **9**, that illustrate this effect, see S. I. Goldberg, F.-L. Lam, and M. S. Sahli, *J. Chem. Eng. Data*, **14**, 406 (1969).

[14] E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p 216.

Figure 1. Nmr spectrum of *cis*-N-methyl-N-neopentyl-4-methylcyclohexylamine oxide.

Figure 2. Nmr spectrum of *trans*-N-methyl-N-neopentyl-4-methylcyclohexylamine oxide.

lier findings[15] that the elution order of a pair of isomers does not provide a correlation with the stereochemistry of the compounds.

Resolution of each diastereomeric amine oxide was attempted with (−)-bromocamphorsulfonic acid and (−)-menthoxyacetic acid in a variety of solvents before it was finally accomplished to an undetermined degree of enantiomeric purity through salt formation with (−)-dibenzoyltartaric acid. Specific rotations of the four optically active amine oxides are given in Table II. Pyrolytic elimination of 4-methylcyclohexene from each amine oxide was effected in the heated inlet chamber of a gas–liquid partition chromatography apparatus at three different temperatures, results and details of which are presented in Table II. From each optically active amine oxide, optically active 4-methylcyclohexene was obtained. Thus, leveorotatory olefin was obtained from both the levorotatory *cis*-amine oxide and the dextrorotatory *trans*-amine oxide, while both the dextrororatory *cis*-oxide and the leverotatory *trans*-oxide gave the dextrorotatory olefin.

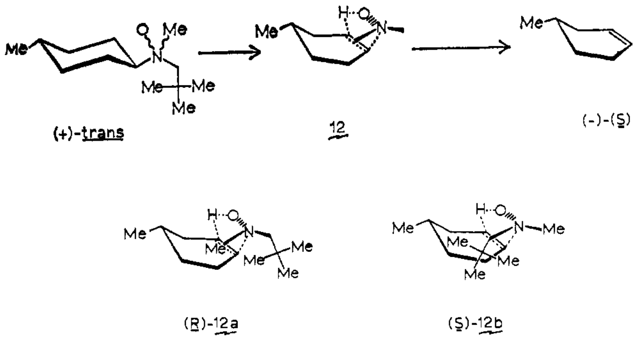

Figure 3. Assignment of absolute configuration at nitrogen in the (+)-*trans*-amine oxide.

Table II. Pyrolyses of Stereoisomeric Amine Oxides

Amine oxide			4-Methylcyclohexene				
Isomer	[α]D, deg	Pyrolysis temp, °C	Isomer	[α]D, deg	Enantiomeric purity, %[a]	Conversion,[b]	% × 10^{-1} [c]
(−)-*cis*-**15**	−2.87 ± 0.20	120	(−)-(*S*)-**14**	−10 ± 0.60	9.4 ± 0.6	3	5
		100	(−)-(*S*)-**14**	−10 ± 0.28	9.4 ± 0.3	3	4
		85	(−)-(*S*)-**14**	−12 ± 1.3	11 ± 1.2	1	2
(+)-*cis*-**16**	+2.90 ± 0.19	120	(+)-(*R*)-**13**	+7.8 ± 0.37	7.2 ± 0.4	3	5
		100	(+)-(*R*)-**13**	+9.1 ± 0.62	8.5 ± 0.6	3	4
		85	(+)-(*R*)-**13**	+13 ± 0.66	12 ± 0.6	1	2
(−)-*trans*-**17**	−0.70 ± 0.05	120	(+)-(*R*)-**13**	+2.0 ± 0.18	1.9 ± 0.2	2	5
		100	(+)-(*R*)-**13**	+3.0 ± 0.43	2.8 ± 0.4		3
		85				Trace	Trace
(+)-*trans*-**18**	+2.35 ± 0.28	120	(−)-(*S*)-**14**	−5.8 ± 0.40	5.4 ±0.4	4	6
		100	(−)-(*S*)-**14**			1	3
		85	(−)-(*S*)-**14**			Trace	Trace

[a] Based on highest reported specific rotation value of 107° [J. Zelikow, *Chem. Ber.*, **37**, 1374 (1904)]. [b] From glpc peak collections. [c] From glpc peak areas.

Discussion

Since absolute configurations of the enantiomeric 4-methylcyclohexenes are known,[16] the only missing configurational element in each of the pyrolysis experiments was the chirality at nitrogen. However, given the validity of the generally accepted, five-centered transition state for *syn* pyrolytic elimination in amine oxides,[6] definition of absolute nitrogen configuration directly follows. This may be illustrated with one of the four pyrolysis series: (+)-*trans*-amine oxide to (−)-(*S*)-4-methylcyclohexene as the predominant enantiomeric olefins (Figure 3).

The absolute shape of the transition state leading to (−)-(*S*)-4-methylcyclohexene from the (+)-*trans*-amine oxide, therefore, must be discussed in terms of **12**, with only the relative spacial disposition of the N-methyl and N-neopentyl groups to be decided.

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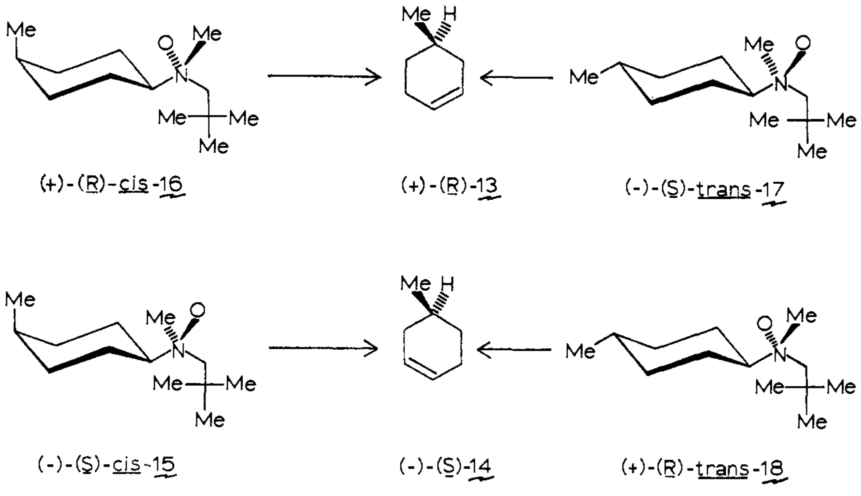
(15) H. Feltkamp and K. D. Thomas, *J. Chromatog.*, **10**, 9 (1963).

(16) S. I. Goldberg and F.-L. Lam, *J. Org. Chem.*, **31**, 240 (1966).

Scheme III



Clearly, the more favorable arrangement is the one (**12a**) in which the bulkier neopentyl group is free of serious nonbonded interactions with the cyclohexyl hydrogens. This judgement, therefore, defines the absolute configuration at nitrogen in the (+)-*trans*-amine oxide as being (*R*) as in **12a** and not (*S*) as in **12b**. In this way nitrogen chiralities in the amine oxides were assigned: (−)-(*S*)-*cis*-**15**, (+)-(*R*)-*cis*-**16**, (−)-(*S*)-*trans*-**17**, and (+)-(*R*)-*trans*-**18**.

Experimental Section

General. Temperatures are uncorrected. Melting points were determined with capillary tubes. Combustion analyses were by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. Infrared (ir) spectra were obtained with a Perkin-Elmer, Model 337, grating spectrometer; the spectra were analyzed with the aid of standard reference works.[17] A Varian, A-60, nuclear magnetic resonance (nmr) spectrometer was used near room temperature for determination of nmr spectra with chloroform-*d* solvent containing 1–4% (v/v) tetramethylsilane (TMS) internal standard. Chemical shifts are reported under the δ convention in parts per million (ppm) relative to TMS (0 ppm). Standard nmr references[18] were consulted to corroborate assignments. Polarimeter measurements were made with a 1-dm microcell using an O. C. Rudolph and Sons, Inc. (Caldwell, N. J.), polarimeter Model 80, equipped with a sodium light source. Gas–liquid partition chromatography (glpc) was carried out on an F & M Scientific Corp. (now Hewlett-Packard, Avondale, Pa.), Model 500, chromatograph.

***trans*-4-Methylcyclohexylamine (1).** To a combined solution of 4-methylcyclohexanone (50 g, 0.45 mol), hydroxylamine hydrochloride (35 g, 0.51 mol in 100 ml of water), and sodium acetate (75 g, 0.92 mol in 150 ml of water) in a 1-l., round-bottomed flask was added enough ethanol (~350 ml) to form a clear solution, which was kept overnight at room temperature. Alcohol was distilled from the solution until the residue became cloudy and separated in layers. The aqueous layer was extracted with three 200-ml portions of ether which were combined with the original organic layer of the reaction mixture, and the whole dried over anhydrous potassium carbonate. Evaporation of the solvent, followed by fractional distillation of the residue, gave 4-methylcyclohexanone oxime: 44 g (77% yield); bp 96° (4.5 mm), lit.[8] bp 114° (14 mm); mp 36°, lit.[8] mp 36°.

In a 1-l., three-necked flask, fitted with an addition funnel, condenser, mercury-sealed stirrer, and nitrogen inlet, was placed lithium aluminum hydride (15 g, 0.40 mol) in 200 ml of anhydrous ether. The mixture was stirred gently during 15 min while a slow stream of nitrogen was passed through the system to displace the air from it. While the system was maintained under a very slight nitrogen pressure, and while the stirrer was operated slowly, a solution of 4-methylcyclohexanone oxime (30 g, 0.24 mol) in 100 ml of anhydrous ether was added at a rate sufficient to maintain a gently reflux. When the addition was complete, the system was heated under reflux (stirring) for an additional 4-hr period before it was allowed to cool to room temperature. Unreacted lithium aluminum hydride was then destroyed carefully by slow addition of 30 ml of water. The resulting suspension of complex inorganic material was brought into solution during 30 min of stirring after addition of a mixture of 200 ml of 20% aqueous Rochelle salt (sodium potassium tartrate tetrahydrate)[19] and 20 ml of 20% aqueous sodium hydroxide. The aqueous phase of the clarified mixture was separated and submitted to continuous extraction with ether during 10 hr. The ether extract was combined with the original ethereal phase, and the whole dried over anhydrous potassium carbonate before the ether was evaporated to a viscous residue. Fractional distillation provided *trans*-4-methylcyclohexylamine (**1**): 15 g (56% yield); bp 71–73° (48–50 mm); $n^{20}\text{D}$ 1.4450 [lit.[8] bp 72–73° (50 mm); $n^{20}\text{D}$ 1.4450]; ir (film) 3350, 3270, 1600, 1370 (CNH_2), 2940, 2920, 2840, and 1445 cm^{-1} (aliphatic CH); nmr spectrum exhibits "*trans*-signal" envelope effect.[13]

2,2-Dimethyl-1-(4-methylcyclohexylimino)propane (2). To a solution of *trans*-4-methylcyclohexylamine (**1**) (9.3 g, 0.082 mol) in 20 ml 95% ethanol was added a solution of pivaldehyde (7.8 g, 0.091 mol) in 20 ml of 95% alcohol. The solution was heated to boiling and placed into a heavy-walled bottle containing freshly prepared Raney nickel (4 g). The system was flushed several times with hydrogen before it was submitted to a hydrogen pressure of 50 psi and shaken for 7 hr. Removal of the catalyst and evaporation of the solvent left a residue that was taken up in 50 ml of 3 *N* hydrochloric acid and washed with ether to remove nonbasic components. The aqueous residue was made strongly basic with 6 *N* sodium hydroxide solution and extracted with three 50-ml portions of ether. The combined and dried ethereal extracts were evaporated to a residue which was distilled to give recovered starting material (4.2 g) and **2,2-dimethyl-1-(4-methylcyclohexylimino)propane (2)**: 4.3 g; bp 103° (45 mm); ir (film) 1670, 1370 (C=N), and 1360 cm^{-1} (*t*-Bu); nmr (CCl_4) δ 7.45 (q, 1, N=C*H*), 2.33–1.10 (m, 10, cyclohexyl protons), and 1.10–0.72 (m. 12, methyl protons). These data plus the fact that reduction gave the expected secondary amines (see below) established the structure as indicated.

***cis*- and *trans*-N-Neopentyl-4-methylcyclohexylamines (3 and 4).** A solution of the imine **2** (4.2 g, 0.023 mol) in 40 ml of anhydrous ether was added to a stirred suspension of lithium aluminum hydride (5.0 g, 0.13 mol) in 50 ml of anhydrous ether at a rate that

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[17] L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," 2nd ed, John Wiley & Sons, Inc., New York, N. Y., 1958; K. Nakanishi, "Infrared Absorption Spectroscopy," Holden-Day, Inc., San Francisco, Calif., 1962; R. T. Conley, "Infrared Spectroscopy," Allyn and Bacon, Inc., Boston, Mass., 1966; collection of infrared spectra supplied by Sadtler Research Laboratories, Inc., Philadelphia, Pa.

[18] L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, Inc., New York, N. Y., 1959; G. V. D. Tiers, "Tables of Tau-Values for a Variety of Organic Compounds," Minnesota Mining and Manufacturing Co., St. Paul, Minn., 1958; N. S. Bhacca, L. F. Johnson, and J. N. Schoolery, "NMR Spectra Catalog," Vol. 1, Varian Associates, Palo Alto, Calif., 1962; N. S. Bhacca, D. P. Hollis, L. J. Hohnson, and E. A. Pier, "NMR Spectra Catalog," Vol. 2, Varian Associates, Palo Alto, Calif., 1963; collection of nmr spectra supplied by Sadtler Research Laboratories, Inc., Philadelphia, Pa.

[19] L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," John Wiley & Sons, Inc., New York, N. Y., 1967, p 983.

sustained a gentle reflux during the addition. The mixture was heated under reflux for 3 hr after the addition was complete. Excess hydride was carefully destroyed, and the separated aqueous phase was extracted with several portions of ether which were combined with the original ethereal phase, and the whole dried over anhydrous potassium carbonate. Removal of the ether followed by distillation of the residue gave an oil [bp 81–83° (4.5 mm); 2.3 g, 53% yield] which was shown by glpc analysis[20] to consist of a mixture of what was subsequently shown (see below) to be *cis*- and *trans*-**N-neopentyl-4-methylcyclohexylamines (3 and 4)**, 43 and 57%, respectively.

Anal. Calcd for $C_{12}H_{25}N$: C, 78.61; H, 13.75; N, 7.64. Found: C, 78.91; H, 14.01; N, 7.20.

Benzenesulfonamides were prepared from a portion of the mixture of isomeric amines and benzenesulfonyl chloride in 10% aqueous sodium hydroxide; mp 81–83°.

Anal. Calcd for $C_{18}H_{29}NO_2S$: C, 66.83; H, 9.04; N, 4.33. Found: C, 67.14; H, 9.10; N, 4.12.

A mixture of **N-nitroso derivatives** were obtained by treating a portion of the isomeric amines, dissolved in 10% hydrochloric acid, with sodium nitrite. The yellowish-white crystalline material that formed was collected and recrystallized; mp 50–51°.

Anal. Calcd for $C_{12}H_{24}N_2O$: C, 67.87; H, 11.40; N, 13.20. Found: C, 68.20; H, 11.39; N, 12.75.

Identical mixtures of the isomeric secondary amines (**3** and **4**) were directly obtained from two reductive amination procedures. In the first, a solution of pivaldehyde (7.80 g, 0.0907 mol) in absolute ethanol (20 ml) was added to a solution of *trans*-4-methylcyclohexylamine (**1**) (9.20 g, 0.0814 mol) in ethanol (25 ml) and warmed slightly before 1.2 g of 5% palladium on powdered charcoal catalyst[21] was added. The mixture was kept under a hydrogen pressure of 50 psi and shaken during 6.5 hr. After the catalyst was removed and the solvent evaporated, the residue was taken up in 20 ml of 6 *N* hydrochloric acid and washed with an equal volume of ether. The acidic aqueous phase was made strong basic by addition of 25 ml of 6 *N* sodium hydroxide solution. After the liberated amines were extracted into three 30-ml portions of ether, the combined ether extracts were dried and evaporated to a colorless oil which, upon fractional distillation [bp 80° (4.5 min)], gave 11.5 g (60.0% yield) of the mixture of isomeric amines (infrared and glpc[20] analyses).

The second reductive amination procedure gave the mixture of isomeric amines [2.10 g. 33.6% yield] by hydrogenation (54 psi, 5% palladium on charcoal[21]) of a mixture of neopentylamine (3.00 g, 0.0345 mol) of 4-methylcyclohexanone (3.86 g, 0.0345 mol) in 20 ml of absolute ethanol at room temperature for 6 hr.

Separation and Identification of the Amines 3 and 4. By means of a large number of chromatographic runs,[20] each followed by collection of the two peaks, approximately 10 g of each isomeric amine was accumulated. *cis*-**N-Neopentyl-4-methylcyclohexylamine (3)**: $n^{20}\mathrm{D}$ 1.4480; ir (film) 3350 w, 2950 s, 2910 s, 2860 s, 2845 s, 2800 s, 1470 m, 1450 m, 1370 m, 1360 m, 1140 m, 1120 m, 1105 m, and 1095 m cm^{-1}; nmr spectrum reproduced in ref 13. *trans*-**N-Neopentyl-4-methylcyclohexylamine (4)**: $n^{20}\mathrm{D}$ 1.4458; ir (film) 3350 w, 2950 s. 2930 s, 2870 s, 2800 s, 2710 m, 1470 m, 1450 m, 1375 m, 1365 m, and 1125 s cm^{-1}; nmr spectrum reproduced in ref 13. Configurational assignment to each amine was based on the relative shapes of the signal envelopes of the cyclohexyl protons in the nmr spectra.[13] Thus, the compound that gave the narrow nmr signal envelope (cyclohexyl protons) was assigned the nondiequatorial isomer (*cis*), while the diequatorial form (*trans*) was assigned[13] to the amine that gave the broad cyclohexyl proton signal envelope.

cis- **and** *trans*-**N-Methyl-4-methylcyclohexylamines (8 and 9).** N-Methylation of the secondary amines was tried with methyl iodide and with formic acid and formaldehyde (Eschweiler–Clarke). The latter procedure was found to be better, and initial preparation and characterization of the tertiary amines were carried out on a mixture of the stereoisomeric amines.

A mixture of formic acid (90% aqueous; 5.1 g, 0.01 mol), formaldehyde (37% aqueous; 2.26 ml, 0.0300 mol), and the *cis*- and *trans*-amines (**3** and **4**) (2.75 g, 0.0150 mol) was heated to 95–100° when vigorous evolution of carbon dioxide began. After the gas evolution subsided the heating was continued during 8 hr. When the mixture had cooled to room temperature, 10 ml of 4 *N* hydrochloric acid was added and the entire solution was evaporated to a pale yellow, syrupy oil which was taken up in 6 ml of water. Addition of 5 ml of 18 *N* sodium hydroxide liberated the basic material which was extracted in two 30-ml portions of ether. Evaporation of the combined and dried (potassium carbonate) extracts gave a colorless residual oil which, after fractional distillation, provided a mixture of the isomeric tertiary amines (**8** and **9**): 2.45 g (82.8% yield); bp 87–88° (4.8 mm).

Anal. Calcd for $C_{13}H_{27}N$: C, 79.11; H, 13.79; N, 7.10. Found: C, 79.08; H, 14.11; N, 7.29.

A portion of this material was converted to picrate salt, which after recrystallization (ethanol) had mp 108–110°.

Anal. Calcd for $C_{19}H_{30}N_4O_7$: C, 53.51; H, 7.09; N, 13.14. Found: C, 53.47; H, 7.19; N, 13.22.

In this manner each stereomeric secondary amine was converted to its N-methylated tertiary amine counterpart. The nmr spectrum determined from each isomeric tertiary amine (spectra reproduced in ref 13) still displayed cyclohexyl proton signal envelope shapes consistent with the generalization[13] used to make the configurational assignments to the secondary amines.

cis-**N-Methyl-N-neopentyl-4-methylcyclohexylamine (8)**: bp 70–71° (4.5 mm); $n^{20}\mathrm{D}$ 1.4569; ir (film) 2950 s, 2915 s, 2860 s, 2850 s, 2780 s, 1490 s, 1470 s, 1390 s, 1370 s, 1250 m, 1240 m, 1200 m, 1190 m, 1135 m, 1110 s, 1100 m, 1065 m, 1050 s, 1035 s, 1020 m, 990 m, and 865 m cm^{-1}.

trans-**N-Methyl-N-neopentyl-4-methylcyclohexylamine (9)**: bp 88–89° (4.5 mm); $n^{20}\mathrm{D}$ 1.4527; ir (film) 2950 s, 2915 s, 2850 s, 2840 s, 2770 s, 1490 s, 1460 s, 1380 m, 1360 s, 1250 m, 1205 m, 1195 m, 1145 m, 1120, 1080 m, 1040 s, 1025 m, 1010 m, and 870 m cm^{-1}.

(±)-*cis*- and (±)-*trans*-N-Methyl-N-neopentyl-4-methylcyclohexylamine Oxides (10 and 11). Two procedures were investigated for oxidation of the tertiary amines to their oxides. While both provided the desired products, the procedure using peracetic acid led to much greater yields than did the use of hydrogen peroxide.

Peracetic acid[22] (40% aqueous solution; 10 g, 0.067 mol) was added to the tertiary amine (3.6 g, 0.018 mol) contained in a 25-ml volumetric flask that was cooled previously in an ice–salt bath. The reactants were vigorously mixed, and after 30 min the flask was removed from the cold bath and kept at room temperature during 6 days. Glacial acetic acid was then added (final volume of 25 ml), and the extent of amine oxide formation was determined[23] to be quantitative. The entire solution was cooled in an ice–water bath while 20% aqueous potassium hydroxide solution was added until an alkaline litmus reaction was reached. After the mixture was extracted with three 50-ml portions of chloroform, the combined extracts were dried (potassium carbonate) and evaporated to the desired amine oxide (3.4 g, 82% yield). In this way each isomeric racemic oxide was prepared; nmr signal envelope shapes (see Figures 1 and 2) consistent with assigned stereochemistry. The **(±)-*cis*-amine oxide (10)** was obtained as a hydrated, white solid in 98% yield from the *cis*-tertiary amine (**8**); mp 52–53°; ir ($CHCl_3$) 3110 m (broad), 2955 s, 2910 s, 2860 s, 2850 s, 2500 m, 1460 s, 1360 ms, 1250 ms, 1090 m, 1045 m, 1010 m, 990 m, 960 m, 935 m, 910 m, 890 m, 880 m, 860 m, 835 m, and 660 s cm^{-1}; nmr, see Figure 1.

Anal. Calcd for $C_{13}H_{27}NO(H_2O_2)_2$: C, 62.59; H, 12.53; N, 5.62. Found: C, 62.74; H, 12.44; N, 5.85.

The same procedure when carried out on the *trans*-tertiary amine gave the **(±)-*trans*-amine oxide (11)** as a colorless, viscous, hydrated oil in 95% yield; ir ($CHCl_3$) 3115 m (broad), 2950 s, 2910 s, 2870 s, 2500 m, 1490 ms, 1460 s, 1410 m, 1370 ms, 1250 ms, 1090 m, 1045 m, 995 m, 975 ms, 960 ms, 940 m, 910 ms, 890 ms, 785 s, 730 m, and 660 s cm^{-1}; nmr, see Figure 2.

Resolution of (±)-*cis*- and (±)-*trans*-Amine Oxides (10 and 11). A. **(+)- and (−)-*cis*-N-Methyl-N-neopentyl-4-methylcyclohexylamine Oxides (16 and 15).** A solution of (±)-*cis*-amine oxide (**10**) (10.5 g, 0.0421 mol) and (−)-D-dibenzoyltartaric acid (15.0 g, 0.0424 mol) in absolute ethanol was prepared at room temperature and then kept in the refrigerator overnight. The mass of white crystalline salt which was collected and air-dried amounted to 15.5 g; mp 130–134° and $[\alpha]^{26}\mathrm{D}$ −66.1 ± 0.78° (*c* 2.71, methanol). The entire amount of material was redissolved in 250 ml of warm absolute ethanol. The solution was allowed to cool to room temperature and kept in the refrigerator overnight to provide 11.36 g of recrystallized salt; mp 153–154°, $[\alpha]^{16}\mathrm{D}$ −72.0 ± 0.87° (*c* 2.41, methanol). Four more recrystallizations, carried out in the same

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(20) Column (16 ft × 0.25 in.), packed with Diatoport-W (60–80 mesh) containing 15% (w/w) Carbowax 20M, run isothermally (100°) with helium at 100 cc/min. Retention times: *cis* isomer, 23.8 min, *trans* isomer, 26.8 min.

(21) Matheson Coleman and Bell commercial material.

(22) FMC Corporation, Buffalo, N. Y.

(23) For details of the iodometric method used, see: A. C. Cope and H. H. Lee, *J. Amer. Chem. Soc.*, **69**, 964 (1957); D. Severn, *Org. Reactions*, **8**, 392 (1953).

manner, left 3.58 g of white crystalline material with no significant improvement in melting point (154°) or rotational magnitude {$[\alpha]^{26}\mathrm{D}$ −71.9 ± 0.50° (*c* 3.08, methanol)} over the singly recrystallized salt. The multiply recrystallized material was treated with cold, 20% aqueous potassium hydroxide solution, followed by extraction of the liberated amine oxide into three 30-ml portions of chloroform. White, crystalline, (+)-*cis*-**amine oxide (16),** 1.32 g, $[\alpha]^{22}\mathrm{D}$ +2.90 ± 0.19° (*c* 8.07, chloroform), was obtained after removal of the chloroform.

The filtrate obtained from the initial crystallization of the levorotatory salt was reduced to one-half of its volume and kept in the refrigerator overnight. A crop of white crystalline material was obtained: 1.40 g, mp 127–130°, $[\alpha]^{26}\mathrm{D}$ −61.9 ± 0.60° (*c* 2.74, methanol). The filtrate from this crystallization was also reduced to one-half volume, but no crystallization could be induced. Instead the solution was evaporated under reduced pressure to 6.2 g of a residual oil that slowly crystallized to a mass of pale yellow material; mp 88–93°, $[\alpha]^{27}\mathrm{D}$ −37.0 ± 0.47° (*c* 3.45, methanol). The entire quantity was taken up in 30 ml of 20% aqueous potassium hydroxide solution and extracted with three 30-ml portions of chloroform. Evaporation of the combined and dried extracts gave crystalline (very pale yellow) (−)-*cis*-**amine oxide (15)**; 2.0 g, $[\alpha]^{26}\mathrm{D}$ −2.87 ± 0.20° (*c* 14.19, chloroform). Infrared spectra determined from the (+)-*cis*-amine oxide, the (−)-*cis*-amine oxide, and the (±)-*cis*-amine oxide were superimposable.

B. **(+)- and (−)-*trans*-N-Methyl-N-neopentyl-4-methylcyclohexylamine Oxides (18 and 17).** After a solution of (±)-*trans*-amine oxide (9.18 g, 0.0392 mol) and (−)-D-dibenzoyltartaric acid (14.0 g, 0.0396 mol) in 50 ml of absolute ethanol was kept in the refrigerator overnight, the deposited white crystalline salt was collected and air dried; 14.5 g, mp 151–152°, $[\alpha]^{23}\mathrm{D}$ −66.0 ± 0.39° (*c* 4.57, methanol). This material was recrystallized from 200 ml of absolute ethanol to give 7.93 g of salt; mp 155–156°, $[\alpha]^{23}\mathrm{D}$ −69.0 ± 0.62° (*c* 4.22, methanol). A second recrystallization gave a slight improvement in melting point (155.5–156.0°) and rotatory magnitude {$[\alpha]^{27}\mathrm{D}$ −72.4 ± 1.0° (*c* 2.77, methanol)}, but no further improvement in these properties was obtained after four additional recrystallizations. The entire quantity of multiply recrystallized material (4.44 g) was taken up in 30 ml of cold 20% aqueous potassium hydroxide solution and extracted with three 30-ml portions of chloroform. The combined extracts were dried (potassium carbonate) and evaporated under reduced pressure to (−)-*trans*-**amine oxide (17)**; 1.02 g, $[\alpha]^{29}\mathrm{D}$ −0.70 ± 0.05° (*c* 11.2, chloroform).

The filtrate from the initial recrystallization above was evaporated to one-half of its volume and kept in the refrigerator overnight. The white crystalline material (1.56 g) obtained had mp 139–141° and $[\alpha]^{23}\mathrm{D}$ −65 ± 0.45° (*c* 3.88, methanol). Reduction to half-volume of the supernatant obtained from this crystallization followed by cooling of the concentrate in the refrigerator overnight failed to give any additional crystallization. Subsequent evaporation of the remaining ethanol, however, provided 4.33 g of crystalline salt; mp 110–112°, $[\alpha]^{23}\mathrm{D}$ −16.5 ± 0.72° (*c* 2.36, methanol). This material was treated with 30 ml of cold 20% aqueous potassium hydroxide solution, followed by extraction with three 30-ml portions of chloroform. Evaporation of the combined and dried chloroform extracts gave (+)-*trans*-**amine oxide (18)**; 0.42 g, $[\alpha]^{27}\mathrm{D}$ +2.35 ± 0.28° (*c* 5.33, chloroform). Infrared spectra determined from each enantiomeric *trans*-amine oxide and from (±)-*trans*-amine oxide were all superimposable.

Pyrolyses of the Stereoisomeric Amine Oxides. Each pyrolysis was carried out in the heated sample inlet chamber of a gas–liquid partition chromatograph.[24] The pyrolysate was carried out in a helium stream (55 psi, 80 cc/min) onto the column[20] which was maintained at 70°. Repeated runs in each case followed by collection of the peak due to 4-methylcyclohexene provided the olefin in sufficient quantities to corroborate its identity (infrared spectra) and to determine its specific rotation. Pyrolysis data are accumulated in Table II. Calculations of conversion percentages to olefin were based upon actual weights of collected olefin samples and also based upon calibrated area measurements of olefin glpc peaks. In each case, however, the values obtained (Table II) were fairly uncertain because of the hygroscopic character of the amine oxides and the consequent difficulty in knowing the actual weight of a given amine oxide sample during pyrolysis.

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[24] F & M Corporation, Model 500.

Stereochemistry of Deamination of 2-Phenylethylamine

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Abstract: Nitrous acid deamination of *erythro*-2-phenylethylamine-1,2-d_2 affords 2-phenylethyl acetate with 52% retention of configuration under conditions where 25–27% label rearrangement occurs with $PhCH_2C^*H_2NH_2$. Deamination of unlabeled amine in CH_3CO_2D results in incorporation of only 0.06 atom of deuterium per molecule. These results are consistent, although not uniquely so, with deamination proceeding *via* three distinct processes, one of which leads to a phenonium ion.

Recently we reported on the relation between the extent of label rearrangement in, and stereochemical course attending, solvolysis of 2-phenylethyl sulfonate esters.[2] In all cases we noted that the per cent retention of configuration in the products was twice the label rearrangement. This result is demanded if a symmetrical phenonium ion is involved and was taken as support for this hypothesis, in contrast to the equilibrating classical ions concept. It seemed important to us to determine the relation between product configuration and label rearrangement in other reactions producing the 2-phenylethyl cation; this paper describes results attending deamination.

In his classic work in the 3-phenyl-2-butyl system, Cram reported[3] on the deamination of the optically active *threo*- and *erythro*-amines. In contrast to the results attending formolysis the deamination products were formed with greatly reduced stereospecificity and considerable hydrogen and methyl group migration. This led Cram to suggest that products were formed, in part, from "hot"carbonium ions whose formation was subject to ground-state conformational control. A considerable fraction of phenonium ions were converted

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[2] R. J. Jablonski and E. I. Snyder, *J. Am. Chem. Soc.*, **91**, 4445 (1969).

[3] (a) D. J. Cram and J. E. McCarty, *ibid.*, **79**, 2866 (1957); (b) D. J. Cram, *ibid.*, **86**, 3767 (1964).